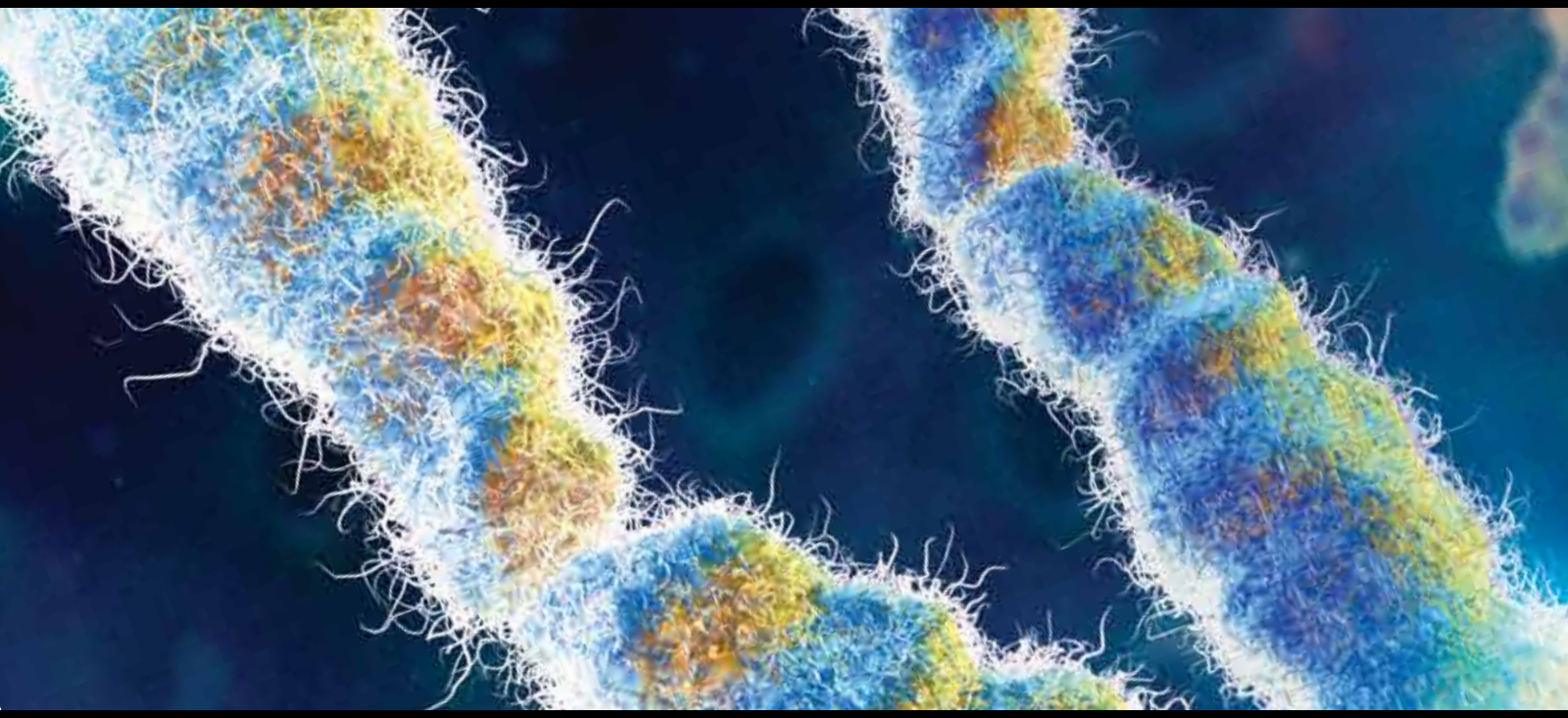
Journal of Aging Research

Aging, Physical Activity, and Disease Prevention

Guest Editors: Ben Hurley and Iris Reuter



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Editorial Board

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Editorial

Aging, Physical Activity, and Disease Prevention

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Although no amount of physical activity can stop the biological aging process, regular exercise can counteract some of the adverse physiological, psychological, and cognitive consequences of aging [1]. Age and physical inactivity are primary and secondary (indirect) risk factors for a long list of adverse chronic conditions [2, 3], whereas increasing physical activity from midlife to old age results in reduced rates of chronic disease and death [3, 4].

Our Call for Papers was driven by a growing body of evidence showing strong associations between physical inactivity and age-related chronic disease, as well as reductions in risks or incidence of chronic disease with exercise training [1]. Despite the overwhelming evidence for the role of physical activity in reducing the incidence of mortality, morbidity, and quality of life in chronic disease, a relatively small portion of the population are physically active worldwide [5] and even fewer older adults exercise regularly with sufficient intensity, duration, and frequency to receive optimal benefits for disease prevention [1]. Physical inactivity is especially prevalent in highly developed countries [5]. For this reason, more research is needed to understand and overcome barriers for habitual exercise and sport participation (see 3rd paper in this issue).

A recent study ordered reasons for participating in exercise programs and found that social aspects followed by the intent to improve physical fitness and/or prevent chronic diseases ranked among the highest reasons in older adults. With the increasing number of elderly, especially in the highly developed countries, it is important, yet challenging, to offer attractive and accessible physical activity programs to elderly. Qualified supervision, medical evaluations, and evidence-based individualized exercise prescriptions are also important for older sedentary adults, particularly those with underlying cardiovascular disease [6]. Besides cardiovascular and metabolic disease prevention, physical activity might also help reduce the risk of dementia [7, 8] and maintain cognitive function [9]. Since the risk of dementia is strongly associated with age and the number of adults surviving to advanced age will increase markedly in the near future, preventive measures become increasingly important. In this context, there is even some evidence that biological aging of the brain might be slowed down and that brain areas most affected by the aging process might benefit most from regular exercise [10].

This special issue covers a wide array of topics on the aging and physical activity and their relationship to disease and disability prevention. The papers show how aging and physical activity are associated with disability, mortality, behavioral change, home-based counseling interventions, bone and connective tissue health, telomere biology, Parkinson's disease, diabetes, hypertension, cancer, inflammation, antioxidants, sleep apnea, and cognitive function.

The first paper investigates the impact of physical activity on disability in Mexico and the USA The second paper focuses on the relationship between physical activity and mortality rates over a 7-year period in the UK The influence of aging on social cognitive characteristics associated with physical activity and whether improvements in psychosocial factors influence age-related declines in physical activity are discussed in the third paper. The fourth paper assessed the qualities of a counseling intervention on sustaining a physically active lifestyle. The authors of the fifth paper provide a review of the potential benefits of aerobic exercise training and whole-body vibration training on bone mineral density in older populations and discuss possible mechanisms for effects of each intervention. A review of the bone mineral density literature is also highlighted in the sixth paper, but with a focus on how it applies to physical performance and

other components of body composition. The risk of osteoporosis is described in the seventh paper by assessing the relationship of physical activity, hip fractures, and disability from hip fractures. The eighth paper highlights the role of exercise on the prevention and treatment of osteoarthritis, whereas the ninth paper explains the benefits of both aerobic and resistance exercise training for patients with rheumatoid arthritis. The authors of the tenth paper show how physical and leisure activity can help counteract the association of wheelchair use and poor health perception. The eleventh papre describes the relationship between physical activity and telomere biology as it applies to age-related diseases and longevity. A flexibility and relaxation program is compared to regular walking versus a Nordic walking program in patients with Parkinson's disease in the twelfth paper. The authors of the thirteenth paper review the literature on resistance training and glucose tolerance with applications to diabetes risk in older adults and potential mechanisms of action. The fourteenth paper investigates the effects of aerobic exercise training on the formation of a signaling molecule that influences vascular tone known as eicosanoids. The fifteenth paper reviews the literature on the use of strength training as an intervention to offset some of the deleterious side effects of hormone therapy used by prostate and breast cancer patients. The sixteenth paper studied the role of specialized G-proteins that increase cAMP known as melanocortin 3 receptors on the anti-inflammatory process of resistance training. The antioxidant potential of Tai Chi training is explained in the seventeenth paper, and the last paper describes the role of cognitive function on lower-body physical performance in older African American women.

Ben Hurley
Iris Reuter

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Research Article

The Impact of Physical Activity on Disability Incidence among Older Adults in Mexico and the United States

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Evidence suggests that transitions among older adults towards healthy habits, such as physical activity, appear underway in developed countries such as the USA but not in developing countries such as Mexico. However, little is known about the potential benefit of physical activity in preventing disability among elders in countries at different stages of epidemiological transition. We explore the impact of physical activity on the disablement process among elders in Mexico compared to the USA. Data are from two waves of the Mexican Health and Aging Study and the Health and Retirement Study. We examine the impact of exercise on the transition from no disability to ADL limitations two years later. Findings indicate that exercise is more common in the U.S. than in Mexico. There is a positive effect of exercise on negative outcomes in both countries. However, the protective effect of exercise is stronger in the U.S. than in Mexico.

1. Introduction/Background

The United Nations [1] estimates that approximately 650 million people across the world (or 10% of the world's population) are living with a disability. Due to population aging and medical advances, this number is expected to continue to increase [1]. Research has shown that lifestyle risk factors, such as vigorous physical activity, can have a protective effect against disability. Specifically, data shows that exercise, even if not started until later in life, can result in the postponement of disability [2, 3]. In addition, researchers cite lifestyle differences as one of the contributors to health inequalities in populations [4].

The prevalence of disability varies across countries, however. Additionally, some countries are further along in adapting healthy lifestyle behaviors. Two particularly interesting countries to examine are Mexico and the United States. These countries are of interest because despite having different socioeconomic, demographic, and epidemiological profiles, they are closely linked geographically, economically, and socially. The United States population started to age earlier, and the process started under more advantageous economic conditions compared to when Mexico began to age. Additionally, the speed of aging is much faster for Mexico. Predictions show that the Mexican population over age 60 is expected to grow from 6% of the total population in 2000 to 15% in 2027. Compared to the United States and other developed countries, this 27-year pace is relatively fast. It will take the United States 70 years to reach a similar percentage in 2013 [5]. In addition to a rapid process, this is also "premature" in Mexico, due to the lack of infrastructure and lagging economic development [6]. The two countries are also in different stages of the epidemiological transition, as indicated by the current morbidity rates and mortality due to noncommunicable and communicable diseases. In Mexico, communicable diseases are more prevalent, while the relative importance of chronic conditions such as cardiovascular diseases and cancer is higher in the United States [5]. These contrasts mark different stages of transitions for the two countries that we compare.

A recent report [7] finds that the levels of disability prevalence, as measured in terms of limitations in activities of daily living (ADLs), were lower in Mexico than in the United States despite the lower level of socioeconomic development in Mexico compared to the USA. One possible explanation for this finding may be that the two countries are at different

stages of the epidemiological transition. The current cohort of older adults in Mexico experienced higher infant and childhood mortality levels, and it is likely that only the "strongest" survived into old age [7]. In other words, persons surviving into old age in Mexico are relatively more robust than those surviving into old age in the USA and therefore have a lower disability rate. Furthermore, life tables appear to support this hypothesis. The numbers indicate that while life expectancy is lower in Mexico than in the USA at younger ages, beginning at age 75, the life expectancy actually becomes higher for Mexico than in the United States [8].

Little is known about how lifestyle risk factors, such as lack of physical exercise, can impact functional limitations in societies with very different demographic, epidemiological, and lifestyle behaviors profiles. It is possible that the impact of lifestyle on disability may be very different in Mexico than in the USA in part because the current cohorts of older adults in Mexico are more selected than in the United States. This paper therefore explores the impact of physical activity on disability transitions, among older adults in Mexico compared to the United States. Specifically, we postulate that since the selection of survivors among older adults is currently lower in the USA compared to Mexico overall, a healthy lifestyle (such as physical exercise) is likely to have greater beneficial effect in the USA than in Mexico. This hypothesis is of relevance for global aging because it means that lifestyle changes are likely to have differential impact on health according to the stage of the epidemiological transitions in which societies are.

2. Methodology

2.1. Data Sources. The proposed research takes advantage of the comparability of the Mexican Health and Aging Study (MHAS) and the Health and Retirement Study (HRS). To examine disability transitions across Mexico and the USA, we use two waves of the Mexican Health and Aging Study (MHAS: 2001 and 2003) and the RAND version of the Health and Retirement Study (HRS: 2000 and 2002). We examine 13,224 individuals at baseline in the HRS (2000) and 11,064 persons at baseline in the MHAS (2001). To determine transitions we observed disability outcomes both at baseline (2001 for MHAS and 2000 for the HRS) and two-year followup (2003 for MHAS and 2002 for the HRS).

The Mexican Health and Aging Study (MHAS) is a nationally representative prospective panel study of community-dwelling individuals born prior to 1951. The study was conducted by researchers at the University of Pennsylvania, University of Maryland, University of Wisconsin, and the Instituto Nacional de Estadística, Geografia e Informática (INEGI) in Mexico and funded by the National Institutes of Health/National Institute on Aging. The MHAS used a multistage cluster sampling methodology that randomly selected households with at least one individual aged 50 or older. Two waves were collected in 2001 and 2003. At baseline, approximately 15,000 eligible persons and their spouses were interviewed, with a response rate of 90.1%. A direct interview was conducted when it was possible, and proxy interviews were obtained when the subjects were in poor health or were temporarily absent (7.3% of the baseline sample were proxy interviews).

The Health and Retirement Study (HRS) is an ongoing large-scale longitudinal study nationally representative for community-dwelling adults over age 50. It is conducted by the University of Michigan with support from the National Institute on Aging (NIH/NIA). The HRS used a multistage national area probability sample of households in the United States and oversampled Blacks, Hispanics, and persons living in the state of Florida. We used the RAND version of the HRS dataset, which compiled all waves of the HRS data and used bracketing methods to minimize nonresponse in certain variables (see RAND [9] for more details). Respondents received direct interviews when possible and proxy interviews were conducted when subjects were unable to respond or were unavailable (7.5% of the baseline survey were proxy interviews).

We compare elders living in the community in Mexico to community-dwelling non-Hispanic whites who were born in and living in the United States. The MHAS survey was only conducted among elders living in the community because most long-term care is provided by families in that country. We addressed this limitation by excluding persons that were institutionalized in the USA from the analyses. This allows for a straightforward comparison by focusing on community-dwelling elders in both countries.

Additionally, only persons that identified as non-Hispanic white and who reported being born in the USA were included in the USA sample. Because both the HRS and MHAS interviewed age-eligible respondents and their spouses regardless of age, we only include persons aged 51 and older for the HRS and adults 52 years and older for MHAS, at baseline. Finally, we only included subjects with complete information on each variable in our analyses.

2.2. Variables. Because the MHAS is highly comparable to the HRS, the measures used in the analyses are very similar. The outcome of ADL limitations was measured using five components: bathing, toileting, transferring into/out of bed, walking, and eating. Each of the components in the questionnaire was coded disabled if the respondent answered "Yes" or "Cannot do" to having difficulty in performing the activity. If the respondent answered "Do not do" then the response was coded as missing. However, if they answered "Do not do" and received help performing the activity, they were coded as disabled.

2.2.1. Independent Variables. Our focal independent variable is whether or not respondents reported vigorous physical activity or exercise (note that we use the terms physical activity and exercise interchangeably throughout the remainder of the paper). The question used for this measure was similar across the two studies. Both the MHAS and the HRS asked respondents whether on average they had participated in vigorous physical activity or exercise three times a week a more. Vigorous activity or exercise was defined to include any activities such as sports, heavy housework, or a job that

involve physical labor. This is a standard question and has been used extensively in the literature to operationally define self-reported physical activity (e.g., [4, 10, 11]). Research has shown support for using self-reported historical physical activity measures to assess physical activity performance. One such study found that self-reported historical walking, running, and jogging activities had reasonable validity when compared with objective measures, such as treadmill performance. Moderate Spearman's correlations between objective and self-report measures were significant for all correlations in the study ($P < .001$) [12]. There was one difference in the questions across studies. In Mexico, the question asked the respondent to reflect on the average over the last two years, whereas in the USA the respondents were asked to estimate over the past 12 months.

Because only one measure was available to capture the complex behavior of physical activity, it is important to establish validity of the focal independent variable. In order to establish construct validity (the ability of the measure to correspond to the theoretical concept under study), the physical activity measure must be related to other measures consistent with plausible hypotheses [13]. We assessed construct validity using the following two hypotheses: (1) respondents reporting problems with basic activities of daily living (walking, bathing, eating, toileting, and transferring in and out of bed) would be significantly less likely to report doing physical activity at baseline and (2) these correlations should remain significant across subgroups (e.g., gender and age). Results for both MHAS and HRS supported the hypotheses. The correlation coefficients between physical activity and the five ADL measures were consistently negative and significant. Specifically, the correlations between walking and physical activity were -0.159 in the USA and -0.099 in Mexico. For bathing and physical activity, the correlations for the USA sample were -0.168 and -0.088 in the Mexican sample, while for eating and physical activity, the correlations were -0.102 in the USA and -0.052 for Mexico. The correlations between transferring in/out of bed and physical activity were -0.123 in the USA and -0.059 in Mexico. Finally, the correlations between toileting and the physical activity measure were -0.119 in the USA and -0.062 in Mexico. Additional correlation results are available upon request. While the correlation coefficients had a lower magnitude in the Mexican sample than in the USA sample, all were significant ($P < .01$). We performed the same correlations by gender and age categories (51–59, 60–69, 60–79, 80+). The results remained significant across subgroups. Moreover, while significantly correlated at all ages, the correlations were stronger for older cohorts than for younger cohorts. This is in the expected direction and suggests robust findings.

Research has shown that disability rates vary by whether persons live in rural or urban areas; thus, we added a control variable for area of residence (reference category: rural). The measurement differed across the two data countries. For the United States, the HRS dichotomous variable was created using the 1993 Beale rural-urban continuum codes (see HRS [9]). The codes were collapsed into urban area (population size 250,000 or more) and rural (population less than 250,000). For Mexico, we used the MHAS locality size measurement to code areas with 100,000 or more people as urban. All other localities were coded as rural.

This study also controlled for wealth and having access to health insurance. Wealth was measured using household's net worth of homes, businesses, rental properties, capital, vehicles, and other debts and assets. Due to high nonresponse rates in these single items, both the HRS and MHAS used unfolding brackets to recover the nonresponse (RAND; Wong & Espinoza [9, 14], resp.). Health insurance was coded as a binary variable, where respondents were classified as having health insurance if they reported having at least one health insurance, regardless of type of insurance. Finally, additional control socioeconomic and demographic variables included age (continuous), gender (reference category: male), marital status (categorical: married and union, reference category; widowed; single, separated, or divorced), and education (continuous).

2.3. Statistical Methods. We begin by comparing prevalence of self-reported disability and physical activity among all older adults across the two countries regardless of disability level. For these descriptive results, we show data from the full sample at baseline in the United States and Mexico. This allows us to estimate and compare the prevalence across countries cross-sectionally. Due to the difference in age structures across the two countries, prevalence of ADL limitations and prevalence of physical activity (Table 2) is age standardized, using the weighted average of the two countries as the standard [15]. Age-adjusted rates of disability let us compare relative differences across the USA and Mexico. We also provide cross-sectional weighted descriptive data for both countries according to the exercise variable.

In order to determine if physical activity influences the incidence of disability, we next conduct a series of separate analyses by country across time. For this portion of the analyses, we select only those respondents that did *not* report any ADL limitation at time 1 and examine their status two years later. Because our study is based on longitudinal data, we face the issue of attrition and death by the followup period two years later (unobserved respondents). The followup outcome is therefore measured by five categories: remaining nondisabled across the two years, moving from no disability to one disability, from no disability to two or more disabilities, from no disability to death and those that are lost to followup. Table 1 shows the sample distribution of the outcome by country. Because we do not have data on disability status for those lost to followup, these cases were dropped in the longitudinal analyses. Both datasets showed a 5% loss to followup over the two years. In a separate analysis (not shown here), we found similar sample characteristics of those lost to followup across both studies.

We used multinomial models to determine the likelihood of moving to one of the followup categories over two years (reference group: remaining nondisabled). We first considered each country separately. We then combined the panel surveys from the two countries and included a country indicator (reference group: United States) to identify significant differences across countries.

Table 1: Sample size for outcome at time 2 for persons with no ADL limitations at time 1.

	United States					
	Observed			Not observed		Total
	No ADL limitations	1 ADL limitation	2 or more ADL limitations	Death	Loss to followup	
Unweighted *N*	9490	501	236	514	529	11270
(% within country)	(84%)	(4%)	(2%)	(5%)	(5%)	(100%)
	Mexico					
	Observed			Not observed		Total
	No ADL limitations	1 ADL limitation	2 or more ADL limitations	Death	Loss to followup	
Unweighted *N*	8907	328	326	300	568	10429
(% within country)	(85%)	(3%)	(3%)	(3%)	(5%)	(100%)

Notes: unweighted statistics; USA data included persons age 53 and older at time 2; Mexican data included persons 54 years and older at time 2; both samples include only community-dwelling persons with no ADL limitations at baseline.

The estimators of the multinomial model indicate the relationship of the outcome variable across categories of the independent variables that are interpreted as a relative risk ratio compared to a reference category (Hilbe [16]). In order to facilitate the interpretation of results, we also present figures of the estimated probabilities of the outcome variable based on the multivariate models. We estimated the general probabilities of each outcome category at followup by exercise, and we break down these predicted probabilities by age.

3. Results

Table 2 shows the age-standardized prevalence of functional limitations by country in Table 2(a) as well as the prevalence of exercise according to functional limitations in Table 2(b). Table 2(a) shows the prevalence of functional limitations across the two countries at baseline. The data confirmed previous research that overall disability rates were higher in the total USA elderly population than in the Mexican elderly population. Whereas 11.5% of elders in the USA reported at least one ADL limitation, about 10.6% of persons in Mexico reported a disability. However, Mexico showed higher prevalence rate for each individual ADL limitation measured. This somewhat counterintuitive finding suggests a higher degree of overlap of ADL limitations among persons in Mexico, which is confirmed when examining the number of ADL limitations reported. The pattern appears most pronounced in the percent with five ADL limitations. Less than one percent of the sample in the USA reported problems with all ADL limitations, whereas nearly two percent reported having limitations in all five areas in Mexico.

Table 2(b) compares the prevalence of physical activity in the USA and Mexico by ADL limitation categories, age standardized. In general, the prevalence of exercise is higher in the USA than in Mexico, where approximately 46% of persons in the USA reported doing vigorous physical activity, compared to less than one-third (29%) of elders in Mexico. When prevalence of physical activity is broken down by functional limitations, this pattern is perhaps most striking for those without any ADL problems. Nearly half (44%) of elders without a disability in the USA reported exercising, compared to 27% of elders without a disability in Mexico. However, for persons with one disability or with two or more disabilities, the difference between countries becomes very small.

3.1. Descriptives Bivariate. Table 3 provides prevalence of vigorous physical activity by main characteristics of the sample separately for each country. In both countries, the propensity to exercise is higher among younger individuals. In all age categories, the percent reporting physical activity is lower in Mexico than in the United States. In both countries men are more likely to report exercising than women, although the gender gap is much larger in Mexico than in the United States. Additionally, in the USA, there appeared to be a gradient in physical activity with assets, where those with higher assets had higher rates of physical activity. Such a gradient was not found in Mexico. In fact, those with lower assets were slightly more likely to exercise. Similarly, there was a slight gradient in physical activity with educational attainment in the USA, whereas such a pattern was not found in Mexico.

While for the USA sample there were not large differences in exercise behavior by area of residence and having health insurance, these showed important differences for the Mexican sample. Persons living in an urban area were more likely to report exercising than those living in a rural area in Mexico. Those persons without health insurance in Mexico were also more likely to exercise, compared to those that were insured.

3.2. Multinomial Models. Table 4 presents results for a series of multinomial models predicting going from zero ADLs at baseline to either one ADL, two or more ADLs, or death at followup. All models used the group that remained without any limitations as the reference category. Results show that the focal independent variable, physical activity, is significantly protective for each of the negative outcomes in the USA regression model (Model 1). However, in the

Table 2

(a) Age-standardized prevalence of ADL limitations at baseline, by country

	United States (unweighted $N = 13,224$) (weighted $N = 49,603,001$) Standardized rate	Mexico (unweighted $N = 11,064$) (weighted $N = 12,836,032$) Standardized rate
Percent reporting at least one ADL limitation	11.5%	10.6%*
Percent reporting each ADL limitation:		
Walking	5.2%	7.5%*
Bathing	5.0%	5.3%*
Eating	2.1%	3.0%*
Transferring in/out of bed	4.6%	7.2%*
Toileting	4.2%	5.2%*
Total number of ADL limitations reported:		
None	88.5%	89.4%*
One	6.2%	3.2%*
Two	2.7%	2.4%*
Three	1.3%	1.7%*
Four	0.7%	1.4%*
Five	0.6%	1.9%*

(b) Age-standardized prevalence of physical activity at baseline by country and functional limitations

	United States (unweighted $N = 13,224$) (weighted $N = 49,603,001$) Standardized rate	Mexico (unweighted $N = 11,064$) (weighted $N = 12,836,032$) Standardized rate
Percent reporting physical activity	45.9%	28.6%*
By number of functional limitations (at time 1)		
0	43.9%	27.2%*
1	1.3%	0.5%*
2 or more ADL limitations	0.6%	0.5%*

Notes: Age standardized using the weighted average of the two countries as the standard; population 51 years and older in the USA and 52 years and older in Mexico; weighted statistics using community-dwelling population only; *significant differences between countries at $P = .01$.

model examining Mexico only (Model 2), physical activity is significantly protective only for the worst outcomes (2+ ADLs and death).

Model 3 combines both countries to create a panel model with a country identifier variable. These results show that the level of disability is significantly different between the United States and Mexico. Also, the propensity to go from no ADL to a worse outcome is smaller in Mexico.

Finally, Model 4 adds in an interaction variable between physical activity and country. The results indicate that engaging in physical activity prevents negative health outcomes in both Mexico and the United States, although the effect is less protective in Mexico than in the United States. This is not the case for death, however, where exercise is protective for death in both countries, and the effect is not significantly different. In other words, the effect of physical activity on death has the same protective effect in both countries.

Additional models (results available upon request) examined a variety of potentially interesting interactions. In order to determine if the effect of physical activity is different across various characteristics, we ran Interactions between physical activity and gender, physical activity and age, and physical activity and education. None of these interactions were significant in the models. Finally, in order to test whether physical exercise was more beneficial across groups within countries, we ran interactions for country and education as well as country and area of residence. None of the interactions were significant in the models.

3.3. Predicted Probabilities. Figures 1 and 2 show the predicted probabilities of the outcome at time 2 by country and various demographic groups. Figure 1 visually charts the previous models predicting the probability of going from no

Table 3: Prevalence of physical activity at time 1 according to main characteristics, by country.

	United States		Mexico	*P*-value across countries
Age*		Age*		
51–59	49.6%	52–59	39.4%	.000
60–69	50.0%	60–69	32.7%	.000
70–79	43.0%	70–79	22.9%	.000
80+	28.9%	80+	14.2%	.000
Sex*		Sex*		
Male	50.8%	Male	42.7%	.000
Female	41.3%	Female	23.1%	.000
Marital status*		Marital Status*		
Married, union	49.1%	Married, union	29.3%	.000
Single, divorced, separated	43.0%	Single, divorced, separated	35.8%	.000
Widowed	34.7%	Widowed	21.9%	.000
Education*		Education**		
<12 years	41.9%	0 years	31.4%	Na
12 years	47.4%	1–5 years	35.1%	Na
>12 years	52.6%	6 years	29.4%	Na
		7+ years	30.4%	Na
Assets*		Assets***		
Low	37.3%	Low	33.2%	.001
Medium	44.6%	Medium	31.7%	.000
High	51.4%	High	31.5%	.000
Location***		Location*		
Urban	46.8%	Urban	39.1%	.000
Rural	45.1%	Rural	24.3%	.000
Health insurance		Health Insurance*		
Uninsured	47.2%	Uninsured	38.6%	.000
Insured	45.6%	Insured	27.0%	.000
	5,965		**3,667**	
Total sample ($n = 13,224$)	45.10%	Total sample ($n = 11,064$)	33.10%	

Notes: Percentages are weighted statistics; sample sizes may vary due to missing values; data may not add to 100% due to rounding; HRS included persons age 51 and older at time 1; MHAS included 52 years and older at time 1; HRS and MHAS data includes only community-dwelling populations. Statistical comparisons based on unweighted data. Statistical test of the difference across categories for each variable *within* each country is reflected by embedded asterisks: $*P < .001$, $**P < .05$, $***P < .1$. Statistical test of the difference *between* the two countries is reported in the final column (*P* value). Difference in education is not tested between countries because of the difference in educational categories.

ADL limitation at time 1 to one ADL limitation, 2 or more limitation, or to death at time 2, by physical activity and by country. The figure indicates that those who exercise have a lower probability of transitioning to a worse disability status or to death in both countries. The differences appear to be most dramatic for the United States.

Figure 2 presents predicted probabilities of outcome at time 2 by age. As expected, the probability of disability or death increased with age in each country, regardless of physical activity. However, the probability curve for transitioning to one ADL is nearly the same in Mexico for exercisers and nonexercisers. On the other hand, for the United States, there is a clear advantage for those who exercise, with a lower probability of transitioning to one ADL, especially at the older ages.

A protective effect appears for Mexico as well as for the USA when examining the probability of transitioning to two or more ADLs at time 2. Those who exercise in the USA have similar probability of transition to two or more ADLs as those who exercise in Mexico. The probability curve is lower for those who do not exercise in the United States than for those who do not exercise in the United States.

The final graph in Figure 2 shows the probability of death at time 2 by age, physical activity, and country. The results

Table 4: Multinomial models for outcome at time 2 for persons without ADL limitations at Time 1, united states and mexico.

	Model 1 United States			Model 2 Mexico			Model 3 Panel model			Model 4 Panel model with interaction		
	One ADL	2 ADLs +	Death	One ADL	2 ADLs +	Death	One ADL	2 ADLs +	Death	One ADL	2 ADLs +	Death
Age	1.06***	1.07***	1.09***	1.05***	1.07***	1.07***	1.05***	1.07***	1.08***	1.05***	1.07***	1.08***
	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.00)	(0.01)	(0.00)	(0.00)	(0.01)	(0.00)
Female	1.08	1.23	0.50***	1.40**	1.46**	0.59***	1.20*	1.36**	0.55***	1.23**	1.38**	0.55***
	(0.11)	(0.18)	(0.05)	(0.18)	(0.20)	(0.08)	(0.09)	(0.13)	(0.04)	(0.10)	(0.14)	(0.04)
Single	0.60***	0.93	0.63**	1.03	1.16	1.47	0.74**	0.95	0.96	0.77*	0.96	0.97
	(0.09)	(0.24)	(0.10)	(0.20)	(0.22)	(0.30)	(0.08)	(0.13)	(0.11)	(0.08)	(0.13)	(0.11)
Widowed	0.85	1.24	0.84	1.12	0.95	1.72***	1.04	1.06	1.35*	1.06	1.07	1.36*
	(0.14)	(0.34)	(0.15)	(0.17)	(0.15)	(0.27)	(0.12)	(0.14)	(0.16)	(0.12)	(0.14)	(0.16)
Education	0.96*	0.93**	0.95**	0.95**	0.90***	0.98	0.95***	0.91***	0.97*	0.95***	0.91***	0.97*
	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.02)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)
Wealth med	0.77*	0.94	0.64***	0.85	0.93	0.97	0.80*	0.94	0.74**	0.80*	0.94	0.74**
	(0.09)	(0.16)	(0.08)	(0.12)	(0.13)	(0.15)	(0.07)	(0.10)	(0.07)	(0.07)	(0.10)	(0.07)
Wealth high	0.59***	0.66*	0.53***	0.88	0.83	0.75	0.68***	0.74*	0.60***	0.68***	0.75*	0.60***
	(0.07)	(0.12)	(0.07)	(0.13)	(0.13)	(0.12)	(0.06)	(0.09)	(0.06)	(0.07)	(0.09)	(0.06)
Urban	0.85	0.85	1.08	0.84	1.00	1.30	0.86*	0.93	1.17	0.86	0.93	1.18
	(0.08)	(0.12)	(0.11)	(0.11)	(0.13)	(0.18)	(0.07)	(0.09)	(0.10)	(0.07)	(0.09)	(0.10)
Insurance	0.86	0.93	1.22	1.23	1.22	0.86	1.13	1.19	0.94	1.16	1.20	0.95
	(0.24)	(0.44)	(0.45)	(0.16)	(0.16)	(0.12)	(0.13)	(0.15)	(0.12)	(0.14)	(0.15)	(0.12)
Exercise	0.35***	0.36***	0.43***	0.89	0.55***	0.52***	0.48***	0.44***	0.45***	0.35***	0.35***	0.42***
	(0.04)	(0.06)	(0.04)	(0.12)	(0.09)	(0.08)	(0.04)	(0.05)	(0.04)	(0.04)	(0.06)	(0.04)
Country							0.42***	0.72	0.51***	0.35***	0.66*	0.49***
							(0.06)	(0.14)	(0.08)	(0.05)	(0.13)	(0.08)
Country* exercise										2.51***	1.55*	1.20
										(0.42)	(0.34)	(0.23)
Number of obs	10,683			9,184			19,867			19,867		
Pseudo-*R*-square	0.0969			0.0637			0.0827			0.0845		
LR chi2	994.01			484.73			1484.9			1517.06		
Prob>chi2	0.000			0.000			0.000			0.000		

Notes: HRS included persons age 51 and older at time 1; MHAS included 52 years and older at time 1; ADL: activities of daily living; cells indicate relative risk ratios, standard Errors in parentheses, reference category; no ADL limitations at time 2.
*** P-value < .001, ** P-value < .01, * P-value < .05.

indicate that exercise has a buffering effect on death for both countries. While the probability of death is higher for the USA than in Mexico regardless of exercise, the impact of exercise appears to be similar across both countries.

It is interesting to note that in each of the figures the differences appear especially pronounced at older ages.

4. Discussion and Conclusions

This paper compared the impact of physical activity on the incidence of disability among older persons in two countries at different stages of the epidemiologic transition, Mexico and the United States. To our knowledge, this is the first paper to examine the importance of physical activity on predicting transitions in disability using a comparative approach across two countries.

Results showed that physical activity was more prevalent in the USA than in Mexico. This supports recent evidence that transitions among older adults towards healthy lifestyle habits, such as avoiding tobacco and binge alcohol drinking, or exercising, appear to be underway in the USA but not yet in Mexico [4]. There are several potential explanations

	1 ADL		2 + ADLs		Death		No ADLs	
	Exercise	No exercise	Exercise	No exercise	Exercise	No exercise	Exercise	No exercise
U.S.	0.058	0.022	0.0244	0.0094	0.0465	0.0216	0.8711	0.947
Mexico	0.0305	0.0279	0.0279	0.0159	0.0270	0.0143	0.9147	0.9419

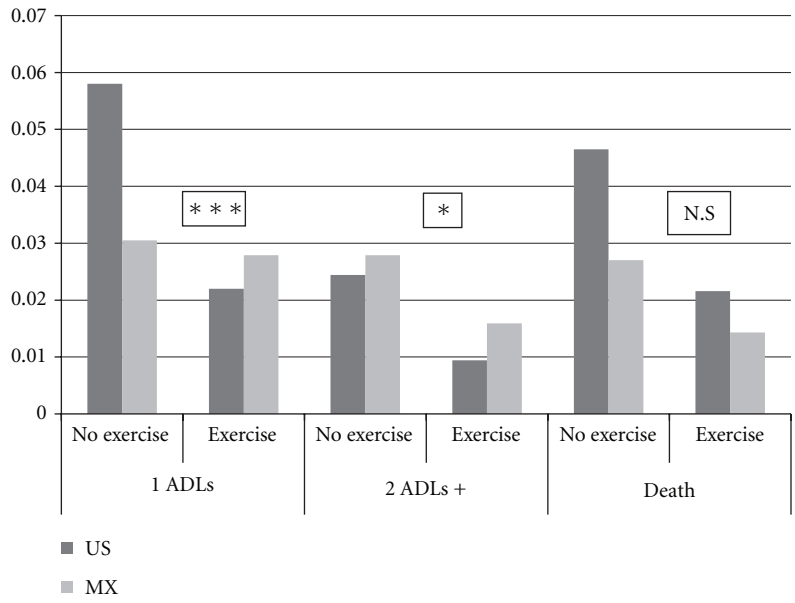

Figure 1: Probabilities of outcome at time 2, by country and exercise at time 1, for persons without ADL limitations at time 1. Notes: $^{*}P$ value < .05, $^{**}P$ value < .01, $^{***}P$ value < .001; across country significance, N.S: not statistically significant across countries.

for this finding. One is that the survey questions were asked in a slightly different way across the two countries, and because physical activity was self-reported, it is possible that the interpretation of the question may have been different across the two samples. Another more plausible explanation was posited by Wong et al. [4] that the two countries are at different stages of a "lifestyle transition," where transitions to healthier lifestyles have progressed further in the USA than in Mexico. Social and policy changes impacting healthier lifestyle choices have occurred earlier in the USA and have been more extensive [4], which may in part explain this disparity in levels of exercise between the two countries.

We also found differences in physical activity across groups, including gender, which echoed findings by Wong et al. [4]. Men had nearly twice the prevalence rate of physical activity than women in Mexico (43% versus 23%, resp.). While the gender gap was not as large in the USA, men were still more likely to exercise than women. Although there were no large differences in physical activity prevalence by area of residence and health insurance status in the USA, there were notable differences by these groups in Mexico. It is possible that those uninsured or those living in an urban environment in Mexico may be employed in more physically demanding labor, which would be categorized as vigorous exercise in the surveys. It may also be possible that the logistics of exercising (e.g., accessing a gym) are easier in urban areas or that a culture of exercise has been adapted to a greater extent in urban areas of Mexico compared to rural areas of the country.

The results also show that not only is the level of disability different across the USA and Mexico, but that the effect of physical activity on disability is significantly different across the two countries. Overall, we found a beneficial effect of physical activity against onset of disability or death at followup in both countries. However, we also found that the protective effect of physical activity on disability is stronger in the USA than in Mexico. This supports our initial hypothesis that physical activity is less protective among the Mexican older population since they represent a more selected group of survivors than in the US. In other words, we speculate that older adults in the USA are more disabled at older ages and therefore are more likely to benefit from a lifestyle intervention. This result has important implications for aging in developing countries that are lagging in the epidemiological transition. We should expect that policies that are implemented in the countries towards healthy lifestyles should have lower impact while the countries are in early stages of the transition compared to the likely impact that similar policies may have later on.

One limitation of this study is the question used to determine physical activity in the surveys. Physical activity is a complex behavior and can be difficult to describe [17]. The question determining physical activity asked about exercise broadly, including everything from sports to physical

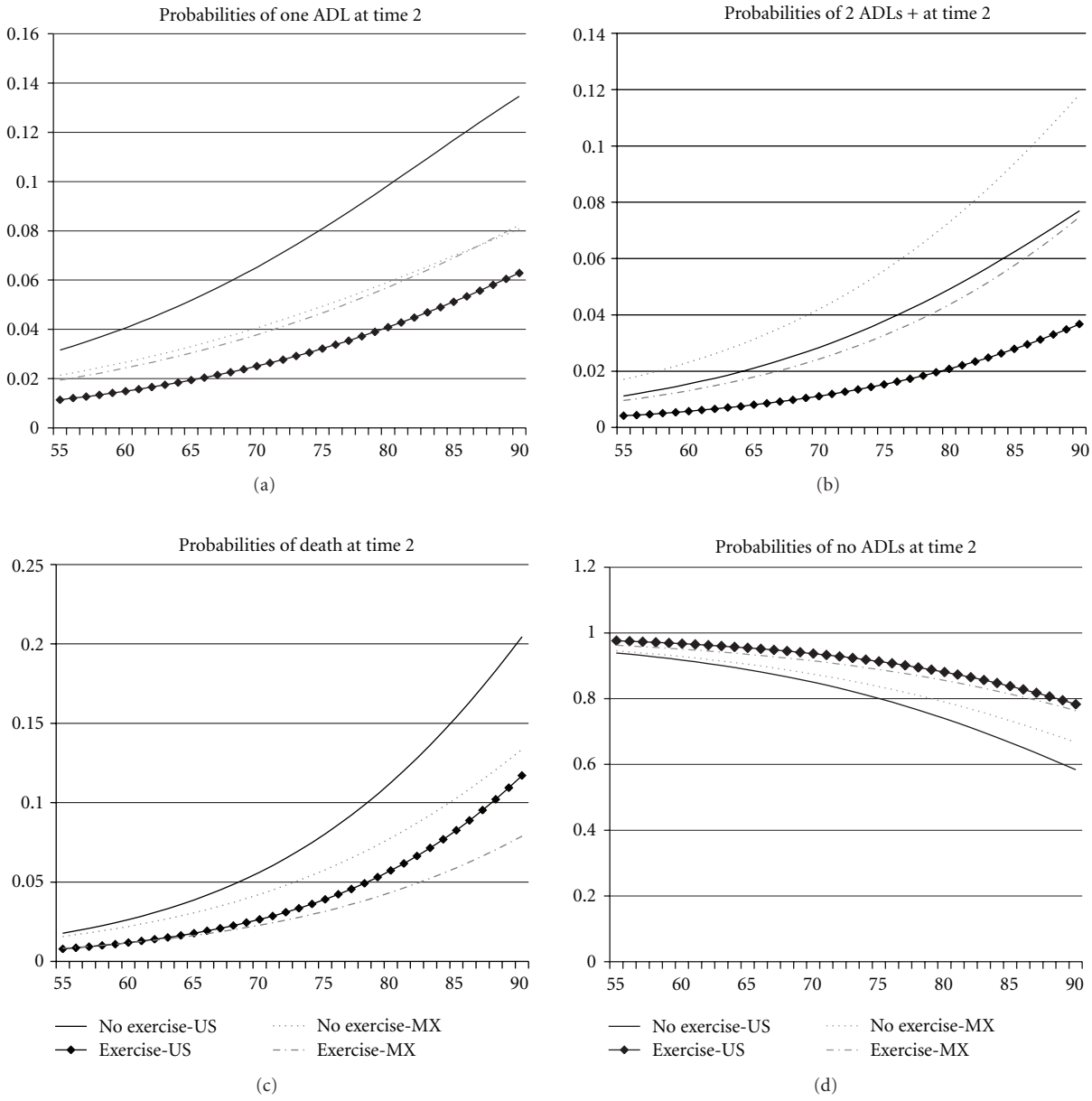

Figure 2: Probabilities of outcome at time 2, by country, exercise, and age for persons without ADL limitations at time 1.

labor. We are therefore unable to differentiate between those who exercise because of daily occupation-related physical labor and those that train at a gym, for example. It is likely that the various types of exercise may have different impacts on health. For instance, those working dangerous and physically demanding jobs may not see a benefit from their regular physical exertion, whereas those training in a gym may see the benefits of an exercise routine. This may be particularly the case when comparing these two countries with different cultures and at different lifestyle transitions. In rural Mexican communities, outdoor sports may be more prevalent, whereas gyms with modern fitness equipment may be more prevalent in urban USA areas. Similarly, recommendations by the Centers for Disease Control and Prevention and American College of Sports Medicine (CDC/ACSM) include an emphasis on the value of moderately intense activity, which we were unable to capture [18]. It was not possible to control for the type of activity or for the intensity of the activity in these surveys, and it is not clear how shorter or more moderate bouts of activity may impact functional limitations. More objective data would allow for a more precise measurement of physical activity. Future research should consider including measures such as metabolic equivalent task (MET) values, which allows the researcher to determine both the intensity and rate of exercise.

Finally, the wording of the activity question was identical across the two surveys except for the different time frames the respondents are asked to reflect on. Respondents in Mexico were asked about their average exercise in the last two years,

whereas those in the USA were asked about their average over the past year. This is a limitation when comparing physical activity rates across countries, and the results should be interpreted with caution. However, the issue of timing is less of a concern when comparing the effects of physical activity on disability *within* each country, which is the main focus of this study.

As the epidemiological and demographic transitions continue to run their course in developing countries such as Mexico, it is likely that the levels of old age disability will increase. As the results of this study confirm, lifestyle changes such as exercise can help in the avoidance of chronic and disabling conditions. This is particularly important in the design of policies for older adults, since our work has shown that the beneficial effects of physical activity extend to these age cohorts in a developing country such as Mexico. However, our work has shown also that the positive effect of physical exercise may be dependent on the stage of the transition that societies are undergoing. This is informative, not only to expect lower impact of exercise on health overall compared to more developed countries, but also to motivate the search for modified or alternative exercise interventions to achieve a higher impact in countries that are early in the epidemiologic transition. Nevertheless, policies aimed to encourage physical activity in Mexico may play particularly important roles in preventing negative health outcomes. Our work has also indicated avenues of further work for future population-based studies, in order to better capture the concept of physical exercise among older adults.

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Research Article

Higher Levels and Intensity of Physical Activity Are Associated with Reduced Mortality among Community Dwelling Older People

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Introduction. There is limited evidence on physical activity and mortality in older people. *Methods*. People aged 75–84 years (n = 1449) participating in a randomized trial of health screening in UK general practice were interviewed about their physical activity (PA) and were assessed for a wide range of health and social problems. Mortality data were collected over 7 years of followup. *Results*. Full information on PA and potential confounders was available in 946 people. Those in the highest third of duration of PA had a lower mortality, confounder-adjusted Hazard Ratio (HR) = 0.74, and 95% Confidence Interval (CI) 0.56–0.97, compared to the lowest third. Similar benefits were seen when categorized by intensity of PA, with those in the highest group having a lower mortality, confounder-adjusted HR = 0.61, and 95% CI 0.47–0.79, compared to the lowest category. *Conclusions*. Our results suggest the importance of providing older people with opportunities for physical activity.

1. Introduction

Epidemiological evidence links many chronic diseases to physical inactivity [1, 2]. The benefits of increased physical activity and exercise and the harmful effects of inactivity are well recognized [3, 4]. Although studies of the general population show the positive effect of physical activity on both physical and psychological well-being in adults of all ages, relatively few studies have focused on the older age groups, specifically on those aged 75 years and over. Physical activity and its health effects are more complex in this age group reflecting changing physiology, and the higher likelihood of multiple morbidities. Regular physical activity brings a health benefit in terms of maintaining or increasing strength, power, endurance and flexibility of muscles even in the older elderly [4, 5]. It could be said to be more critical at older ages since everyone will lose strength over time and lack of activity can lead to poor bowel function, falls, and to deterioration in performance of daily activities such as dressing, climbing stairs or rising from a chair. Current public health recommendations for physical activity in the UK are at least 30 minutes of moderate intensity at least five times a week, and these are also recommended for people aged 65 and over [6, 7]. The World Health Organization recommends older people should take at least 30 minutes of aerobic exercise on most, if not all, days and strength training 2 to 3 days a week [8]. Observational studies of adult populations [9–15] have shown reduced or delayed risk of mortality with increased physical activity but included relatively small proportions of the oldest age group. Only four out of 22 large studies covered in a recent review of moderate activity included people aged 75 years and over [15]. This is a fast growing age group in many western countries but with the least evidence on physical activity. Even studies specifically in older people tend not to provide results for people aged 75 years upwards. Thus, more evidence is required for the oldest age group.

We investigated the association of physical activity and mortality in a community-based study of older people aged 75 to 84 years.

2. Methods

The Medical Research Council (MRC) Trial of the Assessment and Management of Older People in the Community was a cluster randomized trial in UK general practice aimed at evaluating the benefit of different approaches to the assessment and management of older people. Details of the MRC trial design and results have been reported elsewhere [16, 17]. The methods are summarized briefly below.

2.1. Study Participants. 106 practices from the MRC General Practice Research Framework were selected to provide a sample representative of the UK mortality experience (Standardized Mortality Ratio) and deprivation level (Jarman score based on the 1991 UK census data). All patients aged 75 years or over on the general practitioner lists were invited to participate in the trial unless they were in long-stay hospital or nursing homes or were terminally ill. Practices were randomised to "universal" or "targeted" assessment. In the "universal" arm all patients were invited to an in-depth assessment by the study nurse, while in the "targeted" arm only selected patients were invited. The in-depth assessment covered a wide range of physical, social, and psychological problems. Practices in the "universal" arm were asked to take part in a separately funded add-on study on nutrition and physical activity, to which 51 out of 53 agreed. In these practices, randomly selected persons aged 75–84 years from the lists of the 51 practices were invited for an interviewer-administered questionnaire on their diet and physical activity and to give a blood sample. Written informed consent was obtained from all participants, and all relevant ethics committees gave approval for the add-on nutrition and physical activity study.

2.2. Data Collection

2.2.1. In-Depth Assessment. Data were collected at the in-depth assessment by the study nurse through interviews and measurements. Sociodemographic data included marital status, living circumstances, frequency of seeing relatives and friends, and housing tenure. We used the MiniMental State examination (MMSE) [18] for cognitive impairment, the Geriatric Depression Scale (GDS) [19] for depression and the Rose Chest Pain questionnaire [20] for angina. Participants were asked whether they had been diagnosed by a doctor for a variety of conditions including cancer, diabetes, stroke and heart attack, hip fracture and emphysema. They were also asked whether they were able to carry out certain activities of daily living (ADL) including cutting toenails, dressing, cooking, doing housework, climbing stairs (with aids if necessary), washing, and walking 50 yards (with aids if necessary). Participants were asked about difficulties in hearing or reading newsprint, current and past smoking behavior, usual alcohol pattern and consumption of wine, beer and spirits over the previous week, and about any recent (in previous six months) serious indicators of poor health: unintentional weight loss (defined as 7 pounds (equivalent to 3.2 kg) or more) and number of falls. Physical measurements included height, weight, waist, and hip circumference, and sitting systolic and diastolic blood pressure. A non fasting blood sample was taken and sent for analysis for a routine biochemical screen and also for cholesterol (total, HDL and LDL). Participants were asked to bring all current medications to the assessment and details were recorded by the study nurse.

2.2.2. Physical Activity. We adapted questions from the Structured Physical Activity Questionnaire used in the Allied Dunbar National Fitness Survey [21]. Predominantly closed format questions were asked about daily activities such as walking (to shops and elsewhere), stair climbing, housework, indoor and outdoor maintenance and "do it yourself" (DIY) activities. Leisure activities such as gardening, sports and dancing were also recorded. Frequency (number of times per week/activity) and duration (in minutes per week) were recorded for most activities. Intensity was recorded for walking and housework and maintenance (speed of walking, light/heavy work). The activity recorded was that of an average week.

The interviews were carried out between 1995 and 1998 in patients' homes by trained staff from the UK Government's Office for National Statistics (ONS). ONS provided date of death and cause of death coded using the International Classification of Diseases, 9th revision (ICD-9) for deaths reported up to September 2002 and 10th revision (ICD-10) after that date.

2.3. Data Preparation. In order to investigate whether greater duration or greater intensity of physical activity (PA) is associated with mortality, we created two measures of physical activity—the total time spent on physical activity per week and the intensity of activities undertaken. The total amount of physical activity in minutes per week was calculated by adding the time (in minutes) spent on individual activities (e.g., walking, light and heavy housework and household maintenance/DIY, sport, and exercise) multiplied by their weekly frequencies. Gardening was recorded as a seasonal activity. In order to calculate minutes spent gardening in an average week in a year, we multiplied the reported time spent on gardening per week in summer/winter by the relevant number of weeks in that particular season and added these together to get the total time spent gardening in a year. Finally, we divided this by the number of weeks per year to get the average time spent gardening per week. The intensity of physical activity was calculated according to the type of activity performed: Category 1—light PA defined as time spent on feet while shopping, light housework and light maintenance, Category 2—moderate PA defined as time spent walking, for example, to shops and elsewhere, and gardening, Category 3—heavy PA defined as time spent on heavy housework, heavy maintenance/DIY, sport and exercise. Since some people performed activities falling

into more than one of the above categories, intensity was subsequently recategorized into 3 exclusive categories: "l;ow" (any light PA but not medium or high PA, <60 minutes of moderate PA, no heavy PA), "medium" (≥60 minutes of moderate PA, no heavy PA), "high"(any amount of heavy PA). Total physical activity time in minutes per week was categorized by tertiles.

Data from the in-depth assessment were summarized as follows: body mass index (BMI) (weight/height^2) and waist to-hip ratio (WHR) categorized in sex-specific quintiles; alcohol consumption (total units drunk in the previous week); smoking history (never, ex and current), marital status (single, married, widowed, divorced), housing tenure (owner, rental, and assisted), living alone or with others, seeing people other than spouse (daily, 2-3 times per week, more than twice a week, and rarely), cognitive impairment categorized as normal or mild, moderate and severe (MMSE > 17, >12 and <17, ≤12, resp.), depression (score of >5 on GDS), history of cardiovascular disease (heart attack, stroke, or angina), unable to do >1 ADL, number of falls; and whether taking prescribed medicines or not. The Carstairs local area deprivation score was obtained by linking the participants' postcodes to national census data [22]. We categorized the Carstairs score based on the UK quintiles of distribution.

2.4. Statistical Analysis. Analyses were performed using Stata 10 software using the "svy" command on a weighted sample (pweight command) to take account of the cluster (general practice) sample design. Cox proportional hazards was used to investigate the association of PA with mortality based on deaths reported by ONS up to the end of September 2005. The proportional hazards assumptions for different levels of total physical activity and intensity were tested by plotting the Nelson-Aalen proportional estimates of the hazard function.

Univariable descriptive analysis was first undertaken to describe the relationship between physical activity (total PA and intensity of PA) and mortality. Characteristics of participants by thirds of total PA or by intensity category were examined using tests for linear trend. Potential confounders and possible causal pathways variables from the in-depth assessment were selected *a priori* on their expected relationship with physical activity and mortality.

Analyses were performed for all participants (n = 1449) and also for participants with a full set of physical activity, socioeconomic and health assessment data (n = 946) to allow for full adjustment for potential confounding. Three models were used. Model 1 adjusted for age and sex only. Model 2 adjusted for possible confounders including socioeconomic and psychosocial factors. Variables initially considered for inclusion in model 2 were BMI, WHR, units of alcohol, smoking, GDS, Carstairs index, marital status, housing tenure, living alone, and frequency of contact with people. Model 3 additionally included variables that could be on the causal pathway. Variables initially considered for inclusion in model 3 were: LDL and HDL cholesterol, self reported doctor diagnosis of emphysema, cancer, diabetes, CVD, hip fracture, ADLs hearing and seeing difficulties, number of falls, unintentional weight loss, medication and MMSE. Variables were dropped from the models if the P value was >0.1 and the hazard ratios for physical activity were not changed by more than 5%.

3. Results

Of the 2959 people randomly sampled, 2040 were eligible to take part in the physical activity survey, 587 did not respond and 1453 completed the interview. A further 4 subjects with insufficient data were excluded from the analysis at the data cleaning stage. Compared to responders, nonresponders were more likely to be women (63% of nonresponders compared to 55% of responders) ($P < .01$) and current smokers (16% of nonresponders compared to 11% of responders) ($P < .01$); the mean ages were similar in non responders (79.4 years) compared to responders (79.0 years). In analyses adjusting for age and sex, there were no differences by response for BMI, history of CVD, cancer, hip fracture, weight loss, alcohol consumption, difficulty with ADLs, marital status or living alone. Nonresponders had slightly higher GDS scores (2.2 in nonresponders compared to 1.9 in responders) ($P = .03$) and slightly lower MMSE scores (25.6 in nonresponders compared to 26.3 in responders) ($P = .03$). There was no differences in the mortality rates between responders and non responders either in crude analyses or analyses adjusted for age, sex and smoking. There were 946 participants with complete data on baseline characteristics and confounding factors (65% of the people who completed the interview). The characteristics of this subsample were similar to those in the full sample (n = 1449) (Table 1). The median followup time for mortality was 7.8 years. Of those with data on all characteristics 453 (47.9%) had died by the end of September 2005 (Table 2). Nearly a half (49.8%) of the total sample and a similar proportion (49.2%) of the subsample reported levels of moderate or high physical activity which were less than the current UK minimum recommendations of 5 × 30 minutes per week. Apart from other daily physical activities, 25% of the sample total and 24% of the subsample did sport and exercise, mainly weekly exercises/keep fit at home, dancing, cycling, swimming, class exercises/keep fit supervised classes, golf, and various others as listed in the physical activity questionnaire.

In univariable analysis, age, history of stroke and CVD, depression, ability to perform activities of daily living, and taking medications were all inversely significantly associated ($P < .01$) with both total duration of and intensity of PA (Tables 3 and 4). In addition, intensity of PA was inversely associated with cognitive impairment and emphysema. There were increasing proportions of homeowners across increasing thirds of total duration or intensity of PA ($P < .001$). Longer duration and greater intensity of PA were associated with greater proportions in the least deprived (as defined by Carstairs) areas and smaller proportions in the most deprived areas. Total duration of any physical activity was strongly associated with thirds of intensity; those in the highest intensity group had the highest duration of physical activity ($P < .0001$) (Table 4).

Table 1: Characteristics of all persons in the PA study and of those with full data.

	All eligible persons ($N = 1449$)		Complete data ($N = 946$)
	$n - x$[1]		
Age[2]	1444	79.3 (75.0, 86.6)	79.2 (75.1, 86.6)
Men (%)	1449	45.0	45.0
BMI (kg/m^2)[3]	1370	26.5 ± 4.3	26.4 ± 4.2
Home owner (%)	1410	64.5	65.5
Systolic blood pressure (mm Hg)[4]	1413	148.8 ± 21.5	148.4 ± 21.3
Current smoker (%)	1415	10.0	9.2
History of CVD[5]	1407	24.2	22.7
History of Emphysema	1411	1.8	1.8
History of Cancer (%)[6]	1406	7.8	8.6
Diabetes (%)	1415	7.2	6.3
Hip fracture (%)	1410	2.7	2.2
Recent weight loss (%)	1405	2.3	2.6
MMSE score <12/<17[7]	1417	2.9	2.0
GDS score >5[8]	1417	6.9	6.8
Unable to do >1ADL[9]	1416	21.4	18.4
On prescribed Medication (%)	1371	81.6	81.4

[1] Not all 1449 participants had a complete data set on all characteristics, reported values are based on the complete records.
[2] Mean, interquartile range in parenthesis.
[3] $\bar{x}$ ± SD.
[4] $\bar{x}$ ± SD of average of 2 readings while sitting.
[5] History of heart attack, stroke or angina.
[6] Excluding skin cancer.
[7] MiniMental State Examination (MMSE) <12 if language section could not be completed, otherwise <17.
[8] 15 item Geriatric Depression Score (GDS).
[9] ADL: Activities of Daily Living.

Table 2: Study participants, person-years at risk, number of deaths and crude death rate by tertile of total duration of PA, and category of intensity.

$N = 946$	Total PA			Intensity of PA		
	Tertile 1	Tertile 2	Tertile 3	Low	Moderate	Heavy
Person years[1]	6.1 (2.9)	6.9 (2.7)	7.3 (2.4)	5.9 (3.0)	6.7 (2.7)	7.2 (2.5)
Deaths (%)	187 (41.3)	139 (30.7)	127 (28.1)	138 (30.5)	137 (30.2)	178 (39.3)
Crude death rate[2]	98.0	65.7	50.1	111.8	69.5	53.3

[1] $\bar{x}$ ± SD Time at risk /person.
[2] Per 1000 person years.

We observed an inverse trend for all cause mortality with both total PA and with the intensity of PA after adjusting for age and sex (Model 1) (Table 5). The associations were attenuated slightly but remained significant when adjusted for confounders (Model 2) and further attenuated after additionally adjusting for confounders and possible causal pathway variables (Model 3). In Model 3, those in the highest third of total PA or highest intensity of PA had Hazard Ratios (HR) of 0.74, 95% Confidence Interval (CI) (0.56, 0.97) and HR of 0.61, 95% CI (0.47, 0.79), respectively (Table 5). We ran a sensitivity analysis to examine the effect of excluding people in the highest intensity group who had less than 60 minutes high-intensity activity per week ($n = 102$). The results were essentially unchanged from the model that included all people in that group. The results for the full sample ($n = 1449$) in models 1 and 2 were similar to the results for both models when only the subsample of participants with full data ($n = 946$) was used (data not shown).

4. Discussion

In our study, we found that both higher levels of physical activity (PA) and higher relative intensity of PA were associated with lower mortality. This inverse trend was apparent after adjusting for a wide range of confounders. Ill health, discomfort, fear of adverse effects, and well-meaning efforts of others to protect older persons from potential

Table 3: Characteristics of the study participants by tertile of total duration of PA (min/wk).

PA total $N = 946$	Tertile 1 313	Tertile 2 302	Tertile 3 331	P value (r trend)
Cutoffs (min of PA/wk)	<370	371, 802	805, 3644	
Median	180	560	1136	
Mean	173	567	1312	
Age (mean)	79.68	79.20	78.72	.002
Men (%)	45.9	45.8	44.4	.73
BMI (kg/m^2)	19.5	13.7	17.9	.71
Lowest fifth (%)				
LDL (mean)[1]	4.51 ± 1.5	4.58 ± 1.6	4.74 ± 1.5	.18
HDL (mean)[1]	1.18 ± 0.52	1.22 ± 0.45	1.23 ± .5	.07
Systolic blood pressure[2]	148.47 ± 32	145.99 ± 29	150.56 ± 30	.42
Diastolic blood pressure[2]	73.97 ± 18	74.77 ± 18	75.40 ± 16	.25
Carstairs (1,5%)[3]	17.0, 15.9	26.0, 7.6	24.1, 5.0	.006
Single (%)	5.5	8.7	6.0	.98
Home owner (%)	53.7	69.3	74.7	<.001
Lives alone (%)	47.2	47.7	43.6	.58
Current smoker (%)	12.4	6.5	8.0	.16
Emphysema (%)	2.4	1.8	1.2	.19
Cancer (%)[4]	8.1	9.7	7.5	.75
Diabetes (%)	8.5	6.0	3.9	.039
CVD[5]	32.5	23.3	16.4	<.001
Hip fracture (%)	3.5	1.3	0.9	.059
Recent weight loss (%)	3.8	2.7	1.0	.026
MMSE score <12/<17[6]	3.5	0.8	0.9	.030
GDS score >5[7]	13.0	4.1	4.3	<.001
Unable to do >1 ADL[8]	35.3	14.2	5.3	<.001
Medication (%)	89.8	83.1	71.3	<.001

[1] $\overline{x}$ ± SD.
[2] $\overline{x}$ ± SD of average of 2 readings while sitting.
[3] Carstairs deprivation index, quintiles 1&5.
[4] Excluding skin cancer.
[5] History of heart attack, stroke, or angina.
[6] MimiMental State Examination (MMSE) <12 if language section could not be completed, otherwise <17.
[7] 15 item Geriatric Depression Score (MMSE).
[8] ADL: Activities of Daily Living.

harm all potentially contribute to activity limitations. Since ill health may also be a consequence of low physical activity we included variables in a third model, which we conjectured to be possible consequences of physical activity such as hip fracture, falls, and history of heart attack. After adjustment for potential confounders as well as possible causal pathways variables (comorbidities) a significant trend of lower mortality with increased levels of duration and intensity of PA persisted.

Observational studies in the general adult population which included people aged 75 years and over have found a reduced risk of mortality with increased physical activity in both older women and men [9, 13, 14]. The evidence has been inconsistent as to the levels of physical activity required to maximize health benefit. A recent systematic review of the benefits of moderate activity found a 19% reduction in mortality risk with 2.5 hours per week compared to no activity. The additional survival benefit from 7 hours activity per week was fairly small (24%) [15]. Interestingly the benefit was somewhat stronger in the older age group (65 years and over) compared to the younger age groups. Other studies have been conducted specifically in the older age group [23–26]. It is problematic to make a direct comparison between these studies and ours due to different methods of assessment and categorization of physical activity, different length of followup,and lack of stratified analysis by age 75

Table 4: Characteristics of the study participants by category of intensity of PA.

Intensity $N = 946$	Low 219 (light + <60 min/wk of moderate PA)	Medium 275 (>60 min/wk of moderate, no heavy PA)	High 452 (heavy PA, any amount/wk)	P value (r trend)
Median	120	188	120	
Mean	228	293	188	
Total duration of PA				
Median	130	275	803	$P < .0001$
Age (mean)	79.89	79.34	78.77	<.000
Men (%)	37.2	49.2	47.0	.14
BMI (kg/m^2)	20.8	16.8	15.6	.22
Lowest fifth (%)				
LDL (mean)[1]	4.63 ± 1.58	4.61 ± 1.5	4.61 ± 1.5	.93
HDL (mean)[1]	1.16 ± .54	1.24 ± .49	1.22 ± .48	.34
Systolic blood pressure[2]	147.06 ± 33	148.33 ± 32	149.41 ± 27	.253
Diastolic blood pressure[2]	73.74 ± 18	74.33 ± 19	75.43 ± 16	.079
Carstairs[3] (%)	17.9, 15.8	23.4, 10.7	23.7, 5.6	.019
Single (%)	6.5	9.7	4.9	.12
Home owner (%)	55.7	63.4	72.6	<.001
Lives alone (%)	46.8	45.9	45.8	.88
Current smoker (%)	11.7	8.0	8.3	.39
Emphysema (%)	4.0	1.5	0.9	.012
Heart attack (%)	16.7	13.0	8.2	.001
Stroke (%)	13.0	6.3	4.8	<.001
Cancer[4] (%)	6.4	7.1	10.1	.10
Diabetes (%)	9.8	5.4	4.7	.019
CVD[5]	34.7	24.3	18.5	<.001
Hip fracture (%)	2.4	2.1	1.5	.35
Recent weight loss (%)	3.0	2.4	2.4	.72
MMSE score <12/<17[6]	4.8	1.7	0.2	<.001
GDS score >5[7]	10.1	4.1	4.9	<.001
Unable to do >1ADL[8]	43.0	11.3	10.0	<.001
Medication (%)	91.5	79.8	76.9	.001

[1] $\bar{x}$ ± SD.
[2] $\bar{x}$ ± SD of average of 2 readings while sitting.
[3] Carstairs deprivation index, quintiles 1&5.
[4] Excluding basal cell carcinoma.
[5] History of heart attack, stroke, or angina.
[6] MiniMental State Examination (MMSE) <12 if language section could not be completed, otherwise <17.
[7] 15 item Geriatric Depression Score (GDS).
[8] ADL: Activities of Daily Living.

years and over. The UK Nottingham Longitudinal Study on Activity and Ageing measured customary physical activity (type, frequency, and duration) in people aged 65 years and over categorized as low, intermediate, and high [23]. Relative to the high group, an increased 47% 12 year mortality risk was observed in men for the "intermediate" group and a 75% increased mortality for the "low" group. The increased risk was observed only for the low-activity group for women. A prospective study conducted in the US of community dwelling people aged 65 years and over found that walking more than 4 hours/week was associated with a 27% reduced risk of death [27]. However, this association was substantially diminished by adjustment for cardiovascular risk factors and measures of general health status. Other studies in older people have reported improved survival from any level of physical activity compared to none [24], or a mortality

Table 5: Hazard ratios (95% CI, *P* value) by tertile of total PA and category of intensity referent to the first tertile/category.

MODEL		Total PA			Intensity		
		T1	T2	T3	Low	Medium	High
	$N = 946$[1]	313	302	331	219	275	452
(1) (adjusted for age and sex)		1	0.66	0.54	1	0.57	0.45
	CI		(0.50, 0.87)	(0.40, 0.71)		(0.41, 0.79)	(0.37, 0.55)
	P value		0.004	0.0001		0.001	0.000001
	P trend		0.0001			0.0000001	
(2) (adjusted for age, sex and potential confounders[2])		1	0.73	0.58	1	0.61	0.50
	CI		(0.55, 0.96)	(0.43, 0.80)		(0.44, 0.85)	(0.40, 0.62)
	P value		0.025	0.001		0.004	0.00001
	P trend		0.001			0.00001	
(3) (adjusted for age, sex, potential confounders and possible causalpathways[3])		1	0.84	0.74	1	0.74	0.61
	CI		(0.60, 1.17)	(0.56, 0.97)		(0.51, 1.07)	(0.47, 0.79)
	P value		0.3	0.04		0.1	0.001
	P trend		0.04			0.001	

[1] Participants with complete data on all variables in the models.
[2] BMI, smoking status, Carstairs, GDS, marital status, living alone, housing tenure.
[3] BMI, smoking status, MMSE score, Carstairs, GDS, marital status, living alone, housing tenure, HDL, diastolic BP, history of emphysema, cancer, CVD, diabetes, hip fracture, ADLscore, weight, loss, and medication.

benefit from 3 or more hours per week of activity of at least moderate-intensity compared to none, even among frail people [26] and a lower mortality rate over 10 months among frail people who did at least 2 hours activity a week [28]. A US-based study of people aged 65 years and over found those who walked more than 4 hours per week had a lower mortality although this was significant only among persons aged 75 years and older [27]. Bembom et al. concluded that the benefits of at least 22.5 metabolic equivalents (MET) hours per week could be greater for people aged 75 and over than for aged 54–74 years, but they had little detail on physical activity [25].

We had no information on previous leisure activities in our study. Other studies have shown that the greatest declines in physical activity over time are associated with the highest mortality rates in men but not in women [29], but that increasing leisure time activities even in later life is beneficial [30, 31]. The levels of habitual physical activity (of moderate or high intensity) in our study based on a community sample of people aged 75–84 years are reasonably high for this age group with half of participants achieving the current recommendation of at least 5×30 minutes of moderate physical activity per week. The Health Survey for England (HSE) reported that 72% of men and 82% of women aged 75 and over do not achieve at least 30 minutes per day on one- to four- days a week of at least moderate intensity [32]. Direct comparison between our study and the Health Survey for England is not possible, because we did not measure frequency. The closest comparison is that 42% of participants in our study managed less than 120 minutes of at least moderate physical activity per week. This difference may be partly accounted for by the fact that the HSE categorized heavy housework and outdoor maintenance/DYI as moderate activity for the survey population of all ages. Our judgment was that for people aged 75 years and over, intensity of heavy housework as defined in our study (e.g., scrubbing floors on knees, moving furniture, spring cleaning, and polishing brass) and outdoor maintenance/DIY (e.g., washing, polishing and repairing the car, carpentry, erecting a fence or shed, brick/concrete laying, moving heavy loads,etc.) requires energy expenditure justifying inclusion in the heavy-intensity of PA category. Other studies in Europe which have included either domestic and DIY activities [33] or leisure time activities [14] have reported higher levels of PA in older people with up to two thirds of participants reporting moderate or high levels of physical activities.

Data on PA in our study covered a large range of typical activities in older people and took account of widely varying intensities and frequencies. Low level everyday mobility activities as well as shorter bouts of activities (e.g., time spent on feet in shops and stair climbing) were recorded. These are not usually counted in other studies such as the HSE even though some activities, such as hoovering, are included in the UK Department of Health recommendations. It is controversial whether domestic activity has health benefits [33]. Domestic activity and shopping were included in a category of "consumptive" activity that did not predict mortality among people aged 70 and over during a 10–13 year follow-up after the analyses were adjusted for demographic factors, education, comorbidity, and physical and cognitive functioning [34]. On the other hand, in a wider agegroup there was some indication of reduction in all-cause mortality for men and women over an average follow-up of 8 years [35]. Some authors have suggested that psychosocial

pathways, such as stress, may limit the benefits of domestic work [34], at least for some groups [36]. It is possible that our study participants were more health conscious and active than in the HSE survey. This could further explain the overall higher levels of PA achieved by our study subjects. In view of this, the intensity variable may be considered a better measure of PA performed. We categorized people in the high-intensity group on the basis of performing any high-intensity activity. We found no difference in models that excluded or included people with less than an hour's heavy activity a week.

We used questions adapted from the Allied Dunbar National Fitness Survey. We could not identify any validation studies conducted on the survey instrument. Discriminant validity was suggested in our study by the predictive association with thirds of physical activity and health status. Similar to other studies which used questionnaire methods to assess physical activity, we cannot exclude errors in the reporting of physical activity, for example, due to recall problems, over reporting due to perceived social desirability and the collection of data at a single point in time. However, results of assessment by a seven-day physical activity recall interview administered in a community health survey, a randomized clinical trial, and two worksite health promotion programmes suggest that physical activity recall provides useful estimates of habitual physical activity for research in epidemiological and health education studies [37]. Moreover, self-report has some advantages over objective measures in that the latter often have to exclude those in the worst physical state [26].

Undertaking physical activity is a complex behavior. Descriptive variables may be meaningfully partitioned into various categories as long as they are mutually exclusive of each other [38]. In preparation for constructing new summary measures of PA from the questionnaire we conducted a structured review of the literature specific to the question of categorizing self-reported physical activity into relevant derived physical activity variables in older people. This work was further supported by conducting an overview of the exercise physiology of old age. The most frequent categorization of PA found was by total quantity (in minutes per week) and by intensity, frequency, and type of PA (e.g., walking). From the point of view of the older person the most problematic measurement is the intensity of activity undertaken. The frequently used classification of physical activity by rate of energy expenditure using energy expenditure values in METs based on young adults can be misleading due to the bigger effort, and thus higher energy expenditure, required in older age to accomplish given tasks. We have, therefore, taken the approach used mainly in Scandinavian studies where physical activity is graded in levels using a modified version of the scale developed by Grimby [14, 39, 40]. We categorized participants into categories of "inactive" (engage in no or very few activities of only light intensity of not more than 30 minutes/week), "lightly active" (engage in light- and moderate-intensity activities up to one hour/week), "moderately active" (engage in light and moderate intensity activities up to 2.5 hours/week), "active" (engage in moderate physical activities for more than 2.5 hours/week and including at least 30 minutes of heavy intensity activity or active exercise/week) and "highly active" (engage in moderate physical activity for more than 4 hours/week or heavy intensity activity or exercise for over 2 hours/week). However, given the relatively high volume of physical activity performed by participants in our study and reduction in our original sample size due to incomplete data on confounders and co-morbidities, we categorized physical activity into tertiles by total amount of PA and three mutually exclusive categories of intensity (low, medium, and high) described in detail in the methods section.

There are a number of limitations in our study. Although we took account of a large number of potential confounders there may be other unmeasured confounders which could have attenuated our results. People with higher levels and intensity of physical activity had fewer health problems than those with the lowest levels. In common with other observational studies of physical activity in older people, it is difficult to establish whether poor health is a consequence of low physical activity or whether low physical activity is a consequence of poor health. Since poor health is associated with mortality, we controlled for this by including the major health conditions in our models. Although we did not have information on the severity of some conditions such as emphysema or angina, we included a measure of functional limitation (ADL) as a proxy indicator of poor health. We did not have any objective measures of physical activity. Using data from the US NHANES survey, Troiano et al. found differences in levels of physical activity based on self-report compared with accelerometers suggesting over estimation by study participants [41]. However, as noted by the authors, accelerometry may underestimate physical activity because it does not take account of activities such as bicycling, swimming, and upper body activities.

Our results do not apply to people in long-stay hospital or nursing homes (an exclusion criterion for the trial) in whom physical activity levels are likely to be substantially different from the community sample. The response rate in our study was 71% and nonresponders were more likely to be women and current smokers. However, there were no other major differences in health measures between responders and nonresponders, and the mortality rates were similar. The 35% of responders who did not have full data on possible confounders were similar to those with full data. Moreover, the Model 1 and 2 mortality estimates for those with incomplete data were essentially the same as those with complete data.

Our results for people aged 75 to 84 years support the existing evidence that physical activity is beneficial and is associated with improved survival in those aged 75 years and over. Regular physical activity and/or exercise enable older people to retain higher levels of functional capacity (notably cardiovascular and neuromuscular function) and possibly slow the age-related decline in cognitive function. The benefits of increased levels of exercise in relation to mortality found by us and in previous studies apply to a range of daily activities and are by no means specific to structured exercise. Our study also shows that doing more strenuous physical activity (as well as light and moderate) has benefits

in terms of survival. Significant natural reduction in muscle mass and consequent loss of strength is a natural irreversible process. However, considerable strength improvement of existing muscle mass with vigorous training is possible into the ninth decade of age [42]. Since muscle strength is crucial to mobility, performing heavy physical activity will also undoubtedly lead to increased self-sufficiency in older age and there is a case for making resistance training a core component of disability postponing programmes for the elderly.

Although we were not able to report on the frequency of exercise below the weekly time unit and cannot, therefore, say with certainty how many times per week physical activity should be performed, the nature of our observations about daily customary activities suggests that activity took place on most, if not all, days. If customary physical activity such as housework, gardening, shopping, and walking is the main or sole component of physical activity for older people, it should be emphasized that increased activity (above the current recommended level) has considerable longevity benefit. While recommendations for older people appropriately focus on the provision and promotion of physical activity classes [6], this should be integrated with an approach which additionally emphasizes home-based activities.

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Research Article

Aging and the Social Cognitive Determinants of Physical Activity Behavior and Behavior Change: Evidence from the Guide to Health Trial

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Part one of this study investigated the effect of aging on social-cognitive characteristics related to physical activity (PA) among adults in the baseline phase of a health promotion intervention. Participants' questionnaire responses and activity logs indicated PA levels and self-efficacy declined with age, while social support and the use of self-regulatory behaviors (e.g., goal setting, planning, and keeping track) increased. With age participants were also less likely to expect PA to interfere with their daily routines and social obligations. Part two of the study was among overweight/obese, inactive participants completing the intervention; it examined whether improvements in psychosocial variables might counteract declining PA associated with age. After treatment, participants were more active and decreased body weight regardless of age, and improved self-efficacy, outcome expectations, and self-regulatory behaviors. In a causal model, increases in self-efficacy at 7-months lead to increased PA levels and, albeit marginally, weight loss at 16 months; increased PA was associated with greater weight loss. Aging adults who were more confident exercised more and as a result lost more weight. This longitudinal study suggests interventions that offset the effect of aging on self-efficacy may be more successful in helping older participants become more active and avoid weight gain.

1. Introduction

The role of psychosocial functioning in adopting and maintaining healthy physical activity levels in aging adults has been highlighted by recent research [1–7]. Exercise self-efficacy, social support from significant others, positive outcome expectations, and engaging in physical activity self-regulation contribute to maintaining active lifestyles. It is important, however, to examine how aging influences psychosocial determinants of physical activity, how declines in these variables might lead to lower levels of activity, and how interventions might counteract these influences.

Social cognitive theory (SCT) provides a framework that has been recommended by the surgeon general as useful for organizing, understanding, and promoting physical activity [8]. Generally, SCT posits that personal, environmental, and behavioral factors are reciprocally influential in determining behavior and behavior change. *Personal factors* influencing physical activity include age, race, gender, and potentially malleable psychosocial variables, such as self-efficacy and outcome expectations. *Environmental factors* key to physical activity adherence involve social support, such as modeling by family and friends, support from exercise partners, and feedback from exercise leaders [9]. *Behavioral factors* essential to sustained physical activity are predominantly self-regulatory behaviors; Bandura suggests that, for most people exercise success depends on the ability to self-monitor (i.e., plan and track), set goals and evaluate their exercise behavior [9, page 415].

Social cognitive theory also specifies how personal, environmental, and behavioral variables relate to each other as illustrated in Figure 1 [9, 10]. Self-efficacy stems from

personal variables, such as the individual's age, gender, and general health, and from environmental variables, such as access to safe exercise facilities and social support for physical activity [9]. SCT posits that individuals who believe they can be physically active (i.e., higher self-efficacy) will expect favorable results from physical activity (i.e., outcome expectations) and will be more likely to implement the self-regulatory behaviors essential to adopting and maintaining an active lifestyle [9, 10].

Despite the widespread use of SCT among physical activity researchers (including studies targeting aging adults) little in known about the effect of aging on these important variables. Previous studies have generally focused on the relation between social cognitive variables and physical activity among the elderly (mean age 60–79.5) [2–5]. Very little research has examined how psychosocial variables might be influenced by advancing age or how SCT variables might mediate the influence of aging on physical activity. One exception: Ayotte et al. [1] found among older white adults married for 15 years or more (mean age ~59 years) that although the sample's physical activity levels did not decline with age, perceptions of the benefits associated with exercise did decrease.

Broader evidence will be needed to determine if deteriorating psychological functioning precedes declining physical activity levels generally associated with age [11]. Further, interventions targeting psychosocial variables to increase physical activity will need to be evaluated to determine if they operate as theorized among aging adults. The purpose of the current study was to examine the effects of age on physical activity levels and physical activity-related social support, self-efficacy, outcome expectations, and self-regulatory behavior among a diverse group of aging adults enrolled in the Guide to Health (GTH) trial [12]. Further, the study sought to examine whether the long-term effects of the SCT-based GTH intervention on physical activity levels and body weight of overweight/obese inactive aging adults were mediated by earlier changes in psychosocial variables in a manner consistent with SCT.

2. Methods

2.1. Recruitment and Procedures. Participants were recruited as part of a larger study to test the effectiveness of a health promotion intervention designed to reach adults living in nonmetropolitan areas through their churches [12]. In southern and rural regions of the US, regular church attendance (once a month or more) among aging adults is common (54% of adults over age 40 in 2006) [13]. Men and women from 14 churches (3 United Methodist, 8 Baptist, and 3 predominantly African American Baptist) were recruited at their churches through meetings, newsletters, church bulletins, pulpit announcements, posters and word of mouth to participate in an Internet-based program designed to help them adopt healthier eating and physical activity habits.

Following American College of Sports Medicine guidelines [14], church members who reported heart or lung disease, asthma, diabetes, kidney/liver disease, autoimmune diseases, estimated low fitness (i.e., <3 METs) [15], bone and joint problems, or cancer within the last five years were required to have medical clearance before participating in the physical activity portion of GTH.

Research staff obtained informed consent approved by the Virginia Tech Institutional Review Board and instructed participants in how to complete paper and pencil questionnaires and the 7-Day Step Counter and Activity Log (see below); height and weight were measured during church assessment sessions. Participants returned completed questionnaires and logs to research staff at the church or via postage paid envelopes. Physical activity assessments from baseline and the 16-month followup point and psychosocial assessments at baseline and at the 7-month posttest were included in the current analyses. After baseline, participants were assigned within their churches to one of three GTH treatment conditions, GTH alone (GTH-Only), GTH plus church supports (GTH-Plus), or control waiting and were assessed immediately following the GTH intervention (7-month posttest) and ten months later (16-month followup).

Baseline participants over 40 years of age ($n = 703$) contributed data to *part one* of the current study. Of baseline participants over 40, 73% ($n = 515$) completed the 16-month followup assessment; 204 were classified as "weight challenged and inactive" (i.e., BMI ≥ 25; daily steps <7500 [16]; moderate intensity exercise <30 minutes 5 days a week and vigorous intensity exercise <20 minutes 3 days a week [17]). Weight challenged and inactive adults over 40 who completed the 16-month assessment contributed data to *part two* of the current study.

2.2. The Guide to Health Intervention. The Internet-based GTH program, accessible from any computer connected to the Internet, consisted of 12 weekly SCT-based modules of 15–20 screens [12]. Modules targeted social support (e.g., getting someone to remind you to walk; adding healthier foods in ways acceptable to family members), self-efficacy (i.e., guided, gradual behavior change, e.g., increasing steps 500 steps per/day and increasing F&V by one serving per day), outcome expectations, (i.e., providing feasible and acceptable strategies, e.g., building steps into one's normal routine and switching to acceptable fat- modified foods), and self-regulation (i.e., anticipating and planning for barriers to change, e.g., walking at the mall in bad weather, bringing fruit for a snack when healthy alternatives are not available at the workplace).

Church-based supports provided in churches in one study condition included prompts from the pulpit and in church bulletins, reports of church progress toward behavior change goals, and a church-wide "step-drive" [12] and were designed to garner support for behavior change from the churches' social networks. Church supports were faded after the 7-month assessment and ended prior to the 16-month assessment.

3. Measures

3.1. Physical Activity

3.1.1. Verified Step-Counts. Participants received a pedometer (Accusplit 120E step counter; San Jose, CA) and a "7-Day

Table 1: Physical activity beliefs survey: scale descriptions.

Variable description	Sub-scale	# items	α
Social support from family for physical activity		3	.68
Self Efficacy	Overcoming barriers	11	.89
	Meeting goals in daily routine	9	.89
Positive physical, and self-evaluative expectations		3	.81
Negative physical, social, and self-evaluative expectations		6	.85
Self regulation (se of goal setting, planning, and self-monitoring)		7	.83

α = Cronbach's alpha coefficient of internal consistency.

Step Counter and Physical Activity Log" to keep track of their physical activity for one week. Participants wore the pedometer and made a daily record of steps accumulated during the week. Participants were instructed to *not* reset their pedometers during the week and to let the steps accumulate until the seventh day. Step-logs and pedometers were returned to the research site where staff used the accumulated step-count reading on the pedometer to verify steps logged for the week [18]. Mean daily step counts (total steps ÷ days of pedometer use) served as one measure of physical activity in the baseline model in part one of the study. Change in mean daily step counts (16-month assessment minus baseline) served as one measure of physical activity in the behavior change model in part two of the study.

3.1.2. Physical Activity Log. In addition to logging steps, participants were asked to record each morning, afternoon and evening for one week "any physical activity comparable to how you feel when you are walking at a normal walking pace." For each participant, the number of minutes spent walking per day was computed. Minutes walked per day served as a second measure of physical activity in the baseline model in part one. In addition, the total number of MET minutes engaged in exercise was summed across logged activities to calculate exercise MET-hours/week. Exercise was defined as planned, structured, and repetitive body movement done to improve or maintain ... physical fitness [14]. The MET equivalent (i.e., the ratio of work metabolic rate to a standard resting metabolic) for each logged activity was computed. Based on Ainsworth [19] activities of moderate or higher intensity ($\geq$3 METs) done to maintain/improve fitness that lasted at least 10 minutes, were used to compute exercise MET-hours/week. Change in participants' exercise MET-hours/week (16-month assessment minus baseline) served as a second measure of physical activity in the behavior change model in part two. (Note: the nonlinear relationship between age and MET-hours/week at baseline prevented its use in the baseline model of part one).

3.2. Social Cognitive Variables. The Physical Activity Beliefs section of the Health Beliefs Survey [18] measured physical activity-related social support, self-efficacy, outcome expectations and self-regulation (see Table 1). Baseline scores for social cognitive variables were used as measures in the baseline model. Change scores (baseline scores subtracted from scores at 7 months) were used as measures of SCT variables in the behavior change model.

4. Statistical Methods

Structural models were analyzed with latent-variable structural equation modeling (SEM, LISREL 8.8, [20]); model fit was evaluated with root mean square error of the approximation ($RMSEA$) $\leq$ .05 (P close fit > .95 or *alpha* = .05) and with Chi-square evaluated with *alpha* = .05 or <3 times degrees of freedom (normed chi-square; [21]). We assumed no measure to be error free, so, for latent variables with only one indicator (e.g., age, gender, and race), we set error terms to the measure's variance times estimated error [21]. In order to make full use of the available data, full information maximum likelihood estimation was employed. Prior to analyses, measures were examined for outliers and normality. The distributions of the baseline physical activity measures and, with few exceptions, the distributions of change measures were skewed or displayed unacceptable kurtosis; these measures were normalized using the Blom proportional estimate formula in SPSS 18.0.

Using procedures appropriate for evaluating change in group-randomized trials [22], complex-sample, latent-variable SEM with 14 clusters (churches) nested in 3 ordinal study conditions (0 = control, 1 = GTH, 2 = GTH Plus Supports) evaluated whether the effects associated with level of GTH treatment on physical activity were mediated by underlying SCT variables. Further, the behavior change model was re-evaluated to determine if and how change in physical activity (and preceding changes in social cognitive variables) were related to differences in weight at 16 months.

In both parts of the study, effect mediation (e.g., mediation of the effect of age on physical activity or the effect of treatment on change in physical activity) was examined when (1) the predictor variable had a significant total effect on the outcome variable, (2) the predictor variable had a significant total effect on the presumed mediating variable, and (3) the mediating variable had a significant total effect on the outcome variable (evaluated one-tailed in the direction of the hypothesized effect [23–26]). Mediation was evaluated with z' [25], which in its various versions consistently had more power and lower Type 1 error than other mediation tests [25–27] including in cluster randomized designs [22, 28, 29]. Z' was used to determine upper and lower critical values for the mediated effect (ab) based on an empirical distribution

of indirect effects [25]; lower and upper confidence limits of *ab* that did *not* include zero were interpreted as a significant mediating effect.

5. Results

5.1. Part One: Demographic, Psychosocial, and Behavioral Characteristics.

5.1.1. Demographic Characteristics. Participants in part one of the study ($n = 703$) had a mean age of 58.11 years (SD = 11.08), 23% were African American, 66% female, 90% attended church at least once a week, 20% reported annual household incomes less than $20,000 (median income ~ $50 k); 22% reported 12 years or less education ($M = 14.8$, SD = 2.4), 75% were overweight or obese, and 48% were inactive. About half ($n = 339$) of the over-40 participants reported one or more health problems requiring clearance to participate in the PA intervention; 99% received written medical clearance. The number of participants in each health issue category was as follows: 220 reported heart disease, 133 bone or joint problems, 101 pulmonary disease, 82 diabetes, 73 thyroid disease, and 39 other diseases.

5.1.2. Physical Activity Levels. Baseline step-count and activity logs indicated the over-40 participants took an average of 6507.20 steps (SD = 3252.52) and reported walking an average of 23.95 minutes (SD = 32.64) per day during the initial assessment phase. A comparison of physical activity among *40s-group* ages 40–51 (the *40s-group*, $n = 213$), ages 52–61 (the *50s-group*; $n = 241$), age 62 and up (the *60s+-group*, $n = 249$) revealed that activity levels decreased significantly with age. Participants in the *40s-group* took 26% more steps and walked 40% more minutes per day than participants in the *60s+-group* (see Table 2).

5.1.3. Perceived Social Support for Physical Activity. Responses to the Physical Activity Beliefs Survey indicated that, prior to intervention, participants' perceived some, although not strong, social support from their families for physical activity ($M = 3.44$, SD = .85 on a 1–5 scale). Perceived social support was highest among participants in the *60s+-group* compared to participants in the 40s- and *50s-group*, and higher among the *50s-group* than participants the *40s-group* (see Table 2).

5.1.4. Self-Efficacy. Mean self-efficacy scores indicated participants had positive, but not complete, confidence in their abilities to increase physical activity in their daily lives ($M = 72.54$, SD = 20.04 on a 100 point scale). Participants' confidence in being able to overcome barriers to physical activity, on the other hand, was more neutral ($M = 58.17$, SD = 21.62 100 point scale). Unlike social support which increased with age, participants' self-efficacy for physical activity decreased. Participants in the *60s+-group* reported lower confidence in their abilities to add exercise to their daily routines than participants in the 40s- and *50s-group*s, and self-efficacy for overcoming barriers to exercise was higher in the *40s-group* than the *60s+-group* (see Table 2).

5.1.5. Outcome Expectations. Responses to the *negative* outcome expectations items indicated participants did not expect that increasing physical activity would interfere with social and time management responsibilities ($M = 7.66$, SD = 4.05 on a 25 point valued outcome 5 expectations scale). Negative outcome expectations declined (improved) with age; participants in the *60s+-group* had lower negative outcome expectations than those in the *40s-group* (see Table 1). Participants did, however, expect *positive* outcome from being more active—agreeing that increasing physical activity would lead them to better physical and emotional health ($M = 18.56$; SD = 5.58 on a 25 point valued expectations scale). Although, the *50s-group* had higher positive outcome expectations than the *60s+-group* (see Table 2), these groups did not differ from the *40s-group*s.

5.1.6. Self-Regulation. Finally, participants indicated they seldom (rated 2 on the 5 point scale) or occasionally (3 on the scale) implemented physical activity self-regulatory behaviors in the three months prior to the intervention ($M = 2.41$, SD = .89). These behaviors, however, increased with age and were more frequent among participants in the *60s+-group* as compared to participants in the *40s-group* (see Table 2).

5.2. Part One: Social Cognitive Determinants of Physical Activity among Aging Adults. The nature of the relationships between baseline social cognitive variables, physical activity, age, gender, race, and health status was investigated by modeling these variables in a manner consistent with SCT and evaluating the model with structural equation analysis. The SCT model of baseline physical activity (see Figure 2) provided a good fit to the data ($RMSEA = .046$, P (close fit) = .97; $X^2_{(392, N=703)} = 975.14$, $P < .001$; X^2/df ratio = 2.49) explaining 18% of the variance in physical activity observed among the aging adults. Standardized direct, indirect, and total effect coefficients generated by the structural analysis are listed in Table 3; significant direct effects are printed in Figure 2 (covariance matrices and factor loadings associated with the analyses are available from Eileen Anderson-Bill).

5.2.1. Age, Gender, Race, and Health Status. Within the model, age exerted the strongest total effect on physical activity ($\beta_{(\text{total})} = -.41$; see the last row in Table 3); greater age was associated with lower levels of physical activity. Age also influenced social support (($\beta_{(\text{total})} = .37$), self-efficacy ($\beta_{(\text{total})} = -.14$), negative outcome expectations ($\beta_{(\text{total})} = -.23$), and self-regulation ($\beta_{(\text{total})} = .25$).

Participants' race also influenced physical activity ($\beta_{(\text{total})} = -.24$); African American participants had lower levels of physical activity than participants of other races (97% of whom were white). African American older adults also expected more positive outcomes ($\beta_{(\text{total})} = .09$) and fewer negative outcomes ($\beta_{(\text{total})} = -.12$) than white participants.

Table 2: Age-related differences in physical activity and related social cognitive variables.

	Age group	Mean	SD	F	P	Compared Groups	$t(p)$
Steps/day	40s	7315.67	3054.50	23.95	<.001	40s versus 50s	−1.34 (.54)
	50s	6918.41	3363.12			40s versus 60s+	6.45 (<.001)
	60s+	5417.64	3017.65			50s versus 60s+	5.27 (<.001)
Min walked/day	40s	27.93	38.83	3.43	.03	40s versus 50s	.93 (.44)
	50s	24.93	31.34			40s versus 60s+	2.56 (.04)
	60s+	19.83	27.61			50s versus 60s+	1.66 (.96)
Social support	40s	3.17	.79	18.41	<.001	40s versus 50s	−3.67 (<.001)
	50s	3.48	.83			40s versus 60s+	−6.04 (<.001)
	60s+	3.66	.87			50s versus 60s+	−2.46 (.04)
SE: daily routine	40s	74.38	17.78	4.25	.02	40s versus 50s	−.55 (1.00)
	50s	75.43	18.65			40s versus 60s+	3.33 (<.001)
	60s+	68.04	22.41			50s versus 60s+	4.01 (<.001)
SE: barriers	40s	58.13	19.97	9.31	<.001	40s versus 50s	−1.44 (.45)
	50s	61.13	20.81			40s versus 60s+	1.39 (.50)
	60s+	55.26	23.45			50s versus 60s+	2.92 (.01)
Negative OE	40s	8.07	3.94	3.71	.03	40s versus 50s	.51 (1.00)
	50s	7.87	4.22			40s versus 60s+	2.55 (.03)
	60s+	7.03	3.90			50s versus 60s+	2.11 (.11)
Positive OE	40s	18.76	5.41	3.59	.03	40s versus 50s	−.73 (1.00)
	50s	19.16	5.45			40s versus 60s+	1.83 (.21)
	60s+	17.73	5.80			50s versus 60s+	2.62 (.03)
SR: goal setting and planning	40s	2.50	.88	5.68	<.001	40s versus 50s	−1.55 (.36)
	50s	2.64	.96			40s versus 60s+	−3.36 (<.001)
	60s+	2.80	.95			50s versus 60s+	−1.85 (.20)
SR: tracking	40s	1.73	1.01	4.18	.02	40s versus 50s	−1.24 (.65)
	50s	1.87	1.15			40s versus 60s+	−2.87 (.01)
	60s+	2.05	1.23			50s versus 60s+	−1.68 (.28)

SE: self-efficacy, OE: outcome expectations, SR: self-regulation.

Social support, self-efficacy, and self-regulation among aging adults were not influenced by race.

Gender (female = 0, male = 1) did not exert an overall effect on physical activity (i.e., its total effect was insignificant). Women in the sample, however, had higher levels of self-efficacy ($\beta_{(\text{total})} = -.09$), positive outcome expectations ($\beta_{(\text{total})} = -.19$), and self-regulatory behavior ($\beta_{(\text{total})} = -.14$).

Participants who reported health concerns requiring medical clearance (see above) were less physically active than participants who did not ($\beta_{(\text{total})} = -.14$), had lower levels of physical activity self-efficacy ($\beta_{(\text{total})} = -.09$), and higher negative outcome expectations ($\beta_{(\text{total})} = .12$) for physical activity, but the effect of health status on physical activity was larger independent of these variables ($\beta_{(\text{direct})} = -.14$).

5.2.2. Social Support. Social support from family members contributed to aging adults' physical activity levels ($\beta_{[\text{total}]} = .12$, $P < .05$); an effect that was largely indirect through self-efficacy and self-regulation (β [indirect] = .10, $P < .001$; indirect/total ratio = .83). Social support was strongly predictive of self-efficacy ($\beta_{[\text{total}]} = .34$, $P < .001$) and of whether aging adults engaged in self-regulatory behavior ($\beta_{[\text{total}]} = .43$, $P < .001$). Participants who perceived support from their families for physical activity were more likely to expressed confidence in their abilities to fit exercise into their daily routines and to overcome barriers to physical activity; they were also more likely to set goals, plan, and self-monitor their own activity levels. The effect of social support on self-regulation was largely direct (β [indirect] = .06, $P < .05$; indirect/total ratio = .12).

5.2.3. Self-Efficacy. Although self-efficacy decreased with age in the sample, aging adults with greater confidence in their being able to manage the logistics and to overcome barriers to physical activity were more active; this moderate effect was almost entirely direct ($\beta_{[\text{total}]} = .12$, $P < .05$; β [indirect] = −.02, $P > .10$; indirect/total ratio = .16). In addition to influencing physical activity, self-efficacy was a strong predictor of outcome expectations in the model (negative outcome expectations; $\beta_{[\text{total}]} = -.27$, $P < .001$; positive outcome expectations; $\beta_{[\text{total}]} = .41$, $P < .001$) and had a moderate effect on self-regulation ($\beta_{[\text{total}]} = .17$, $P < .001$). Participants with confidence in their abilities to maintain an active lifestyle were more likely to expect to reap the benefits from becoming more active and were more likely to engage in self-regulatory behavior.

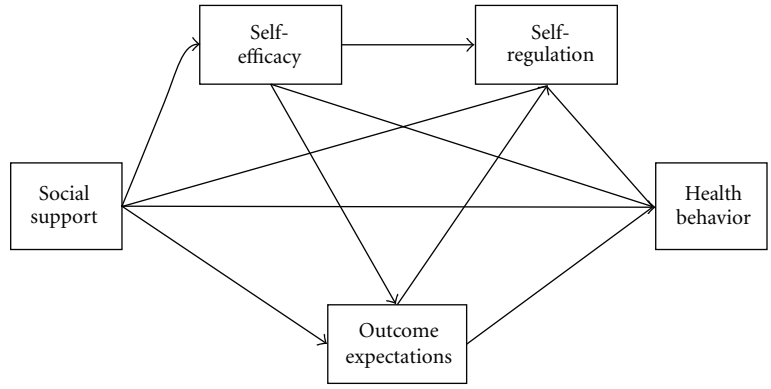

Figure 1: Variable relationships within the social cognitive model of health behavior.

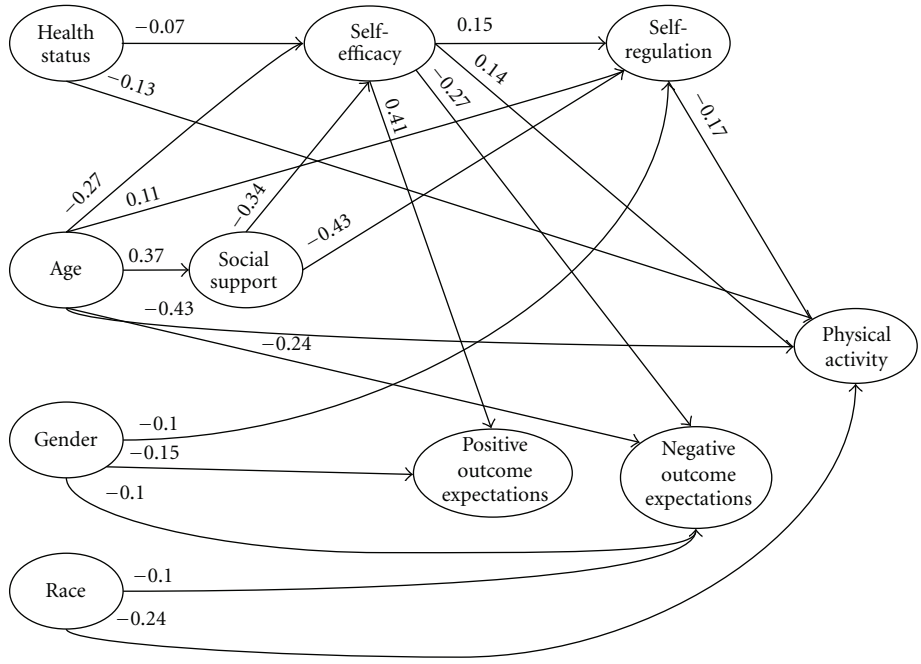

Figure 2: Social cognitive model of physical activity among aging adults: significant direct effects ($P < .05$).

5.2.4. Outcome Expectations. Outcome expectations did not exert a significant effect on aging adults' physical activity (negative outcome expectations; $\beta_{[\text{total}]} = .06$, $P < .10$; positive outcome expectations; $\beta_{[\text{total}]} = -.07$, $P > .10$) nor did outcome expectations influence participants' use of self-regulatory behaviors (negative outcome expectations; $\beta_{[\text{total}]} = -.01$, $P < .10$; positive outcome expectations; $\beta_{[\text{total}]} = .05$, $P > 10$).

5.2.5. Self-Regulation. Enactment of self-regulatory behaviors was a moderate predictor of aging adults' physical activity. Setting activity goals and making plans, adjusting routines to make activity more enjoyable, and tracking daily activity led to higher levels of walking ($\beta_{[\text{total}]} = .17$, $P < .001$). Indeed, self-regulation mediated the effect of age in the sample (Age—Self-regulation—Physical Activity $ab = .055$; CI =.01; .12).

5.2.6. Potential SCT Mediators of Age and Health Status Effects on Activity Levels. Age and health status were important predictors of physical activity and related psychosocial variables. The extent to which the effects of age and health status were mediated by SCT variables was further investigated. The effects of age on physical activity were mediated by social support, self-efficacy, and self-regulation. Older participants' decreased self-efficacy contributed to lower levels of physical activity (Age—Self-Efficacy—Physical Activity $ab = -.02$; CI $= -.04$; $-.001$). On the other hand, the increased social-support (Age—Social Support—Physical Activity $ab = .04$; CI =.002; .09) and self-regulation (Age—Self-regulation—Physical Activity $ab = .04$; CI =.004; .09) associated with greater age contributed to higher levels of physical activity acting as a counterbalance to the negative effects of declining self-efficacy resulting in an insignificant total indirect effect of age on physical activity (β [indirect] = .02, $P = .30$).

Table 3: Standardized direct, indirect, and total effects among latent variables from the social cognitive model of baseline physical activity among aging adults.

Latent variable		Race	Gender	Age	Health	SS	SE	POE	NOE	SR
Social support (SS)	Direct/total	.02	−.05	.37***	−.05					
Self-efficacy (SE)	Direct	.05	−.07	−.27***	−.07	.34***				
	Indirect	.01	−.02	.13	−.02	—				
	Total	.06	−.09*	−.14**	−.09*	.34***				
Positive outcome expectations (POE)	Direct	.06	−.15**	−.04	.01	.05	.41***			
	Indirect	.02	−.04	−.04	−.04	.14***	—			
	Total	.09*	−.19***	−.08	−.03	.19**	.41***			
Negative outcome expectations (NOE)	Direct	−.10	−.10*	−.24***	.09	−.08	−.27***			
	Indirect	−.02	.03	.01	.03	−.09**	—			
	Total	−.12**	−.07	−.23***	.12**	−.17***	−.27***			
Self-regulation (SR)	Direct	.06	−.10*	.11	.00	.43***	.15**	.05	−.01	
	Indirect	.02	−.04	.14	−.04	.06**	.02	—	—	
	Total	.09[a]	−.14**	.25***	−.04	.49***	.17***	.05	−.01	
Physical activity	Direct	−.24**	.02	−.43***	−.13**	.01	.14*	−.08	.06	.17**
	Indirect	.01	−.03	.02	−.01	.10***	−.02	.01	.00	—
	Total	−.24***	−.01	−.41***	−.14**	.12*	.12*	−.07	.06	.17**

[a]$P < .10$; *$P < .05$; **$P < .01$; ***$P < .001$.

Increased social support associated with aging also tempered the negative of age on self-efficacy (Age—Social-Support—Self-Efficacy $ab = .13$; CI .07; .18) illustrated by comparing total and direct effects of aging on self-efficacy in Table 3. Similarly, poor health among aging participants made it more likely they had lower self-efficacy for exercise which mediated the effect of health status on physical activity (Health Status— Self-Efficacy—Physical Activity $ab = -.01$; CI = −.03; −.00004).

5.3. Part Two: Social Cognitive Mediators of Guide to Health Effects among Aging Adults. The extent to which GTH-related changes in psychosocial variables might counteract declining physical activity and increased weight associated with age was investigated among inactive weight-challenged aging adults completing the GTH trial with a complex-sample, longitudinal, latent variable approach to SEM. The models followed SCT incorporating change data for SCT variables computed from the baseline and seven-month assessments (i.e., change variable = 7 months variable minus baseline variable) and incorporating change data for physical activity and weight variables from the baseline and 16-month assessments (i.e., change variable = 16-month variable minus baseline variable). Means and standard deviations of measured variables in the latent-variable model, reported by study condition, are displayed in Table 4.

5.3.1. Guide to Health Effects on Physical Activity. The SCT model of treatment effects on physical activity (see Figure 3) provided good fit to the data: $RMSEA = .00$, 95% CI = .00; .03; P (close fit: $RMSEA < .05$) =.99; *FIML* $X^2(28, N = 204) = 21.11$, $P = .82$; X^2/df ratio = .75) explaining 82% of the variance observed in physical activity change. Standardized direct, indirect, and total effect coefficients resulting from the structural analysis are listed in Table 5; standardized direct effects are printed in Figure 3. Among the inactive, weight-challenged aging adults the GTH intervention (ordinally ranked 0 = control waiting, 1 = GTH-alone, 2 = GTH-plus supports) led to increases at seven-months in self-efficacy ($\beta_{[\text{total}]} = .23$, $P < .001$), in self-regulation ($\beta_{[\text{total}]} = .38$, $P < .001$), and to improved negative outcome expectations ($\beta_{[\text{total}]} = -.09$, $P < .01$). In addition, the GTH had a strong effect on change in participants' physical activity levels at 16 months ($\beta_{[\text{total}]} = .58$, $P < .001$). Participants added more steps and more exercise MET hours/week to their activity routines at higher levels of the intervention. These changes in physical activity and social cognitive variables were independent of participants' age and race ($\beta_{[\text{total}]}$ $P < .10$). Gender, on the other hand was an important predictor of change in physical activity ($\beta_{[\text{total}]} = .29$, $P < .05$); men in the sample made greater increases in physical activity than women.

5.3.2. Social Cognitive Mediators of Effects on Activity Levels. Increases in physical activity at 16 months were predicted by earlier improvements in self-efficacy ($\beta_{[\text{total}]} = .41$ <.05), which significantly mediated the effect of treatment on physical activity (GTH-SE-PA $ab = .093$; CI = .001; .22). Changes in self-regulation and positive outcome expectations, however, did not influence change in physical activity ($P > .10$).

5.3.3. Guide to Health Effects on Weight Management. Although the GTH was not a weight loss intervention, it was hypothesized that participants would not gain typical amounts of weight during the intervention [12]. A final expanded model was evaluated to investigate whether change

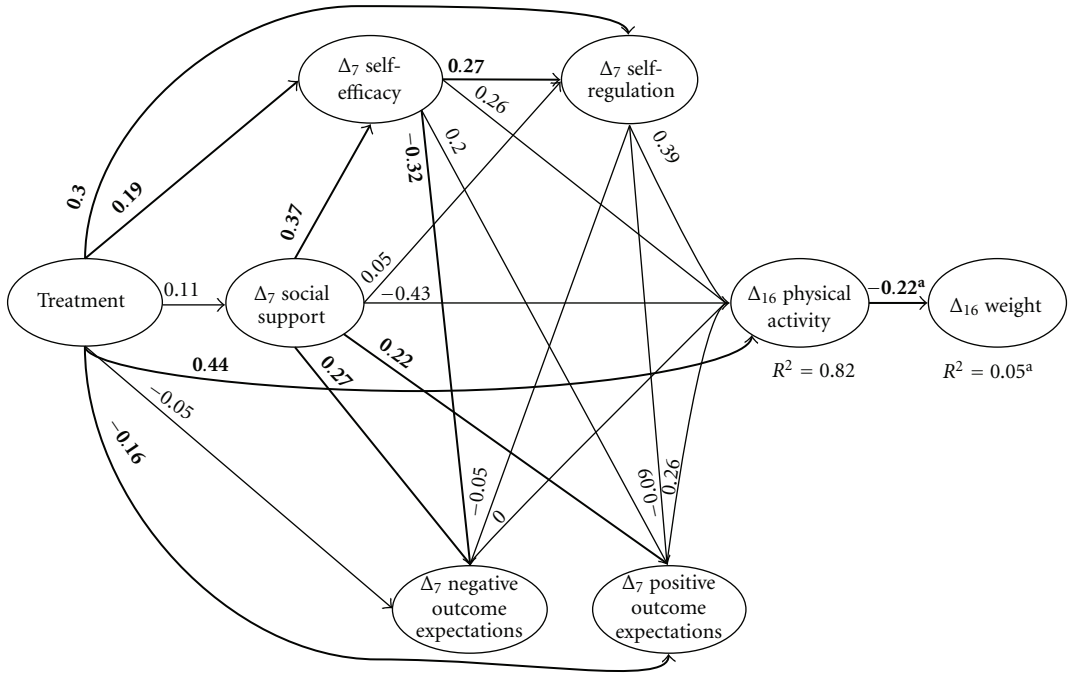

Figure 3: Cognitive model of treatment effects among overweight or obese and inactive aging adults (Δ_7 = change from baseline to 7 months, Δ_{16} = change from baseline to 16 months; significant effects bolded, [a]coefficients generated from expanded model of effects on weight).

Table 4: Descriptive statistics for change in social cognitive variables at 7 months and physical activity and weight change at 16 months.

Change variables	Treatment condition					
	Control waiting		Intervention		Intervention plus church supports	
	M	SD	M	SD	M	SD
	Change at seven-months					
Social support	.30	1.16	.14	1.04	.31	1.02
SE: barriers	−5.28	17.87	−4.70	21.90	4.57	24.25
SE: daily routine	−8.41	18.99	−6.18	18.03	2.93	17.93
Positive OE	1.18	4.47	−.11	3.98	−.33	5.00
Negative OE	.31	3.87	.37	4.46	−.73	3.77
SR: goal setting planning	.28	.77	.97	.95	.90	.90
SR: tracking	.47	1.26	1.67	1.21	1.50	1.44
	Change at 16 months					
Steps/day	427.82	2242.03	1565.61	2964.82	2059.03	2477.74
Exercise MET hrs/week	1.02	15.35	−.13	13.68	10.99	22.44
Weight	−.80	10.94	−1.37	7.24	−3.07	8.82

SE: self-efficacy, OE: outcome expectations, SR: self-regulation.

in body weight at 16 months was related to treatment, to concomitant changes in physical activity or to the preceding psychosocial changes. In the weight change model, treatment was modeled to influence weight through physical activity and earlier SCT variables (see Figure 3). The weight-change model also provided good fit to the change data: *RMSEA* = .00, 95% CI = .00; .00; P (close fit: *RMSEA* < .05) = 1.00; *FIML* $X^2(40, N = 204) = 26.29$, $P = .95$; X^2/df ratio = .66) explaining 5% of the observed weight change among overweight or obese, inactive adults in the sample. Higher levels of the GTH intervention led to greater weight loss ($\beta_{[\text{total}]} = -.12$, $P < .05$) at 16 months. Weight change was independent of participants' age, gender and race ($P > .10$, see Table 5).

5.3.4. Social Cognitive Mediators of Effects on Weight Management. Weight loss at 16 months was associated with treatment-related increases in physical activity ($\beta_{[\text{total}]} = -.22$, $P = .01$) and, albeit marginally, with improvements in self-efficacy at 7 months ($\beta_{[\text{total/indirect}]} = -.09$, $P < .10$).

Table 5: Social cognitive model of GTH treatment effects among inactive, weight-challenged, aging adults: standardized direct, indirect, and total effects among latent variable.

Latent variable	Effect	Cond.	Age	Race	Gender	SS	SE	NOE	POE	SR	PA
Social support (SS)	Direct/total	.11	−.13	.12	−.22**						
Self-efficacy (SE)	Direct	.19**	.11	−.10**	.14	.37***					
	Indirect	.04	−.05	.05	−.08*						
	Total	.23***	.06	−.06	.06	.37***					
Negative outcome expectations (NOE)	Direct	−.05	.14	.01	−.02	.27*	−.32**				
	Indirect	−.04*	−.05	.05	−.08	−.12					
	Total	−.09**	.08	.06	−.10	.15	−.32***				
Positive outcome expectations (POE)	Direct	−.16**	.09	.12**	−.07	.22*	.20[a]				
	Indirect	.07*	−.02	.01	−.03	.07*					
	Total	−.09	.07	.14	−.11*	.29**	.20[a]				
Self-regulation (SR)	Direct	.30***	−.03	.04	−.02	.06	.27**	−.05	−.09		
	Indirect	.08*	.00	−.02	.02	.07	.00				
	Total	.38***	−.04	.01	.00	.12	.27**	−.05	−.09		
Physical activity (PA)	Direct	.44***	−.15	−.02	.21	−.43	.26	.00	.26[a]	.39	
	Indirect	.14	.08	−.03	.08	.22	.15[a]	−.02	−.04		
	Total	.58***	−.07	−.05	.29*	−.21	.41*	−.02	.22	.39	
Body weight	Total	−.12*	.00	.02	−.07	.04	−.09[a]	.02	−.03	−.09	−.22**

[a]$P < .10$; *$P < .05$; **$P < .01$; ***$P < .001$; GTH: Guide to Health; Condi: treatment condition (0 = control; 1 = GTH only; 2= GTH plus).

Changes in physical activity mediated the effect of the intervention on weight loss (GTH-Physical Activity-Body Weight $ab = -.11$; CI = −.25; −.02), suggesting inactive, overweight to obese adults over 40 using the GTH lost weight because of increased physical activity which followed from improved psychosocial functioning.

6. Discussion

Developing effective interventions to counteract the inactivity and weight gain associated with aging would be enhanced by a broader understanding of how aging may influence psychosocial determinants of physical activity, how theoretical variables may mediate the effect of aging on physical activity and whether interventions targeting important psychosocial variables operate to improve activity levels and weight management as theorized in this population. Among a diverse sample of adults ages 40–92 enrolling in a health promotion study, physical activity declined with age, as did self-efficacy and positive expectations for physical activity. Older participants were less confident in their abilities to overcome barriers to physical activity and to incorporate exercise into their daily routine. On the other hand, with age participants were more likely to experience social support for being physically active, were less likely to anticipate negative outcomes resulting from increased PA, and were more likely to plan, set goals, and to fit exercise into their daily schedules. For weight-challenged, inactive adults over 40, outcomes from a successful SCT-based intervention suggest that increasing self-efficacy is an effective mechanism for increasing physical activity and associated weight management.

The present study incorporated demographic, social cognitive and physical activity variables in a series of latent-variable theoretical models to examine first, the determinants of physical activity in a diverse group of 703 adults ages 40–92 recruited as part of the health promotion GTH study and second, the function of theoretical variables in the SCT-based intervention's effects on physical activity and weight change among the subgroup of over-40, weight-challenged inactive participants completing the GTH intervention (n = 204). The sample was racially and socioeconomically diverse and had body composition and activity levels similar to national samples [30, 31]. Structural modeling analysis indicated the theoretical model specifications provided good fit to the data explaining 18% of physical activity at baseline, 82% of physical activity change and 5% of weight change at 16 months.

Age was the strongest predictor of baseline physical activity—as aging progressed in the sample participants took fewer steps and walked fewer minutes per day. Age also affected important social cognitive variables shown to contribute to physical activity in older populations [1–5]. Consistent with declining activity, self-efficacy for being more active decreased with age. Participants in the *60s+*-group reported less confidence in overcoming social, emotional and physical barriers to exercise and in meeting goals of increased exercise than younger participants. Despite declining physical activity and self-efficacy, social support for physical activity increased with age; participants 60s and above, were more likely to perceive their families as doing the things necessary to remain physically fit than participants in their 40s or 50s. Similarly, engaging in self-regulatory behaviors increased with age; participants over 60 were more

likely to plan and keep track of physical activity and more likely to work physical activity into their daily routines than participants in their 40s.

This pattern of age-related effects suggests that even as behavior and self-efficacy decline, supportive environments and increased self-regulation among the aging may present avenues for effective physical activity interventions. Social support has been shown in the current and previous studies with older adults [1] to influence physical activity largely by improving individuals' self-efficacy and use of self-regulatory behaviors indicating effective physical activity treatments should access and enhance aging adults' existing social environments. Similarly, the current findings suggest the self-regulatory behaviors that may be important to physical activity in older adults specifically [1] may become more feasible and acceptable with age. The key issue in efforts to increase physical activity and reduce concomitant health problems among the aging, however, will be to address potential age-related deterioration of physical activity self-efficacy. Self-efficacy in current and previous studies [1, 2, 5] has been found to be important to physical activity in older populations; older adults with higher self-efficacy were more active. Thus, interventions counteracting age-related declines in self-efficacy, primarily through enhanced social support, could be expected to help older adults maintain healthier levels of physical activity and avoid related health issues.

Outcomes associated with the GTH intervention (delivered with and without social supports) among inactive and overweight or obese adults over 40 suggest that unlike previous interventions with weaker outcomes for older participants (i.e., >65 years, 32), the GTH was successful with aging participants regardless of age. Using the GTH program led to greater increases in physical activity and to greater weight loss 16 months after program initiation among weight-challenged, inactive participants over 40. Increased physical activity was a strong predictor of weight loss. Treatment outcomes did not vary by race, but men in the sample made greater changes in physical activity than women even though women made significant changes in social support and positive outcome expectations as a result of the intervention. Physical activity at 16 months was influenced by GTH in part because it led to earlier increases in users' self-efficacy for becoming more active. Although the GTH also increased use of self-regulatory behavior at 7 months among the weight-challenged, inactive, aging adults, these changes did not significantly influence their physical activity levels nine months later. The GTH intervention increased self-efficacy directly rather than through increased social support. Participants' social support was targeted in the intervention through strategies for involving others in their physical activity programs (e.g., find a walking partner, ask family member to remind you of your walking goals) and through church-based social supports in one study condition, but social support remained unchanged at 7 months. The mastery experiences provided by GTH (increasing physical activity gradually over time, providing positive feedback for change, modifying goals in light of achievements) led directly to users' increased confidence in their abilities to be more active and ultimately to their improved physical activity levels.

Strengths of this study include a verified physical activity measure, a large diverse sample of adults, and the use of SEM. The study has several limitations. First, although large, the sample composition presents two challenges—the high rate of church attendance by participants and the expressed interest in changing health behaviors is not typical of most adults such that the models will need to be verified in a more representative population. Second, the racial and gender differences observed among the participants in psychosocial and physical activity variables suggest differences in how SCT may operate among aging African American and White adults and among aging men and women. The current sample size (162 African American participants at baseline, 62 men at the 16 month followup) could not support the multigroup analyses that could isolate these differences. Finally, the role of outcome expectations as delimited by SCT and defined in the current study was ambiguous as noted in previous research [32]. Although PA, decreased with age, participants were less likely to expect that, PA would interfere with their daily routines or their social obligations. Decreased negative outcome expectations did not, however, enhance PA levels. Granted that SCT suggests outcome expectations might not contribute beyond self-efficacy to behaviors like PA where the behavior is the desired outcome [9], some would suggest that as individuals assess their self-efficacy for PA they necessarily take expected outcomes into account. Older adults who fear injury or who expect to be embarrassed by their reduced physical capacities, for example, will have less confidence in their abilities to be active [33].

Despite these limitations, this study suggests declining physical activity levels in aging adults stem in part from deteriorating self-efficacy for being active despite the supportive social environments and increased self-regulatory vigilance associated with age. The outcomes of the GTH trial suggest that for aging adults suffering from inactivity and weight challenges, SCT-based interventions can effectively increase self-efficacy and self-regulation behavior, leading to increased physical activity and better weight management.

Acknowledgments

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Research Article

Long-Term Changes in Physical Activity Following a One-Year Home-Based Physical Activity Counseling Program in Older Adults with Multiple Morbidities

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This study assessed the sustained effect of a physical activity (PA) counseling intervention on PA one year after intervention, predictors of sustained PA participation, and three classes of post-intervention PA trajectories (improvers, maintainers, and decliners) in 238 older Veterans. Declines in minutes of PA from 12 to 24 months were observed for both the treatment and control arms of the study. PA at 12 months was the strongest predictor of post-intervention changes in PA. To our surprise, those who took up the intervention and increased PA levels the most, had significant declines in post-intervention PA. Analysis of the three post-intervention PA trajectories demonstrated that the maintenance group actually reflected a group of nonresponders to the intervention who had more comorbidities, lower self-efficacy, and worse physical function than the improvers or decliners. Results suggest that behavioral counseling/support must be ongoing to promote maintenance. Strategies to promote PA appropriately to subgroups of individuals are needed.

1. Introduction

The number of studies targeting physical activity (PA) behavior in older adults has increased markedly over the past decade. Such studies have largely been effective at increasing PA among older adult participants, and have demonstrated comparable results across home-based and center-based formats [1, 2]. Relatively little is known about the extent to which intervention effects are maintained over the long term, although results from previous research suggest that recidivism upon cessation of intervention is a reality across a variety of populations and behaviors [1, 3–8]. While studies examining adherence at shorter time points (e.g., 6 months) are more common, long-term followups in older adults remain sparse [9]. As a result, strategies to foster PA adherence over the long term in an aging population remain to be identified. To date, much of the research surrounding PA has focused on identifying strategies to increase adoption.

While the evidence supporting the beneficial effects of a physically active lifestyle on chronic disease management is vast [10], similar to pharmacologic therapies, the benefits of PA are directly proportional to adherence rates. Thus, behavioral researchers and public health officials must now also consider the challenge of developing effective strategies to facilitate PA maintenance.

In addition to post-intervention trends, studies on the individual characteristics that determine long-term patterns of adherence are needed. Previous research suggests that psychosocial factors and previous PA behavior are significantly associated with higher PA levels in older adults [6, 7, 11, 12] However, the role of factors such as comorbidity, physical function, and physical performance in determining long-term PA maintenance or decline in older adults remains unclear. Thus, it is unclear whether there may be subgroups of individuals who respond differentially to the cessation of a behavioral intervention. Examining *how* PA levels change following an intervention and identifying the characteristics of those who benefit the most and least is a necessary and important precursor to developing targeted evidence-based programs that promote long-term activity adherence in older adults.

The Veterans LIFE study [13, 14] is a 12-month randomized controlled trial of PA telephone counseling (PAC) to increase PA in older veterans. One year after finishing the study, attempts were made to contact all participants to participate in followup data collection. The first aim of the study was to examine PA levels during a 12-month nonintervention period and determine the effect of participation in the intervention on post-intervention changes. The second aim was to examine behavioral and psychosocial predictors of PA during the post-intervention period. The third aim was to identify three classes of post-intervention PA trajectories: maintenance, gains, and losses and explore the behavioral, functional and psychosocial characteristics of these three groups.

2. Methods

A complete description of the Veterans LIFE study has been reported elsewhere [13]. In brief, this study was a randomized controlled trial comparing a 1-year multicomponent physical activity counseling (PAC) program with usual care (UC). The Durham Veterans Affairs Institutional Review Board reviewed and approved the research protocol, and written consent was obtained from all participants.

Participants in this study were older male patients followed at the Durham Veterans Affairs Medical Center (VAMC) primary care clinics. To participate, patients had to be 70 years of age or greater, able to walk a short distance without human assistance, not regularly participate in PA, not suffer from dementia or severe hearing/vision loss, and be free of serious or terminal medical conditions that would preclude safe engagement in PA.

398 patients were recruited to participate in a 12-month randomized, controlled PAC intervention. Participants were randomized to one of two groups at baseline: PAC ($n = 199$) or UC ($n = 199$). The PA objectives for the PAC group were to walk or perform lower extremity physical activity for 30 minutes or more on 5 or more days of the week and to perform 15 minutes of lower extremity strength training on 3 days each week. UC consisted of usual care received within the context of visits to primary care providers within the same time frame.

Guided by social cognitive theory [15] and the transtheoretical model of behavior change [16], the PAC consisted of baseline physical activity counseling, telephone counseling, endorsement of the study by the patient's primary care provider, automated telephone messaging from the primary care provider, and individualized progress reports. The PAC intervention components and CONSORT diagram illustrating participant flow across the 1-year life of the study have been discussed in detail elsewhere [13]. This study resulted in significant improvements in functional performance and PA in the PAC group but not the UC group [13].

To determine whether participation in the Veterans LIFE study resulted in sustained behavior change 12 months after intervention and identify factors that predict behavior change, attempts were made to recontact all participants one year after finishing the program to ask them to complete measures on-site at the Durham VAMC. Of the 199 men randomized to PAC, 177 completed the study and 123 gave consent for the followup assessment; resulting in a 70% followup response rate. Of the 199 men randomized to UC, 176 completed the study and 115 gave consent for the followup assessment; resulting in a 65% followup response rate. 116 individuals did not return for the 24-month followup data collection.

3. Measures

3.1. Physical Activity. We measured minutes of moderate-intensity *endurance* PA and minutes of moderate-intensity *strength* PA using the Community Healthy Activities Model Program for Seniors (CHAMPS) [17, 18]. The CHAMPS questionnaire assesses the duration of a range of physical activities from which moderate activities can be separated. Minutes of endurance PA were calculated as the sum of brisk walking, running/jogging, cycling/stationary cycle, and aerobic machine items from the CHAMPS. Minutes of strength PA were calculated as the sum of moderate/heavy weight lifting, light strength training, and general conditioning items from the CHAMPS.

3.2. Physical Performance. Rapid gait speed (meters/second) was assessed over two trials of an 8-foot walk test.

3.3. Self-Efficacy. Two items were used to assess self-efficacy separately for walking/endurance activities and strength training activities; the content of these items was created to be consistent with the Veterans LIFE study counseling. The first question asked participants, "How sure are you that you could walk or do another type of endurance exercise for 30 minutes or more on five or more days of the week? The 30 minutes do not have to be all at the same time." The second item asked, "How sure are you that you could do exercises for 15 minutes, three days a week, to make your

legs stronger?" Responses for these two items ranged from 1 (not at all confident) to 5 (extremely confident). A scale score was created by taking the average of the responses on the two items.

3.4. Comorbidities. Number of chronic conditions was assessed using the Older Americans Resources and Services survey (OARS) [19], which surveys 35 medical conditions.

3.5. Physical Function. Self-rated physical function was assessed using the physical function subscale of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) [20]. Scores range from 0–100, with higher scores reflecting better physical function.

4. Statistical Analysis

4.1. Aim 1: Intervention Effects on Post-Intervention Changes in PA. To measure the effect of the PAC intervention on activity levels one year after completion of the study, we compared the activity levels of those formerly in the PAC and UC groups. Differences in minutes of moderate-intensity endurance PA and minutes of moderate-intensity strength PA between the two groups were tested using ordinary least squares, adjusting for 0–12-month change, 12-month PA status, and age, race, education, and number of comorbidities all measured at baseline.

4.2. Aim 2: Behavioral and Psychosocial Predictors of Post-Intervention PA. The association of behavioral and psychosocial factors with post-intervention change in PA was assessed using multiple regression analysis. We identified behavioral and psychosocial factors that in the literature are associated with physical activity behavior change in older adults: PA (endurance and strength PA at Month 12), exercise self-efficacy (Month 12), self-reported physical function (Month 12), and rapid gait speed (Month 12). Two *a priori* regression models containing all five predictor factors were run; one with 12–24 month change in endurance PA as the outcome variable, and one with 12–24 month change in strength PA as the outcome variable. Each model controlled for age, education level, and number of comorbidities. Diagnostics of model fit were run on each model to assess collinearity.

4.3. Aim 3: Evaluating Three Classes of PA Trajectories in the PAC Group. We classified individuals from the PAC group as maintainers, improvers, or decliners based upon their changes in PA levels from 12 to 24 months. In creating these categories we were cognizant of two issues: (1) we wanted the "Improve" and "Decline" categories to capture changes in PA behavior that were sizeable and reflected a *purposeful* increase or decrease in effort, and (2) we wanted the "Maintenance" category to have a similar buffer to minimize the risk of categorizing individuals as improvers or maintainers who had not *substantively* changed their PA behavior after intervention. Thus, group membership was based on the change in moderate-intensity endurance and strength PA from Month 12 to Month 24 using the 12-month median value for each variable as the criterion.

The 12-month median value for endurance PA was 45 minutes. Thus, improvement in minutes of moderate-intensity *endurance* PA was defined as an increase greater than 45 minutes/week from 12 to 24 months, while decline was defined as any negative change greater than −45 minutes/week. Individuals were classified as maintainers when the change in endurance PA minutes from 12 to 24 months was less than or equal to ±45 minutes/week.

The 12-month median value for strength PA was 75 minutes. Thus, improvement in minutes of moderate-intensity *strength* PA was defined as an increase greater than 75 minutes/week from 12 to 24 months, while decline was defined as any negative change greater than −75 minutes/week. Individuals were classified as maintainers when the change in strength PA minutes from 12 to 24 months was less than or equal to ±75 minutes/week.

We also examined whether those who maintained, improved, or declined PA from 12 to 24 months differed significantly on the same behavioral and psychosocial factors identified in Section 4.2. We used a series of pairwise comparisons to determine whether meaningful differences in these characteristics existed between the three classes. As is commonly the case with exploratory analyses, caution is warranted when interpreting the pairwise comparisons as they do not correct for Type I error. We conducted all analyses using SAS Version 9.1 (SAS Inc., Cary, NC).

5. Results

Demographic characteristics have been reported previously [13]. To summarize, study participants were older men (M age = 77 years, Range = 70–92 years) of mixed educational backgrounds, with 26% receiving a college degree and 45% reporting a high school graduate equivalency or less. Study participants reported approximately five chronic conditions ($M \pm$ SD; 5.15 ± 2.44).

As mentioned previously, 30% of the PAC group and 35% of the UC group did not complete the followup data collection. Thus, to determine whether these response trends introduced any bias into our results, we first compared those who completed 24-month followup ($n = 238$) and those who did not ($n = 115$) on treatment arm, demographic characteristics (i.e., age, race, education level), number of comorbidities, minutes of endurance PA, minutes of strength PA, rapid gait speed, and physical function. The only significant differences ($P < .05$) between those lost to followup and those retained were on race and rapid gait speed. Those who completed data collection at Month 24 were more likely to be white and have a faster rapid gait speed than those who did not complete data collection at 24 months.

5.1. Intervention Effects on Post-Intervention Changes in PA. Among those study participants who completed assessments at 24 months, participants in the PAC group reported more minutes of moderate-intensity endurance PA and moderate-intensity strength PA per week at 12 months compared to

Table 1: Minutes of strength and endurance PA at 12 and 24 months by intervention group in participants who completed the 24-month followup.

	Minutes of Endurance PA 12 months	Minutes of Endurance PA 24 months	Minutes of Strength PA 12 months	Minutes of Strength PA 24 months	Adjusted Mean-Level Change of Endurance PA 12 to 24 Months	Adjusted Mean-Level Change of Strength PA 12 to 24 Months
PA Counseling ($n = 123$)	74.6 (10.3)	52.4 (9.2)	55.8 (5.5)	37.3 (6.1)	−10.4	−12.0
Usual Care ($n = 114$)	44.7 (10.7)	43.2 (9.6)	29.5 (5.7)	33.8 (6.3)	−14.3	−4.5

Values represent Means and Standard Errors.

the UC group (Table 1). As expected, after finishing the intervention, minutes of moderate-intensity endurance PA and minutes of moderate-intensity strength PA declined for both groups. Although the declines in endurance PA were greater among the PAC group, they did not differ significantly from those observed in the UC group ($\beta = 21.5$, $P = .22$); the decline in minutes of strength PA, however, was significantly greater in the PAC group ($\beta = 23.1$, $P = .01$). Despite these declines over the last 12 months, minutes of moderate-intensity endurance PA and minutes of moderate-intensity strength PA remained higher among those in the PAC group compared to the UC group.

5.2. Behavioral and Psychosocial Predictors of Post-Intervention PA. Results of the multiple regression analysis indicated that the predictor variables accounted for 51.6% of the variance in post-intervention change in *endurance* PA. Minutes of endurance PA at Month 12 ($\beta = -0.87$), minutes of strength PA at Month 12 ($\beta = 0.26$), self-efficacy ($\beta = 20.62$), physical function ($\beta = 0.96$), and rapid gait speed ($\beta = -47.82$) were all significant predictors of post-intervention change in endurance PA. Collinearity diagnostics indicated high levels of collinearity between 12-month endurance PA and 12–24-month endurance PA change. A subsequent regression model in which 12-month endurance PA was excluded as a predictor variable resulted in a much better fitting model. However, this model indicated no significant effects for any of the other factors and accounted for only 3.0% of the variance in post-intervention change in endurance PA; demonstrating that previous endurance PA is the most important determinant of post-intervention changes in endurance PA.

Relative to post-intervention change in *strength* PA, results of the multiple regression analysis indicated that the predictor variables accounted for 33.2% of the variation. Minutes of strength PA at Month 12 ($\beta = -0.59$), minutes of endurance PA at Month 12 ($\beta = 0.14$), and self-efficacy ($\beta = 11.81$) were all significant predictors of post-intervention change in endurance PA. Collinearity diagnostics indicated low levels of collinearity between 12-month strength PA and 12–24-month strength PA change. Although collinearity among model variables was low, we determined *a priori* to run parallel models for endurance and strength; testing a second regression model in which 12-month strength PA was excluded as a predictor variable. Although this model provided a much better fit, no significant effects for any of the other factors were observed and this model accounted for only 7.6% of the variance in post-intervention change in strength PA. These results demonstrate that previous strength PA is the most important determinant of post-intervention changes in strength PA.

5.3. Group Characteristics of Long-Term Maintenance, Improvement or Decline. Figure 1(a) shows the three classes for post-intervention changes in minutes of moderate-intensity endurance PA for the PAC group. Individuals who improved their minutes of endurance PA from 12 to 24 months ($n = 22$) had moderate rates of endurance PA at Month 12 ($M = 47.3$, SD = 62.8 minutes/week). Individuals who declined in minutes of endurance PA from 12 to 24 months ($n = 39$) had higher rates of endurance PA at Month 12 ($M = 178.4$, SD = 155.0 minutes/week). Individuals who maintained their minutes of endurance PA from 12 to 24 months ($n = 62$) had the lowest rates of endurance PA at Month 12 compared to the other categories ($M = 22.8$, SD = 67.9 minutes/week).

Figure 1(b) shows the three PA trajectories for post-intervention changes in minutes of moderate-intensity strength PA for the PAC group. Individuals who improved their minutes of strength PA from 12 to 24 months ($n = 16$) had moderate rates of strength PA at Month 12 ($M = 54.7$, SD = 59.4). Individuals who declined in minutes of strength PA from 12 to 24 months ($n = 38$) had higher rates of strength PA at Month 12 ($M = 101.8$, SD = 59.1). Individuals who maintained their minutes of strength PA from 12 to 24 months ($n = 69$) had the lowest rates of strength PA at Month 12 compared to the other categories ($M = 30.3$, SD= 33.9).

Characteristics of long-term maintenance, improvement or decline of minutes of moderate-intensity *endurance* PA are shown in Table 2. As expected, minutes of endurance PA at Month 12 was the most consistent discriminant of post-intervention changes in endurance PA. Specifically, the pairwise comparison analyses demonstrated that individuals who declined from 12 to 24 months had significantly ($P < .05$) greater levels of endurance PA to start with (at Month 12) compared to those in the improve and maintenance groups. In addition to 12-month endurance PA, minutes of strength PA, number of comorbidities, self-efficacy, and rapid gait speed at 12 months were also significantly different across the three groups (Ps $< .05$). However, these variables only significantly discriminated those in the maintenance group from the other two groups. Specifically, individuals

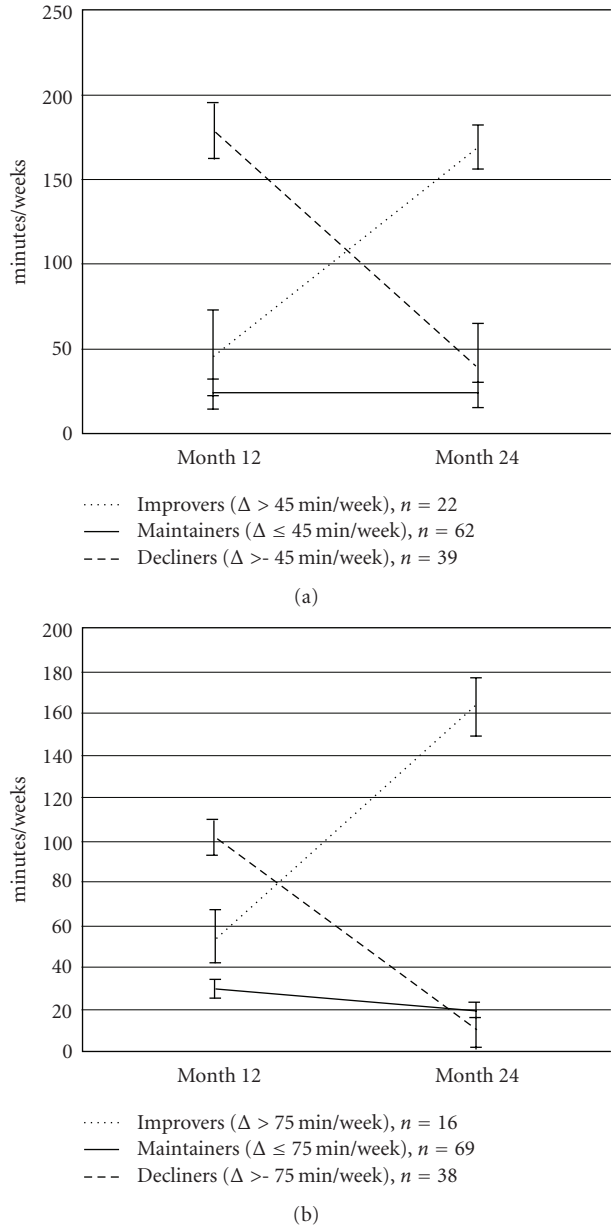

Figure 1: (a) Trajectories of post-intervention changes in minutes of moderate-intensity endurance PA. (b) Trajectories of post-intervention Changes in Minutes of Moderate-Intensity Strength PA (*Note* that values represent means and standard errors).

who maintained their minutes of endurance PA over the 12-month post-intervention period had the lowest rate of activity at 12 months, had more comorbidities, were less efficacious for physical activity, reported worse physical function, and had significantly slower gait speed compared to those in the improve or decline groups ($P < .05$).

Characteristics of long-term maintenance, improvement or decline of minutes of *strength* PA are shown in Table 3. As expected, minutes of strength PA at Month 12 was the most consistent discriminant of post-intervention changes in strength PA. Specifically, the pairwise comparison analyses demonstrate that individuals who declined from 12 to 24 months had significantly ($P < .05$) greater levels of strength PA to start with (at Month 12) compared to those in the improve or maintenance groups. In addition to 12-month strength PA, only self-efficacy at 12 months significantly differed across the three groups; with individuals who maintained their minutes of strength PA over the 12-month after intervention period being significantly less efficacious for physical activity compared to those in the improve or decline groups ($P < .05$).

6. Discussion

The literature is replete with research describing interventions aimed at improving PA; with many of these interventions using behavioral theory-based approaches to modify PA [21–25]. Although declines in PA can be expected following cessation of intervention, there is hope that some behavioral benefit from PA interventions can be sustained beyond the intervention period. In this study we sought to determine if there was any maintenance of PA following a year of no contact with former study participants. As expected, given the cessation of all study-related contact and resources, minutes of moderate-intensity endurance and strength PA among PAC participants decreased following the cessation of the home-based PA counseling program. However, despite these post-intervention declines in the PAC group, minutes of endurance PA and minutes of strength PA at Month 24 remained higher than baseline PA levels (data not shown). Moreover, PA rates in the PAC group remained higher than those in the UC group at 24 months, suggesting some long-term benefit of PA counseling on PA behavior compared to usual care.

Consistent with our expectations and previous reports in the literature, PA at 12 months was the single most important predictor of post-intervention change in activity levels. However, higher levels of PA at Month 12 were significantly associated with *decreases* in PA over the post-intervention period. These results suggest that altering behavior in the short term is not sufficient, in and of itself, to promote behavior maintenance. Indeed, upon cessation of the intervention and the resources and support associated with it, older adults who were successful in changing their behavior during the intervention were the most vulnerable to post-intervention declines. These results underscore the importance of on-going support following a behavioral intervention to improve maintenance and reduce the likelihood of regressing back to a sedentary lifestyle. Strategies to promote maintenance should be a systematic component of any behavioral intervention and warrant future study.

Self-efficacy, physical function, and gait speed also demonstrated significant effects on post-intervention changes in PA. However, PA at Month 12 accounted for a major portion of the variance in post-intervention change in PA, such that in the absence of the 12-month measure of PA, no significant effects were observed for any of these other candidate predictors. These results, coupled with the nonsignificant bivariate associations (data not shown) observed between post-intervention change in PA and

Table 2: Characteristics of maintenance, improvement, and decline from 12 to 24 months: minutes of moderate-intensity endurance PA.

Variable	Maintainers ($n = 62$) M (SD)	Improvers ($n = 22$) M (SD)	Decliners ($n = 39$) M (SD)	Improvers versus Maintainers P-value	Maintainers versus Decliners P-value	Improvers versus Decliners P-value
Weekly minutes of endurance PA	23.5 (63.8)	47.3 (62.8)	178.4 (155)	.35	<.0001*	<.0001*
Weekly minutes of strength PA	41.9 (59.6)	79.3 (47.4)	63.9 (50)	.01*	.05*	.29
Age	80.0 (4.7)	78.6 (5.1)	78.3 (4.4)	.26	.09	.79
Race						
White	45 (73%)	17 (77%)	23 (59%)	.32	.09	.15
Others	17 (27%)	5 (23%)	16 (41%)			
Education						
≤H.S. grad	26 (42%)	11 (50%)	16 (41%)			
Some college	17 (27%)	4 (18%)	15 (39%)	.82	.84	.97
≥College	19 (31%)	7 (32%)	8 (21%)			
Comorbidity	5.4 (2.5)	4.5 (2.2)	4.4 (2.4)	.14	.054	.92
Self-Efficacy	6.7 (2.2)	8.0 (1.4)	8.0 (1.6)	.01*	.0009*	.93
Physical function (SF-36)	62.3 (21.9)	75.7 (20.9)	80.0 (16.9)	.01*	<.0001*	.45
Gait velocity rapid m/s	1.61 (0.47)	1.89 (0.35)	1.89 (0.41)	.01*	<.01*	.96

All variables assessed at Month 12. *Significant at $P < .05$

any of the predictor variables (with the exception of PA at 12 months), suggest that these associations are not independent of PA at 12 months. That these pathways may be indirect is consistent with a social cognitive perspective in which behavior influences, and is influenced by, individual cognitions and abilities [15] and has been demonstrated in previous research with older adults [6, 7].

In an effort to better understand the individual variability following post-intervention behavior and develop tailored clinical interventions to promote physical activity, we conducted extensive exploratory analyses. Based upon their post-intervention changes in PA, individuals were categorized according to three trajectory classes: improvers, maintainers, or decliners. We chose these three groups *a priori*, knowing that recipients of the intervention increased PA during the intervention period [13] and expecting that recipients would fall into three categories during the nonintervention period: improvers, maintainers, or decliners. However, upon examination of the changes in PA during the intervention across the three groups (data not shown) we discovered that these group descriptors did not accurately reflect the trends in our data. Those who increased their minutes of PA *post-intervention* demonstrated small improvements *during* the intervention. In contrast, those who substantially *decreased* their minutes of PA post-intervention were those who had made the most gains *during* the intervention. To our surprise, those who maintained their minutes of PA post-intervention appear to not have taken to the intervention at all. Thus, it appears that in this study the individuals most likely to maintain their activity levels post-intervention were those who *abstained* from making any changes to their behavior at all over the course of an intervention and would be more accurately described as *nonresponders*. Despite this group comprising nearly 50% of the PAC arm, previous analyses report significant improvements in PA during the intervention [13]; underscoring the need for individual-level analyses to detect and characterize these underlying patterns of behavior.

In addition to characterizing the post-intervention change patterns in PA, we had hoped to identify characteristics that would differentiate those who improve, nonrespond/maintain, or decline in post-intervention PA; selecting factors that could be used in clinical care to identify individuals who may need additional support or booster shots (e.g., self-efficacy, physical function, and physical performance). In this sample of older adults, the nonresponders/maintainers had more comorbidities, lower self-efficacy to continue exercising, lower physical function, and slower gait speed than either the improvers or decliners. This pattern of results, together with the significantly lower level of PA at 12 months seen in the nonresponders/maintainers, suggests that the nonresponders/maintainers have physical, functional, and psychosocial disadvantages that make them even less likely to respond to an intervention that is largely home based and unsupervised.

In a previous PA clinical trial of individuals undergoing three months of supervised exercise followed by six months of home-based exercise, we observed significant improvements in fitness and physical function; largely driven by changes occurring during the supervised period. These

Table 3: Characteristics of maintenance, improvement, and decline from 12 to 24 months: minutes of moderate-intensity strength PA.

Variable	Maintainers ($n = 69$) M (SD)	Improvers ($n = 16$) M (SD)	Decliners ($n = 38$) M (SD)	Improvers versus Maintainers P-value	Maintainers versus Decliners P-value	Improvers versus Decliners P-value
Weekly minutes of endurance PA	65.5 (105.1)	113.4 (208.9)	82.2 (104.5)	.14	.05*	.92
Weekly minutes of strength PA	30.3 (33.9)	54.8 (59.4)	101.8 (59.1)	.06	<.0001*	<.01*
Age	79.5 (4.8)	79.0 (4.8)	78.7 (4.5)	.68	.36	.81
Race						
White	47 (68%)	11 (69%)	27 (71%)	.95	.79	.87
Others	22 (32%)	5 (31%)	11 (29%)			
Education						
≤H.S. grad	28 (41%)	6 (38%)	19 (50%)			
Some college	20 (29%)	4 (25%)	12 (32%)	.36	.15	.21
≥College	21 (30%)	6 (38%)	7 (18%)			
Comorbidity	5.0 (2.4)	4.6 (2.3)	5.0 (2.7)	.54	.98	.55
Self-Efficacy	6.9 (2.1)	8.4 (1.9)	7.7 (1.6)	<.01*	.04*	.20
Physical function (SF-36)	67.5 (23.3)	77.2 (17.6)	72.5 (19.8)	.11	.25	.47
Gait velocity rapid m/s	1.71 (0.50)	1.82 (0.25)	1.78 (0.43)	.42	.50	.77

All variables assessed at Month 12. *Significant at $P < .05$

improvements regressed upon transition to home-based exercise [26]. Subsequent analyses indicated that nonadherence to *home-based* PA could be traced back to low levels of PA during the *supervised* portion of the trial. Physical function, physical performance, comorbidity, and symptoms were also related to nonadherence in the home setting [27]. These studies, along with our results here, suggest that we can identify characteristics of individuals who may be poor candidates for home-based interventions and who require on-going support once an intervention has ended.

We expected that factors such as self-efficacy, physical function, and physical performance might distinguish between the improvers and the decliners. However, none of the variables examined proved fruitful. Instead, the differences between these two trajectories rest solely on initial (Month 12) PA levels. This may be due, in part, to the relatively small sample size in each group and concomitant lack of statistical power. These results have implications for future PA interventions, however, for they suggest that consistent with health promotion guidelines [3, 28], individuals who are active at high levels at the end of an intervention are in need of extended resources and support if these changes are to be sustained.

Our decision to classify participants as maintainers, decliners, or improvers in the manner that we did may be unique. Unlike other studies that have assessed success or failure to long-term PA adherence relative to meeting activity guidelines [3, 11, 29, 30], here, success was defined relative to the individual; thus taking into account individual limitations and barriers. Although our PA counseling was directed towards meeting national goals of 150 minutes per week or more of PA, we recognized that this goal was not achievable for many of our participants and endorse the call for older adults with comorbidities to be as physically active as they are able.

Our study has some limitations that must be considered when interpreting these results. First, although every attempt was made to collect 24-month followup data from all of the study participants, and thus minimize drop-out bias, we were unable to do so. However, we did attempt to address this limitation by examining the differences between those who completed measures at 24 months and those who declined participation at 24 months. These analyses suggest that our sample may be biased toward the more physically active and better functioning. However, no significant between-group differences were reported by treatment arm or on other dimensions of health status or self-reported physical function. Second, we recognize that one possible explanation for the pattern of PA change observed here may be attributed to regression to the mean. However, we believe that the significant effects of the intervention demonstrated previously in the PAC group [13] indicate recidivism following the end of an intervention, likely due to the removal of intervention supports and expectations, and not due to some random effect as implied by regression to the mean. Third, although we included variables that demonstrated significant associations with PA in previous studies [3, 7, 29, 31], we acknowledge that our models did not include other intrapersonal, interpersonal, or environmental factors which may influence behavior change.

Despite calls for more studies of long-term PA participation and maintenance [9, 29, 32], we have much to learn,

underscoring the difficulty in understanding (and altering) PA, a complex behavior. However, in this study we did identify a number of important factors which are related to changes in PA behavior over the long term. One of these factors, self-efficacy, is a modifiable construct and as such, is worthy of more investigation. Future studies of long-term maintenance that consider other variables such as environmental supports and barriers are needed. Importantly, our results also suggest that home-based PA may be of limited benefit to certain groups of lower functioning and highly sedentary older adults. Thus, similar to strategies to increase *adoption* and *maintenance* of PA, tailored approaches that target at-risk populations and accommodate individual, functional, and behavioral barriers may also be needed for *sustained* behavior change.

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Review Article

Aerobic Exercise and Whole-Body Vibration in Offsetting Bone Loss in Older Adults

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Osteoporosis and its associated fractures are common complications of aging and most strategies to prevent and/or treat bone loss focused on antiresorptive medications. However, aerobic exercise (AEX) and/or whole-body vibration (WBV) might have beneficial effect on bone mass and provide an alternative approach to increase or maintain bone mineral density (BMD) and reduce the risk of fractures. The purpose of this paper was to investigate the potential benefits of AEX and WBV on BMD in older population and discuss the possible mechanisms of action. Several online databases were utilized and based on the available literature the consensus is that both AEX and WBV may increase spine and femoral BMD in older adults. Therefore, AEX and WBV could serve as nonpharmacological and complementary approaches to increasing/maintaining BMD. However, it is uncertain if noted effects could be permanent and further studies are needed to investigate sustainability of either type of the exercise.

1. Introduction

Osteoporosis, a disorder characterized by the progressive loss of bone tissue and microarchitectural deterioration, remains a public health problem and reduces the quality of life for the aging population [1]. It has been estimated that with increasing age, bone mineral density (BMD) in women decreases 1-2% per year at the femoral neck and spine (excluding the influence of corticosteroid use) [2]. To date, the predominant medical strategies to prevent and/or treat postmenopausal bone loss have focused on antiresorptive medications (i.e., bisphosphonates). However, these treatments might be limited due to adverse side effects, questionable compliance, and long-term safety concerns [3]. Simple aerobic exercises (AEX) like walking, jogging, and running could provide an important role in maintaining and/or increasing bone density in women [4]. Therefore, implementing nonpharmacological treatments that have little or no inherent side effects (like exercise), either alone or in combination with pharmaceutical agents, is critical.

Although regular AEX may improve bone status and/or maintain bone mass preventing fractures [5], relatively vigorous aerobic, weight-bearing, or strength training regimens are even more effective [6]. However, in some cases vigorous exercise may increase the risk of injury, particularly in the elderly. Also, compliance to vigorous exercise is likely to be low in the older population. The published studies examining the positive role for AEX in relation to bone mineral density (BMD) are inconclusive. Several controlled intervention studies have shown positive effects on BMD [7], while others have yielded either mixed [8] or negative results [9]. These differences could be attributed to different study populations (young or old adults), the level of intensity tested (low or high), and/or kind of activities (running, jogging, etc.) employed. To narrow down the discussing realm for this review, we focus on the impact of organized aerobic activities performed on treadmill and other gym equipment, as well as running and/or walking, on BMD in older adults.

Whole-body vibration (WBV) or vibration training is a relatively new type of exercise in the "Wellness" industry. Previously used for astronauts, WBV has been reported to have the positive effect on BMD, similar to that of AEX in both animal [10, 11] and human [12, 13] studies. Some studies also compared the effect of WBV and resistance

training on muscle strength with positive results [14, 15]. Current WBV machines deliver vibrations at a frequency between 15 and 60 Hz. The resonance frequencies of the spine occur between 5 and 15 Hz [16] which are also the frequencies considered to be a causative factor in low back pain [17] and circulatory disorders like Raynaud's phenomenon [18]. However, WBV-related injuries (back pain, muscular discomfort, etc.) can be prevented by limiting the duration to a maximum of 10 minutes and maintaining the posture of the participant in a semisquat stance which involves the leg muscles reducing the transmission of vibrations to the head [19]. Therefore, WBV may be safer to apply and easier to comply with than AEX, particularly in a community setting. However, there is no consensus regarding the benefits, safety, and long-term application of WBV. To our knowledge, there is also no comparison of the effects of WBV and AEX on BMD in elderly. Therefore, the purpose of this paper was to evaluate and compare the effect of AEX and WBV on BMD at various skeletal sites in older population and to explain the possible mechanisms of their action on bone.

2. Methods

Papers on AEX and whole-body vibration published in English were searched using PubMed and MedLine (FirstSearch) databases. Combinations of the following phrases as keywords were used in the search "Aerobic exercise/whole-body vibration," "bone mineral density/content," "older women/female," "older men/male," and "running/walking/jumping" and would have to be present in the title, abstract, or keywords. AEX included treadmill walking, stepping exercise, and jumping. Studies with strength and resistance exercise were not included in this context. After excluding studies with vitamin D and calcium supplementation, or those involving subjects on medications and different chronic conditions, 17 studies were selected and are discussed in this paper for the effects of AEX. After excluding studies that examined WBV but focused on bone implants and those in which medications and other special treatment were used, 4 studies were selected and discussed in this paper. A snapshot of the relevant studies and their overall description is shown in Tables 1 and 2.

3. Effect of Aerobic Exercise on Bone in Older Population

3.1. Organized Aerobic Activities. Women entering menopause face many challenges regarding their bone health, especially those with a history of or current inactivity [37]. Therefore, engaging the elderly in exercise programs is necessary to maintain BMD and increase the quality of life. Most of resistance exercises have shown a positive effect on increasing or maintaining BMD in postmenopausal women [38, 39]. Whether AEX has the same effect is questionable. Results from a meta-analysis revealed that AEX maintained spine and significantly increased femoral neck BMD, suggesting that the femoral neck might be more responsive to high-impact AEX than the lumbar spine [40]. Welsh and Rutherford [33] found that 1-year AEX including high-load step and jumping significantly increased femoral neck and trochanter BMD in a group of previously sedentary men and postmenopausal women. In addition, Chien et al. [21] found that a 6-month AEX intervention, including graded treadmill-walking and stepping, significantly increased femoral neck, but not spine BMD in Chinese postmenopausal women. Even in the chronic stroke population, AEX maintained the femoral neck BMD, while a significant reduction in BMD was observed in controls [32]. These results suggest that AEX has positive impact on femoral neck BMD.

Confounding results still exist as some studies have shown that AEX did not enhance BMD in postmenopausal women [28, 30, 41]. These conflicting results were most likely due to insufficient intensity and frequency of exercise, small sample sizes, and the choice of measurement site employed in each study. The most frequently used duration and frequency of AEX were 30–60 minutes per session, 2-3 times a week. In a community exercise program, it was found that 1 year of AEX combined with strength training did not show an improvement in BMD at several skeletal sites in women aged 60 years and over [28]. Martin and Notelovitz [30] showed that 1 year of moderate AEX did not improve spine or forearm BMD due to inadequate sample sizes to detect small changes in bone. Other limitations were the low intensity of exercise and the lack of the involvement of upper extremities activities. Results from the meta-analysis showed that exercise did not improve femoral neck BMD in postmenopausal women [41] thought resistance training was included in their data analysis. The conflicting conclusion may be due to the combination of aerobic and resistance exercise in their data analysis and the different choice of measurement such as forearm or spine. If we only consider the effect of AEX on BMD, not including other kinds of exercises, AEX seems to increase femoral BMD in older adults.

3.2. Running and Walking. Some longitudinal studies examined the impact of running on BMD in older individuals. Although Wiswell et al. [34] found that 54 male runners aged 40 to 80 years maintained their hip and spine BMD over a 4- to 5-year running period by self-reporting training hours compared to their baseline measurements, the age range used may be too large to draw meaningful conclusions. A similar study revealed that runners exhibited a lower age-related bone loss compared to controls although both runners and controls had a significant decrease in spine BMD after a 5-year followup [31]. A 9-year longitudinal study following the running subjects showed that those who maintained their training volume lost less bone in the spine than those who did not maintain their running regimens [29]. These results demonstrate that running is beneficial to maintain the BMD for elderly. In contrast, Kirk et al. [26] found that postmenopausal runners tended to have lower spine BMD than age- and height-matched controls, indicating that running prevents hip BMD loss, but it may not maintain age-related reduction of spine BMD in older men and women.

Table 1: Snap-shot of the relevant studies* investigating the relationship of aerobic exercise and BMD of various skeletal sites.

Authors (reference)	Design/subjects	Bone measurements (BMD/BMC)	Results
Brook-Wavell et al. 1997 [20]	78 sedentary women were assigned to either brisk walking ($n = 38$) for 1 year or controls ($n = 40$)	DXA (Lunar DPX-L) (GE Medical Systems, Madison, WI) and McCue Ultrasonics (Winchester, UK)	Regular brisk walking for 1 year increased BMD significantly at calcaneus and almost significantly at the lumbar spine in postmenopausal women compared to controls
Chien et al. 2000 [21]	43 postmenopausal Chinese women were assigned to either treadmill walking or stepping exercise ($n = 23$) for 6-month and nonexercise controls ($n = 21$) for 2 years	DXA (XR-26 Mark II machine, Norland Corp., WI)	Femoral neck BMD was significantly increased in postmenopausal women on treadmill compared to controls
Ebrahim et al. 1997 [22]	98 postmenopausal women were randomly allocated to brisk walking ($n = 49$) or placebo group ($n = 48$)	DXA (Lunar DPX) (GE Medical Systems, Madison, WI)	Brisk walking for 2 years had less femoral neck BMD loss than placebo groups
Hatori et al. 1993 [8]	33 postmenopausal women were randomly assigned to 12 controls ($n = 12$), moderate intensity walking ($n = 9$), and high-intensity walking group ($n = 12$) for 7 months	DXA (QDR-1000) (Hologic Inc., Bedford, MA)	7-month high-intensity walking attenuated bone loss at the lumbar spine in postmenopausal women
Ilich-Ernst et al. 2002 [23]	77 older Caucasian women were assessed for past physical activity and past and present walking	DXA (Lunar DPX-MD) (GE Medical Systems, Madison, WI)	Hip bone mass increased in subjects walking at a brisk or fast pace
Ilich and Brownbill 2008 [24]	97 postmenopausal women were compared regarding the walking pace (slow, fast, or brisk)	DXA (Lunar DPX-MD) (GE Medical Systems, Madison, WI)	A significantly higher femoral neck BMD/BMC at a brisk walking pace than a slow walking pace
Iwamoto et al. 2002 [25]	35 postmenopausal women were assigned to either brisk walking and gymnastic training ($n = 15$) or controls ($n = 20$) for 1 years	DXA (XR-26 or XR-36) (Norland, Fort Atkinson, WI)	One year of brisk walking combined with gymnastic training significantly increased the spine BMD
Kirk et al. 1989 [26]	Premenopausal runners ($n = 10$) and postmenopausal women ($n = 9$) runners and matched premenopausal sedentary controls ($n = 10$) and postmenopausal sedentary controls ($n = 9$)	QCT	Postmenopausal runners tended to have lower lumbar spine BMD than premenopausal women runners and age-matched controls
Krall and Dawson-Hughes 1994 [27]	237 healthy Caucasian women were assessed by questionnaire of current and historical participation in outdoor walking	DXA (Lunar DPX) (Lunar Corp., Madison, WI)	Women who walked more than 7.5 miles/week had higher whole body, leg, and trunk BMD than those who walked less than 1 mile/week
Lord et al. 1996 [28]	136 women were assigned to either AEX with strength training ($n = 66$) or control group ($n = 70$) for 42 weeks	DXA (Lunar DPX) (Lunar Corp., Madison, WI)	There was no difference in BMD at different sites
Lane et al. 1998 [29]	Runners ($n = 28$) and nonrunner controls ($n = 27$) were followed for 9 years	QCT	Runners lost less bone in the spine than controls
Martin and Notelovitz 1993 [30]	55 postmenopausal women were assigned to control ($n = 19$), 30-minute AEX ($n = 20$), or 45-minute AEX ($n = 16$) for 12 months	DXA	Moderate AEX did not improve lumbar or forearm BMD
Michel et al. 1992 [31]	Elder runners ($n = 14$) and matched controls ($n = 14$) were followed for 5 years	QCT (Quantitative GE 9800 CT)	Running reduced age-related bone loss both in women and men over 50 years of age
Pang et al. 2005 [32]	63 older people with chronic strokes were randomly assigned to exercise ($n = 32$) with fitness and mobility exercise program and control ($n = 31$) with a seated upper extremity program	DXA (QDR 4500) (Hologic Inc., Waltham, MA)	Exercise group maintained the femoral neck BMD, while a significant reduction in BMD was observed in controls

Table 1: Continued.

Authors (reference)	Design/subjects	Bone measurements (BMD/BMC)	Results
Welsh and Rutherford 1996 [33]	30 men and women were assigned to either high-impact AEX ($n = 15$) for 1-year or nonexercise controls ($n = 15$)	DXA (Lunar DPX-L) (Lunar Corp., Madison, WI)	Exerciser had significantly increased femoral neck BMD after 1-year training, while there were no observed changes in controls
Wiswell et al. 2002 [34]	54-old-male runners were intervened longitudinally over a 5- to 7-year period	DXA (QDR 1500) (Hologic, Inc., Bedford, MA)	Hip and spine BMD were maintained by a 4- to 5-year running period compared to their baseline measurement

DXA = dual energy X-ray absorptiometry, QCT = quantitative computed tomography.
*Reference no. [9] did not show a positive effect on bone and although it is discussed in the text, it is not presented in the table.

Table 2: Snap-shot of the relevant studies* investigating the relationship of whole-body vibration and BMD of various skeletal sites.

Authors (reference)	Design/subjects	Bone measurements (BMD/BMC)	Results
Gusi et al. 2006 [19]	28 postmenopausal women were randomly assigned to either WBV (12.6 Hz, $n = 14$) or walking group (an hour walking, $n = 14$) for 8 months	DXA (Norland Inc., Fort Atkinson, USA)	After 8 months, femoral neck BMD in the WBV group was increased by 4.3% compared to the walking group. There were no observed change at the lumbar spine and other sites of the hip between two groups
Rubin et al. 2004 [13]	24 postmenopausal women were randomly assigned to either WBV (30 Hz, $n = 12$) or placebo vibration devices ($n = 12$) for two 10 minutes per day for 6 months	DXA (QDR 2000) (Hologic, Waltham, MA, USA)	There was no difference between WBV and placebo group. Evaluating people with highest compliance, placebo lost 2.13% of BMD in the femoral neck but WBV group increased by 0.04%
Verschueren et al. 2004 [35]	70 were randomly assigned to WBV (35–40 Hz, $n = 25$), resistance training group ($n = 22$), or a control group ($n = 23$) for 6 months	DXA (QDR-4500A) (Hologic, Inc., Bedford, MA)	Total hip BMD in WBV group significantly increased by 1.51% compared to control group

DXA = dual energy X-ray absorptiometry.
*Reference no. [36] is discussed in the text, but it is not presented in the table as it is a one-subject study.

While these results did not demonstrate positive effect on spine, they are consistent with the mechanostat theory that the BMD of a lower limb, a primary weight-bearing site, benefits the most from running [42].

Ideally, running and walking could be an effective measure to prevent the loss of bone mass for the older population; however, compliance with moderate to intensive exercise is questionable. Low-intensity AEX such as walking has a lower impact force upon the skeleton compared to running; therefore, it might offer an inferior osteogenic stimulus. Walking as a physical activity may be beneficial for postmenopausal women as well as elderly population, but it may depend on walking speed, with brisk and fast pace being more advantageous [27]. Krall and Dawson-Hughes [27] examined the impact of current and past walking on BMD in 237 healthy Caucasian women (43–72 years) and found that women who walked more than 7.5 miles/week had higher whole body, leg, and trunk BMD compared to those who walked less than 1 mile/week. Furthermore, the number of miles walked per week during a 1-year period was positively correlated with the rate of BMD increase in the lower limbs. A recent meta-analysis reported that walking had favorable effects on hip, but not spine [43]. However, an earlier meta-analysis results showed that walking had a positive significant effect on spine but not on femoral BMD [44]. This contradiction is probably due to including the same groups of population twice in their analysis and the combination of other exercise modes with walking.

Based on the observational and intervention studies investigating the influence of different walking regimens on BMD [20, 23, 24], it was suggested that brisk and fast walking pace is more beneficial in specific skeletal sites, for example, foot and calcaneal bones [20]. Ilich-Ernst et al. [23] evaluated the effect of self-reported past and current walking routines (including normal, fast, and brisk pace) on BMD in older Caucasian women and found that both forearm and hip BMD were higher in the subjects that were able to walk at a brisk or fast pace. Similarly, in a 3-year evaluation of the effects of walking and other habitual physical activities (not necessarily aerobic) on BMD in postmenopausal women, Ilich and Brownbill [24] reported that walking at a faster pace, involvement in sports/recreational activities, and even participation in low-impact physical activities were essential in augmenting bone mass. In a randomized study, it was shown that one year of brisk walking significantly increased calcaneal BMD and slightly increased spine BMD, although not significantly [20]. Similarly, a 2-year brisk walking regimen significantly reduced loss of BMD at femoral neck,

but there was no difference at the spine BMD [22]. These results support walking as an effective method of increasing BMD and confirm that a brisk and fast walking pace may, in addition to femoral BMD, also benefit calcaneus and forearm BMD. However, most of the studies have been done in women while older men have been less investigated regarding the osteogenic response to walking and running.

There is a consensus that a combination of aerobic and anaerobic exercise is more effective in improving bone mass than either one alone [45]. One year of brisk walking combined with gymnastic training either increased or maintained the spine BMD in postmenopausal women [25]. Results from an earlier meta-analysis showed that walking with other AEXs significantly affected the BMD at spine, but not hip [46]. Bone mass increases or decreases in response to mechanical loading depending on whether the thresholds controlling bone formation and resorption have been reached [47]. A few studies have demonstrated the importance of walking intensity on BMD preservation in postmenopausal women. Hatori et al. [8] reported that 7 months of walking with an intensity above 110% of the heart rate at its anaerobic threshold attenuated bone loss in the spine of postmenopausal women, whereas walking at an intensity below 90% of the heart rate at its anaerobic threshold had no influence on BMD. Similarly, Borer et al. [48] confirmed that fast walking pace increased leg and total BMD in early postmenopausal women who were engaged in 15 weeks of walking. These studies demonstrate positive effect of walking intensity on BMD at different skeletal sites. The greater response to the higher intensity walking may be due to the elevated ground reaction forces that occur at a faster walking pace. A failure to show increase in spine BMD during a walking study by Cavanaugh and Cann [9] in 55-year-old postmenopausal women may be due to the employment of lower walking intensities. Therefore, a combination of different kinds of AEXs may be the most efficient approach to reach desired exercise intensity to enhance or maintain bone mass at different skeletal sites in postmenopausal women.

4. Possible Mechanism by Which Aerobic Exercise Affects Bone

It is generally accepted that mechanical loading on bones is probably one of the ways to induce skeleton's structural changes and increase bone mass. Physical activity induces a mechanical load on bone tissues due to external forces and muscle contractions, the latter exerting the greater force on bones than any other weight-associated gravitational forces. To withstand the rigor of various functional activities, bone tissue rapidly accommodates changes in its microenvironment [49]. Although the mechanism of mechanical loading effects on bone is not completely understood, it is postulated that it is due to the mechanotransduction of a load. This mechanotransduction is carried out through fluid flow near and between osteocytes (mature cells within the mineralized bone matrix) [50]. In vivo and in vitro studies indicate that mechanical stimuli increase strain, loading frequency, and fluid flow, all of which have an osteogenic effect [51]. However, several conditions must be met to affect bone positively: (1) the strain produced by loading must be of high enough magnitude to exceed the minimum effective strain (or threshold) [52]; (2) the strain should be applied in an intermittent fashion [51]; (3) loading should produce a "different from normal" strain distribution within the bone [51]. In addition, recent research implies that frequent loading on bone without rest may not allow sufficient time for osteocyte fluid flow to recover from inertial dumping between each load cycle. Therefore, fluid flow and subsequent osteocyte stimulation might be reduced or completely inhibited after the first loading cycle. If so, inserting short time periods between loadings will allow for recovery from the inertial dumping effect and facilitate osteocyte stimulation. This effect was recently shown in vivo, in both young and older animals and in two different species (avian and murine); by inserting 10 sec, rest period between each loading cycle greatly enhanced the osteogenic potential of the low-magnitude regimen [53].

While much emphasis is given to the resident bone cells (primarily osteocytes) and their response to the local load imposed on bone, new research implies that response to the mechanical load (exercise) may also be neuronally regulated and therefore systemic, with a resultant effect on multiple bones [54]. Sample et al. [54] showed that in young rats, intense mechanical stimulation of one limb can illicit a response in other limbs and even in the entire skeleton. This newest discovery may explain why increased BMD after localized mechanical stimulation could be recorded in skeletal sites that were not directly stimulated (e.g., increased forearm BMD with walking) [23].

5. The Effect of Whole-Body Vibration on Bone

WBV is a new approach that is currently being tested for its effect on BMD and bone strength [51, 55]. There are two main types of vibration devices/techniques: (a) up-and-down oscillating vibration plates and (b) reciprocating vertical displacements on the left and right sides of a fulcrum, providing the lateral oscillations. Rubin et al. [11, 51] observed an increase in bone formation in weight-bearing sites and a substantial increase in the quality and quantity of trabecular bone in sheep exposed to a low-intensity, high-frequency (20–50 Hz) mechanical stimuli [11]. It is well established that decreased estrogen due to ovariectomy in animal models decreases the bone formation rate resulting in a decrease in bone mass. In rats, Flieger et al. [56] found that low-level, high-frequency mechanical loading (50 Hz) was effective in preventing bone loss shortly after ovariectomy. Even in aging mice, low- and high-intensity WBV significantly increased mineralized bone surfaces [57]. This suggests that WBV may be a suitable bone-sparing therapy.

Bone is known to adapt to different loading conditions and the loading-induced strains are believed to be based on the adaptation of the bone tissue. For that reason, researchers usually administered frequencies at 15–35 Hz to obtain the maximum transmissibility of the mechanical loading

produced by the vibrating plate. While the adaptation to the mechanical loading is most likely the limiting factor, elderly subjects have been shown to benefit from simulated mechanical loading. Early-postmenopausal women who stood on a vertical plate of low magnitude (0.3 g) and high frequency (30 Hz), twice/day (10 minutes each) for a year, showed no difference in BMD compared with controls [13]. However, evaluating those with ≥80% compliance, controls lost 2.13% of bone mass in the femoral neck, whereas treatment group gained 0.04% over one year. When the analysis focused on the lower weight (<65 kg women, a known risk factor for osteoporosis) and those who were compliant, the benefit of treatment became significant and demonstrated a 3% and >2% positive difference at the spine and femoral neck BMD, respectively.

Any potential benefit of WBV strongly depends on compliance and vibration stimulus that can be varied in multiple ways (including type, magnitude, frequency, and duration), and different types of vibration loading are likely to result in different effects on BMD [58]. Low-level mechanical stimuli may be more effective in lighter than in heavier women, particularly for hip BMD. A recent meta-analysis (although published only as an abstract) also showed that low-intensity WBV effectively attenuated postmenopausal BMD decline in hip but not in spine [59]. Another study in postmenopausal women where intervention was employed on a vertical plate, higher magnitude (2.28–5.09 g), and high-frequency (35–40 Hz) for 6 months showed a significant 1.51% net increase in total hip BMD but not in total body or spine BMD [35]. A 5-month study examining an older man (79 years) employing multiple vibration intensities and frequencies to evaluate BMD showed detectable increase in spine, femoral neck, trochanter, and forearm BMD [36]. Though this study demonstrated positive results on BMD, only one participant was examined, therefore, the results cannot be representative of the larger group.

Gusi et al. [19] investigated whether WBV is more effective than walking for maintaining or increasing BMD. They compared the effect of walking and WBV using a reciprocating plate, low amplitude (3 mm), and medium frequency (12.6 Hz), for 8 months on BMD in postmenopausal women. After 8 months, femoral neck BMD was significantly (4.3%) higher in the WBV group than in the walking group. The difference in BMD at spine and other sites of the hip was not significant between two groups. The results suggest that the vibration could be an easier approach to increase BMD at the femoral neck than walking and could be applied to provide a surrogate for suppressed bone loss of hip after menopause. However, at the present time, it is too early to make a conclusion due to insufficient research in elderly adults and varied vibration protocols. Compliance to WBV in elderly population is another critical concern.

6. Possible Mechanism by Which Low-Intensity Whole-Body Vibration Affects Bone

Possible mechanism by which WBV affects bone may be based on the same principle as AEXs that activate the osteoblasts while reducing the activity of the osteoclasts. The strain, magnitude, and frequency are essential factors for the effect of WBV. WBV also increases the sensitivity of musculoskeletal systems to adapt to the mechanical stimulation. Controlled loading study has shown that high-strain magnitude and high-strain rate are the most osteogenic [60]. It has been hypothesized that mechanical stimulation recruits additional osteoblasts and increases the percentage of mineralizing surfaces therefore, increasing the rate of bone formation and decreasing the rate of bone resorption [60].

It has been suggested that the high-frequency vibration may have played an important role in the osteogenic effect. There is a general perception that signals must be large enough to elicit a positive influence on bone mass and morphology. However, the high-frequency stimulation may be capable of influencing skeletal architecture by distributing uniform stresses on bones [61]. Rubin et al. [62, 63] hypothesized that this influence may be achieved directly by mechanical strain, or indirectly through amplification of the signal by intramedullary pressure or fluid flow in bone tissue. The mechanism behind the frequency-dependent adaptive response of bone to stimuli might be the stochastic resonance. Stochastic resonance is a phenomenon in which mechanical noise (broad-band frequency of vibration) enhances the response of a nonlinear system to a weak signal by boosting it over a threshold. The stochastic threshold may be modified through a system such as neuromuscular feedback amplified by the low-level signal [64] or by stimulating skeletal muscle pump activity, resulting in significant effects on circulatory flows and fluid flow through the bone tissue. In addition, previous study has shown that stochastic resonance can enhance mechanosensitivity of different mechanoreceptors in the body, for example, muscle spindles [65]. These findings indicate that vibration stimulation employs multiple ways to influence bone mass and structure.

7. Conclusions

In summary, evaluation of the published literature provides evidence of the effectiveness of AEX and WBV in increasing or at least maintaining bone mass in the elderly. The mechanism could be due to increasing the circulation of fluid and activating the osteoblasts while reducing the activity of the osteoclasts via mechanical stimulation. The osteogenic effects of both AEX and WBV could be site specific (to the spine or hip), depending on the exercise load and the type of exercises. The beneficial effects on bone can be maintained for a longer time if the exercise continues—although the exercise may not maintain the age-related reduction of BMD in elderly. In addition, the risk of injuries or falls could be high and the compliance to AEX particularly in elderly low. Walking is an inexpensive, practical exercise associated with low injury rates and demonstrates high acceptability by elderly. For these reasons, walking could be an appropriate approach to prevent osteoporosis and maintain bone mass. However, there is evidence that the osteogenic effect of load bearing may decline with aging

[66], suggesting either a decrease in osteoblast activity or a desensitizing of osteocytes to mechanical stimuli. Therefore, alternative, more acceptable strategies with a lower risk of injury need to be explored.

WBV should be implemented in an environment where supervision could be provided. Vibration, with increased stresses on the bone, stimulates remodeling but may also decrease bone resorption. Studies show that it may increase femoral neck BMD in postmenopausal women and in lower-weight women, in addition to inhibiting bone loss after menopause. However, just a few studies have investigated the effect of WBV on BMD in older population and different protocols were employed in the studies. In addition, it is still unknown if these short-term effects of low-intensity WBV will persist or whether body will adapt (although the parameters can be constantly changed to account for adaptation). It is not known yet whether the benefits of WBV will disappear after the intervention is terminated, as it has been shown previously with other types of exercise [25]. The on-going "VIBES" trial investigated the effects of WBV on various bone and muscle parameters in postmenopausal women over a 2-year period [67], and results, when available, should provide more insight into the issue. This may shed further light on the mechanism by which WBV operates and may yield future areas of study. Overall, future studies are required to confirm these short-term findings and to investigate whether the long-term WBV and AEX still have positive effect on bone.

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Review Article

Relationship of Physical Performance with Body Composition and Bone Mineral Density in Individuals over 60 Years of Age: A Systematic Review

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The purpose of this review was to examine the relationship between physical performance and body composition measurements, including fat/muscle mass and bone mineral density (BMD) in individuals ≥60 years of age. Various measurements used to assess body composition, BMD, and physical performance (PP) were discussed as well. Medline/PubMed, CINAHL, and SCIE were used to identify articles. After limiting the search for age and kind of physical performance measures, 33 articles were evaluated. Higher fat mass was associated with poorer physical performance while higher muscle mass was a predictor of better physical performance, especially in the lower extremities. Additionally, evidence showed that higher muscle fat infiltration was a determinant of poorer physical performance. BMD was shown to be a good predictor of physical performance although the relationship was stronger in women than in men. Developing standardized methods for PP measurements could help in further investigation and conclusions of its relationship with body composition.

1. Introduction

The aging process is characterized by gradual declines in physical and cognitive functions. Some elderly become frail and experience a decline in muscle mass and strength, as well as functional disability. Preserving physical performance (PP) could secure independent living, which for older adults permits the satisfaction of being self-sustained and drastically reduces economic/health care costs. Studies have shown that functional disability increases dependence [1], risk of falls, cardiovascular diseases, mortality [2, 3], and overall health status of older individuals [1, 4]. In the United States, more than half of individuals >70 years have one or more functional disabilities and only one third of noninstitutionalized individuals >80 years are free of functional disabilities [5].

It is unclear whether the decline in PP can be explained by changes in body composition: fat mass, muscle mass, and/or bone mass (i.e., bone mineral density, BMD). In the older population, the changes in body composition, especially declines in muscle and bone mass, are challenging research topics with regard to PP. Several epidemiological studies have shown inconsistent results examining muscle, fat and/or bone mass predicting PP among older adults [6–10]. Visser et al. [9] reported that higher body fat was associated with functional disability in older Caucasian men and women and Woo et al. showed similar results in older Asian population. Other studies [11, 12] found that low fat-free mass is an independent predictor of functional disability. For example, Reid et al. [12] found that older adults with lower skeletal leg muscle mass were at higher risk for mobility disability. In the study with 1051 community dwelling Caucasian men and women, both lowest quartile of fat-free mass and highest quartile of fat mass were independent predictors of functional disability [6]. In addition, PP in older adults measured by handgrip strength was positively associated

with BMD in various skeletal sites [13, 14], suggesting that there might be positive association between BMD and PP in older adults.

The inconsistent findings regarding the relationship between PP and body composition (fat mass, muscle mass, and BMD) might be due to several reasons: (1) the relationship between muscle mass, fat mass, and/or BMD and PP may be the outcome of interaction between loss of bone and muscle mass [15–17]; (2) the decline of PP may be caused in large part by cognitive decline which is not always assessed; (3)third is the use of different measurements for the assessment of both PP and body composition [18].

The purpose of this review is to examine the relationship among PP and body composition measures of fat mass, muscle mass, and BMD in individuals ≥60 years of age. By examining the literature from clinical studies, several possibilities for explaining the relationship between body composition and PP are explored and discussed. Various measurements used to assess bone and body composition as well as PP measures are also discussed.

2. Methods

2.1. Literature Search. Three major electronic databases including Medline/PubMed, Cumulative Index of Nursing, and Allied Health (CINAHL) were used to search relevant literature using the combination of the following keywords: "body composition," "muscle," "body fat," "physical performance," "physical function," "functional performance", and "bone mineral density." Of 334 retrieved articles, those lacking any measured component of body composition/BMD and PP were excluded, leaving 130 articles. Within the body composition term, body fat and muscle mass were considered. The latter term was sometimes referred to as lean mass, fat-free mass, mineral-free lean mass, or skeletal muscle (depending on how it was described in the original article). Therefore, all four terms are used interchangeably in this review. Physical performaance was sometimes referred to as "functionality," "physical function," and/or "functional performance"— all expressions termed as PP in this review. In addition, only the most widely used PP measures, including sit-to-stand, walking speed, one-leg-stance, and handgrip strength, were examined. Only the studies in which subjects were ≥60 years were considered. If the range of age was not specified in the article, only studies where the average age of subjects was greater than 60 years by one standard deviation away from the mean were included. By limiting the search to human subjects aged ≥60 years, 33 articles were chosen and evaluated. Tables 1 and 2 summarize these studies grouped by similar findings.

2.2. Body Composition and PP Assessments. Measurements of body composition and BMD as well as definition of various PP measures and the ways they are assessed are described as follows.

2.2.1. Body Composition and BMD Measurements. There are several ways to evaluate body composition, including anthropometric measures, underwater weighing, skinfold thickness, or by using techniques such as bioelectrical impedance analysis (BIA), dual energy X-ray absorptiometry (DXA), computed tomography (CT), or magnetic resonance imaging (MRI). The *anthropometric measurements* are the most readily available and inexpensive methods. They include the use of body mass index (BMI, based on height and weight), waist circumference (WC), and waist-to-hip ratio (WHR). Since BMI is used for the assessment of overweight/obesity, and WC and WHR are good surrogate measures of abdominal fat [19], these measures are widely used in many studies [20, 21]. *Underwater weighing* is considered the gold standard for measuring body density and is based on the difference in densities between fat (less dense) and muscle (denser). *Skinfold thickness* could be easier and quicker to perform; however, they can yield inaccurate results and depend heavily on the skills of the individual who performs them. Because of difficulty and inaccuracies in performing underwater weighing and skinfolds, respectively, especially in the elderly, this review did not include the studies that utilized these two methods for body composition assessment.

Recently, other techniques such as *BIA* and *DXA* have become widely used. BIA and/or DXA can estimate/analyze the amount of fat and muscle mass in different body compartments, which gives more detailed information for body composition assessment. Although in some studies [16, 17] DXA produced higher estimates of fat mass compared to the underwater weighing, DXA is more precise than BIA [22], the latter depending heavily on the hydration status of subjects [15]. Other technologies, such as *CT* and *MRI* are also used to measure body composition at the subcompartmental level. CT has been widely used to measure muscle attenuation or intramuscular adiposity as a quantitative method to assess muscle quality. However, safety concerns have arisen regarding the use of CT because of the higher radiation and adverse reactions to contrast agents. Unlike CT, MRI does not utilize radiation; however, it has limited use on persons with implants and ancillary clinical devices such as pacemakers and defibrillators. Both CT and MRI are more expensive, not readily available and used less in research settings.

For the measurement of BMD, *DXA* is the method of choice due to its reliability and the only one used to diagnose osteoporosis [29]. In addition, *quantitative ultrasound bone densitometry (QUS)* is also widely used to assess bone health because of its low cost, easy transport, and radiation-free. Although studies have shown good predictability of fracture risk with QUS, the measurement is limited to the calcaneous region of bone, and it has been shown to be less precise than DXA. Overall, the studies reviewed herein utilized BIA, DXA, and CT to analyze body composition, and QUS and DXA for bone mineral density.

2.2.2. Physical Performance Measures and Assessment. To assess PP such as agility, mobility, and balance, several tasks have been developed including timed chair *sit-to-stand* (STS), *normal/brisk walking*, timed *up-and-go test* (TUGT),

Table 1: Summary of studies examining the relationship between physical performance (PP) and body composition.

Author, year	Participants	*N* (% of women)	Age (year) Mean (SD)	BMI[a] Mean (SD)	Body composition	Physical performance measure	Fat mass	Muscle mass
Fat mass and physical functionality								
Bohannon et al. 2005	Community dwelling women	104 (100)	74.9 (7.5)	28.1 (6.7)	BMI, WC, WHR	Timed STS Unilateral standing (OLS) 25-ft walk	Negative ($r = 0.221$ to 0.397 for STS and 25-FW; $r = -0.231$ to -0.233 for OLS)	N/A
Sharkey and Branch, 2004	Nutrition and Function Study (NAFS)	345 (81)	78.2 (8.4)	34.5% are obese (BMI $\geq$ 30)	BMI	SLEPS (OLS, walking speed, STS)	Negative	N/A
Jankowski et al. 2008	Women and men with low serum DHEA	109 (50)	69 (7)	27.2 (4.8)	BMI, DXA	CS-PFP	Negative (BMI, $r^2 = 0.50$; Fat index (kg/m^2), $r^2 = 0.52$)	NS
Bouchard et al. 2007	NuAge (Canada)	904 (48)	74 (4.1)	27.9 (4.6)	DXA	Walking speed, Balance (OLS)	Negative ($r^2 = 0.48$ with OLS; 0.57 with WS)	NS
Body fat, muscle mass and PP								
Woo et al. 2007	Community dwelling elderly living in Hong Kong	4000 (50)	65+	23.7 (3.3)	BMI, DXA	Walking speed, HGS	U-shape with BMI Negative with fat mass	Positive (ASM with HGS)
Estrada et al. 2007	Women receiving estrogen for osteoporosis for 2 years	189 (100)	67.5 (4.8)	24.4 (3.0)	DXA	Walking speed, OLS, STS, HGS	Negative (AFMI; $r = -0.30$ to -0.016, except HGS)	Positive (ASM of lower limb; $r = 0.18$ with WS; 0.21 with HGS)
Valentine et al. 2009	Community dwelling elderly	134 (63)	69.6 (5.4, F) 70.3 (4.7, M)	28.3 (4.6)	DXA	OLS, TUGT, walking speed	Negative ($r = 0.29$ to 0.38)	Positive (leg to total body ratio; $r = -0.29$ with TUGT, -0.041 with WS in women only)
Visser et al. 2000	Longitudinal Aging Study Amsterdam	449 (52)	75(F) 75.8(M)	26.9 (4.2)	DXA	WS, STS	N/A	Positive ($r = 0.202$)
Reid et al. 2008	Mobility limited community dwelling elderly living in Boston	57 (54)	74.2 (7)	28.9 (6.0)	DXA	SPPB score less than 7	NS	Positive (with 1 kg increase in muscle mass, OR = 0.47, CI [0.25, 0.91])
Newman et al. 2003	Health ABC study	2984 (52)	73.6 (2.9)	27.4 (4.8)	DXA	EPESE score less than 10	N/A	Positive (Sarcopenia, OR = 1.5, CI [1.1, 2.1])

Table 1: Continued.

Author, year	Participants	*N* (% of women)	Age (year) Mean (SD)	BMI[a] Mean (SD)	Body composition	Physical performance measure	Fat mass	Muscle mass
Muscle mass and handgrip strength								
Visser et al. 1998	Framingham Heart Study Cohort	753 (63)	78.2 (0.3)	26.8 (0.3)	DXA, WHR, WC	HGS	N/A	Positive
Payette et al. 1998	Quebec elderly women	30 (100)	81.5 (7.0)	26.0 (4.7)	BIA, BMI	HGS, TUGT	N/A	Positive ($r = 0.62$, HGS) NS (with TUGT)
Lee et al. 2007	Community dwelling elderly living in Hong Kong	4000 (50)	72.5 (5.2)	N/A	DXA	STS, HGS, Walking speed	N/A	Positive (ASMI with HGS; walking speed and STS in women only)
Rolland et al. 2003	EPIDOS study	1458 (100)	70+	25.1 (3.9)	DXA	HGS	N/A	Positive (ASM, $r = 0.24$)
Rolland et al. 2004	EPIDOS study	1458 (100)	70+	25.1 (3.9)	DXA	HGS	N/A	Positive in BMI less than 29
Pedersen et al. 2002	Dannish (Glostrup) community dwelling elderly	226 (47)	80	26.6 (4.5)	BMI, BIA	HGS, PPT	NS	Positive (HGS, $r = 0.40$ for men; 0.22 for women)
Taaffe et al. 2001	Health ABC Study	2619 (51)	73.6 (2.9)	27.1 (4.5)	DXA	HGS	No association ($r = 0.07$ with upper extremity; 0.08 with total)	Positive ($r = .39$ with upper extremity; .32 with total)
Muscle quality and PP								
Misic et al. 2007	Community dwelling elderly	55 (36/19)	69.3 (5.5)	28.7 (4.5)	DXA	Berg balance scale, Walking speed	Negative ($r = -0.35$ with BBS; -0.33 with WS)	NS (Lower extremity muscle mass)
Sipila and Suominen, 1994	Finnish former athletes (A) and controls (C)	33 (100)	73.7 (5.6, A) 73.6 (2.9, C)	N/A	BIA, CT	Walking speed	Negative ($r = -0.48$(A); -0.66 (C))	NS (muscle index)
Visser et al. 2002	Health ABC study	2979 (52)	70–79	27.3 (4.6)	CT (Midthigh)	LEP (walking speed and STS)	Negative (fat infiltration)	Positive
Hicks et al. 2005	Health ABC study (Pittsburg site only)	1527 (48)	70–79	27%	CT (Midthigh and trunk)	Health ABC PPB (STS, OLS, walking speed)	Negative (fat infiltration)	NS

[a] If the mean was not specified, number indicates % of BMI greater than 30; SD: standard deviation; STS: sit-to-stand; OLS: one-leg-stance; HGS: handgrip strength; ASM: appendicular skeletal muscle mass; N/A: not available, no data; NS: not significant.

one-leg stance (OLS), and *handgrip strength* measured with the hand dynamometer. The items including STS, TUGT, and OLS are appropriate to test lower extremity performance but they have to be used with caution in older adults due to possibilities of falls and injuries. Another problem with using these tasks is that many of them have a "ceiling" or "floor" effect. That is, depending on the subject's ability to perform the given task, the subject may max out or may be too weak or frail to be able to perform the task. At the same time, the test needs to be simple and precise. To prevent these problems, different instruments and procedures have been developed and validated to evaluate physical function in older adults. Table 3 presents the instruments and the respective tests for functional performance. For example, the continuous-scale physical-functional-performance (CS-PFP) test or items within the CS-PFP have been widely used to measure the physiological capacity of the elderly or individuals with chronic diseases [28, 30, 31].

Table 2: Summary of studies of the relationship between physical performance (PP) and bone mineral density (BMD).

Author, year	Participants	*N* (% of women)	Age (years, Mean (SD))	Weight (kg)[a] Mean (SD)	Height (cm)[a] Mean (SD)	BMD measure[b]	PP measures	Findings
Madsen et al. 2000	Community dwelling elderly	47 (100)	80.3 (7.0)	60.0 (11.3)	156 (6)	Leg, lumbar spine	Walking speed	NS
Foley et al. 1999	Community dwelling elderly	104 (70)	71.0 (5.3, F) 72.4 (4.0, M)	71.7 (15.8)	160.7 (4.6)	Femur	HGS	Weak ($r^2 = 0.06$)
Cauley et al. 2005	The Osteoporotic Fractures in Men Study (MrOS)	5995 (0)	73.7 (5.9)	83.1 (13.3)	174.1 (6.8)	Femur and lumbar	Walking speed, STS, and HGS	Positive (STS and HGS)NS (Walking speed)
Tang et al. 2007	Elderly living in veterans' home in Taiwan	368 (0)	78.8 (4.1)	62.9 (10.4)	162.6 (5.9)	Calcaneus bone with Soundscan	6-min walking distance	Positively graded association across the quartile
Sun et al. 2009	Community-dwelling elderly women in Japan (200)	200 (100)	65+	23.1 (3.2, BMI)		QUS	Usual and maximum walking speed	Positive ($r = 0.24$ with usual walking speed and .26 with maximum walking speed)
Taaffe et al. 2003	Health ABC study	3041 (52)	74.2 (7)	28.9 (6, BMI)		Femoral neck and trochanter	STS, 6-m walking speed and OLS	Positive (graded association)
Lindsey et al. 2005	Healthy postmenopausal women	116 (100)	68.3 (6.8)	67.9 ± 11.0	161.8 (6.5)	Femoral neck, hip and total	normal and brisk 8 m walking speed, normal step length, brisk step length, OLS, STS, and HGS	Positive (r^2 ranged from 0.19 to 0.38)
Taaffe et al. 2001	Health ABC Study	2619 (51)	73.6 (2.9)	27.1 (4.5, BMI)		Upper limb, lower limb, total	HGS	Positive ($r = 0.26$, 0.17 and 0.15 with upper limb BMD, lower limb BMD and total BMD resp.)
Orwoll et al. 1996	Study of Osteoporotic Fractures	5405 (100)	73.8 (5.3)	66.4 (12.5)	159.2 (6.0)	Distal radius and femoral neck	HGS	Positive
Kritz-Silverstein and Barrett-Conner, 1994	Postmenopausal Caucasian women aged 65 years and older living in Southern California	649 (100)	65+	N/A	N/A	Single-photon absorptiometry for upper limb and DXA for lumbar and spine	HGS	Positive (nondominant arms; r^2 ranged from 0.15 to 0.28)
Bauer et al. 1993	Nonblack women recruited from four clinical centers	9704 (100)	71.6 (5.3)	67.3 (12.6)	159 (6.0)	Distal radius from Osteoanalyzer	HGS	Positive (5 kg increase with 4.9% increase in distal radius bone mass (95% CI [4.1, 5.6])

Table 2: Continued.

Author, year	Participants	N (% of women)	Age (years, Mean (SD))	Weight (kg)[a] Mean (SD)	Height (cm)[a] Mean (SD)	BMD measure[b]	PP measures	Findings
Bevier et al. 1989	Healthy active men and women living in Palo Alto, California	91 (0)	70 (0.7)	70.1 (1.4)	165.8 (1.0)	Radius and lumbar	HGS	Positive ($r = 0.28$ to 0.42)
Kärkkäinen et al. 2009	606 Finnish elderly women	606 (100)	68.0 (1.8)	28.8 (4.7, BMI)		Hip and lumbar spine	OLS, HGS, Walking speed, STS	Positive (Hip BMD, r^2 ranged from 0.16 to 0.23; Lumbar BMD, $r^2 = 0.16$, $P < .05$ with OLS and HGS only)

SD: standard deviation; BMD: bone mineral density; M: male; F: female; STS: sit-to-stand; OLS: one-leg-stance; HGS: handgrip strength; N/A: not available, no data; NS: not significant.
[a]If there is no information on weight and height, BMI is noted instead.
[b]All BMDs were measured by DXA if not otherwise noted.

Table 3: Summary of instruments for physical performance (PP) tests.

Items	Sit-to-stand	Balance	Walking speed	Others
The short physical performance battery [23]	5 repetition	Tandem, semitandem, and side-by-side stands (10 seconds maximum)	4-meter	
The health, aging, and body composition study Physical Performance Battery [24]	5 repetition	Tandem, semitandem, and side-by-side stands (10 seconds maximum)	6-meter at usual walking speed and 6-meter narrow walk	
Summary lower-extremity performance scores [25]	5 repetition	Tandem, semi-tandem, and side-by-side stands (10 seconds maximum) Timed 360-degree turn (turning in a full circle), one to the right and one to the left	8-ft (~2.4-meter) walk	
United states Physical Performance Test [26, 27]	N/A	Timed 360-degree turn	Timed 4.8-meter walking	Writing a sentence, simulating eating, lifting a book above shoulder level, putting on and removing a lab coat and picking up a coin from the floor
Continuous-scale physical-functional-performance test [28]	5 domains: upper body strength, upper body flexibility, lower body strength, balance and coordination, and endurance			

References indicate the validation studies.
N/A: not available.

Another instrument, the United States Physical Performance Test (US PPT) [26, 32], is a functional ability test with seven or nine functional items. The test items simulate daily living activities and measure the time taken to perform them. Each item on a test is scored from 0 to 4 according to time required to perform, which yields a sum score ranging from 0 to 28 [1, 33].

Several test instruments for lower extremity performance are also available. The Short Physical Performance Battery (SPPB) [23] is focused on measuring lower extremity physical function. This tool was developed from the Iowa Established Populations for Epidemiologic Studies of the Elderly study and contains three categories: a balance test, a 4-meter walking speed test, and a timed chair sit-to-stand test for 5 repetitions. Each category has a 4-point maximum, with a total of 12 points possible with a higher score indicating less physical impairment [12, 34]. The Health, Aging, and Body Composition study (Health ABC) also developed the Health ABC Physical Performance Battery (PPB) to measure physical function in the elderly, which is modified from the lower extremity performance portion of the Established Populations for Epidemiologic Studies of the Elderly test [24]. The Summary Lower-Extremity Performance Scores (SLEPSs) introduced by Sharkey et al. [35] also emphasize examining lower-extremity performance. It has four categories including static and dynamic balance, usual walking

speed, and repeated chair sit-to-stand. The total possible score is 14, with higher score indicating better performance. It has been reported that the score distribution is highly skewed; thus it is recommended to construct three categories according to the total score as follows: worst performance (SLEPS: 0–4), intermediate performance (SLEPS: 5–9), and best performance (SLEPS: 10–14). Finally, the Berg Balance Scale (BBS) is especially designed to measure balance function in older adults and includes 14 items to measure dynamics of balance. Items are scored ranging from 0 (worst) to 4 (best), with a maximum attainable score of 56.

Handgrip strength has also been widely used in many studies [9–11, 13, 14, 36–48]. It primarily measures upper body appendicular muscle strength and is a good predictor of functional disability. Factors associated with muscle weakness measured by handgrip strength include decreased physical activity, lower body weight, poor nutritional status, and number of chronic diseases and medication use [42, 49–56]. Besides the functional disability, poor handgrip strength also predicts 5-year mortality in specific popula tions [57–60]. Thus, handgrip strength has frequently been used as a marker for overall muscle strength and health status for the elderly.

3. Results

3.1. Body Composition and Functionality

3.1.1. Overweight/Obesity and Functionality. Results from most studies [10, 38, 39, 61–64] indicate a negative relationship between fat mass and PP in older adults. Bohannon et al. [65] examined the relationship between adiposity and PP in 104 community-dwelling elderly (aged 60–90 years) women in Connecticut. STS, OLS, and a 25-foot walk were timed and used to test PP. In this study, PP had a significant negative association with anthropometries, showing that PP decreased as the adiposity measured by BMI, WC, and WHR increased. Sharkey and Branch [63] examined the relationship between SLEPS and BMI in The Nutrition and Function Study population including both men and women aged 78.2 ± 8.4 years. Based on their PP scores, subjects were divided into the following groups: worst performance (SLEPS 0–4), intermediate performance (SLEPS 5–9), and best performance (SLEPS 10–14). Obese individuals were two times more likely to be in the lower SLEPS performance (SLEPS 5–9) category than nonobese individuals after controlling for chronic health conditions, depression, and demographic characteristics (odds ratio (OR) = 1.99, (95% CI = 0.90, 4.42); $P < .05$).

Interesting results were observed in a study with 4000 community-dwelling adults 65 years and older in Hong Kong [10], showing a U-shaped (quadratic) relationship between BMI and PP where lower and upper extremity performances were assessed by measuring walking speed from a 6-meter-walking test and handgrip strength, respectively. As a result, the overweight group (defined by BMI 23 to 24.9 for Asian population) showed the highest handgrip strength, while both the underweight (BMI < 18.5) and obese II (BMI > 30) groups showed lower handgrip strength. Similar trends were seen in walking performance. The normal-weight group (BMI 18.5 to 22.9) needed a shorter time for a 6-meter walking compared to other BMI groups. Since both low or high fat mass increases the risk of mortality in the elderly, this quadratic trend emphasizes the influence of fat mass on functional limitation and suggests that underweight or overweight could be detrimental for PP in older adults.

Due to the limitation in using BMI as an assessment for body fat, other studies [10, 61, 62] have utilized DXA to quantify fat or muscle mass or have developed indices such as calculated fat index (fat mass (kg)/height $(m)^2$) and appendicular skeletal muscle index (ASMI, appendicular muscle mass (kg)/height $(m)^2$) to investigate different compartments of body composition. Considering both body fat and muscle mass, some studies support that adiposity/obesity but not muscle mass was a stronger determinant of PP in older adults. Jankowski et al. [62] examined fat and muscle mass by DXA and PP by the CS-PFP test in 109 community-dwelling healthy women and men aged 69 ± 7 years. After adjustment for age, the fat index showed a negative relationship with the CS-PFP test score ($r^2 = 0.52$, $P < .001$). In another model controlled for age and sex, BMI was a negative and significant predictor of CS-PFP test score ($r^2 = 0.50$, $P < .001$). Similarly, the NuAge (Nutrition as a Determinant of Successful Aging) study with 904 community-dwelling older adults aged 74.0 ± 4.1 years living in Québec, Canada, showed that a higher percentage of body fat measured by DXA showed shorter timed OLS in both men and women, even after controlling for age, physical activity, and number of self-reported diseases [61]. However, in both of the above studies [61, 62], the ASMI was not an explanatory factor of PP.

Overall, the above studies suggest that adiposity is a stronger determinant of PP than muscle mass in older community dwelling adults. Considering that fat mass index is used to normalize skeletal sizes and distinguish between sex differences, which BMI is not [62], the negative relationship between adiposity and PP is well explained when sex difference is accounted for. However, if fat weight is too high (in case of obesity), negative relationship with PP may occur.

Estrada et al. [39] investigated the relationship between both ASMI and appendicular fat mass index and PP in 189 healthy postmenopausal women (aged 67.5 ± 4.8 years) receiving estrogen for osteoporosis for 2 years. Fat and muscle mass was measured by DXA and adjusted for height to yield skeletal mass and fat mass indices of both lower and upper extremities. Interestingly, handgrip strength showed positive correlations with both ASMI of total and lower limb ($r = 0.21$ and 0.19, resp., $P < .05$). However, total and lower extremity fat indices were negatively correlated with all lower extremity PP tests including walking speed, OLS, and STS. Regarding body composition analyzed by DXA, the participants with lowest quartile of fat mass had the strongest handgrip strength and the fastest walking speed after adjusting for age, physical activity, and number of chronic diseases. This shows that each performance on PP test items is correlated with body composition of the particular site used for testing. Therefore, the study supported the association between physical function and appendicular

fat/muscle mass indicating that the relationship between PP and muscle mass could be site specific.

3.1.2. Muscle Mass and Physical Performance. Several studies [9, 11–13, 45–48, 56, 66] have determined that muscle rather than fat mass is significantly positively associated with PP measures. A study with mobility-limited community-dwelling older adults aged 74.2 ± 7 years showed that lower leg muscle mass was a significant predictor of PP, as measured by Short Physical Performance Battery (SPPB) [12]. Subjects who were able to gain 1kg of muscle mass had 47% less chance for having severe mobility impairment, as defined by an SPPB score less than 7 (after adjustment for number of medical diagnoses, physical activity level, total hip BMD, total leg muscle mass, and total body fat). Total percentage of body fat was not a significant determinant of SPPB scores.

In addition, gender might be another factor that determines the relationship between muscle mass and PP. A study by Visser et al. [56] examined the Longitudinal Aging Study Amsterdam cohort of 449 men and women aged 65 years and older. Lower extremity muscle mass measured by DXA was positively associated with lower extremity performance, as assessed by walking speed and STS, after adjusting for age and height, in men. The association between lower extremity muscle mass and lower extremity performance in women was positive after adjusting for BMI. A study by Valentine et al. [64] demonstrated that both lower extremity muscle mass (%) and body fat mass (%) were positively correlated with faster walking speed in women only. Therefore, not only muscle mass but also % body fat showed a stronger relationship with PP in women, compared to men. However in sarcopenic subjects, the association appeared to be opposite with reference to sex. Newman et al. [66] examined the PP in people with sarcopenia. In this study, sarcopenia was defined as ASMI at the lowest 20% of the distribution of study population in both men and women. The results showed that ASMI was the most significant factor correlated with PP measures examined with the Established Populations for Epidemiologic Studies of the Elderly (EPESE) test. After adjusting for age, race, other lifestyle factors, and physical activity, only male subjects who were classified as sarcopenic had 1.5 times more chance of having an EPESE score of less than 10 (CI = 1.1-2.1). Overall, muscle mass was a stronger determinant of lower extremity PP, particularly in men. In women, both higher muscle mass and lower body fat were positively associated with physical function.

3.1.3. Muscle Mass and Handgrip Strength. The positive relationship between muscle mass and PP has been shown more clearly when functionality was measured with handgrip strength [9–11, 13, 39, 45–48]. The results from the Framingham Heart Study with 753 men and women aged 72–95 years [9] showed that handgrip strength was positively correlated with total body and arm muscle mass measured by DXA after adjustment for age and height (Pearson's r ranged from 0.46 to 0.53, $P < .0001$). An even stronger relationship was shown in the study by Payette et al. [45] in which 30 community-dwelling elderly women (81.5 ± 7 years) were examined. In this study, muscle mass, determined by BIA, was positively correlated with handgrip strength but not with lower extremity performance measured by TUGT. Similar results were shown with an Asian population living in Hong Kong, where health aspects of 4000 community-dwelling elderly aged 72.5 ± 5.2 years were examined [11]. The relationship between muscle mass, measured by DXA, and PP measures including STS, handgrip strength, and walking speed was tested. Subjects were divided into groups based on the tertiles of ASMI. After adjusting for age, the highest tertile of ASMI had the strongest handgrip strength in both men and women compared to other groups. Other PP measures using lower extremities were similar across the tertiles of muscle mass in both women and men, suggesting that PP without direct measurement of muscle strength can be more easily explained by higher body fat rather than muscle mass, as supported by studies discussed above.

Additional studies support the notion that handgrip strength is positively correlated with appendicular muscle mass, especially for upper extremities. The EPIDOS (EPIDemiology of OSteoporosis) study with 1,458 French women aged 70 years or older [47] showed positive association between handgrip strength and appendicular muscle mass from four limbs measured by DXA. Rolland et al. [48] also reviewed this relationship by dividing the EPIDOS cohort according to BMI groups. Although there were no significant differences in handgrip strength among BMI groups, the correlation between appendicular skeletal muscle mass measured by DXA and handgrip strength in lean (BMI < 24) and normal-weight to overweight groups (BMI = 24–29 kg/m^2) was significantly positive ($P < .001$); however, the relationship became weaker (although still significant) in the overweight-obese group (BMI > 29 kg/m^2, $P < .05$). Similarly, Pedersen et al. [46] measured muscle strength including handgrip strength, United States Physical Performance Test (US PPT), and body composition using BIA in 226 older men and women between 70 and 75 years old living in Copenhagen, Denmark. The results showed that the muscle mass measured by BIA was positively correlated with handgrip strength in both men and women. Although the results showed a tendency for the group with BMI < 24 kg/m^2 to have the highest handgrip strength compared to other BMI groups, this tendency was not observed with US PPT. Body fat (%), which showed a strong correlation with BMI, was also not correlated with handgrip strength, indicating that only muscle mass was the explanatory factor for handgrip strength.

Studies also showed that there is site-specific relationship between handgrip strength and muscle mass, especially with upper extremity muscle mass. Taaffe et al. [13] examined the correlation between the handgrip strength and muscle or fat mass in 2,619 community dwelling elderly participating in the Health ABC study. It was found that upper extremity muscle mass had the strongest relationship with handgrip strength ($r = 0.39$), followed by total body muscle mass ($r = 0.32$, $P < .001$). Total body fat and upper extremity fat mass showed no association with handgrip strength. It seems that although handgrip strength has been widely used

to measure general health status and functional ability in the older adults, handgrip strength is more likely to represent upper extremity muscle mass, rather than muscle or fat mass in the total body.

3.1.4. Muscle Quality and Physical Performance. Misic et al. [67] examined balance with the Berg balance test and walking speed in 55 older adults aged 69.3 ± 5.5 years. After comparing with total body fat mass and lower extremity muscle mass measured by DXA, the Berg balance test score and walking speed were negatively correlated with total body fat mass but not lower extremity muscle mass ($P < .05$). However, they found that the most significant predictor for gait was muscle quality, explaining 29–42% of the variance. Sipila and Suominen [68] compared former female athletes ($n = 19$) and controls ($n = 14$) aged 66 to 85 years living in Finland to examine the relationship between walking speed and muscle and body composition measured by BIA and CT. Interestingly, walking speed was the only parameter that was significantly correlated with the relative proportion of fat in both groups ($r = -0.48$ and -0.66 for athletes and controls, resp., $P < .05$). The correlation between muscle index measured by CT and walking speed was not different for athletes and controls.

Composition of muscle has also been explored to measure muscle quality and investigate the relationship with PP in several studies. Higher muscle attenuation expressed as lower fat infiltration (less fat deposited within the muscle) measured by CT is often used as an indicator of better muscle quality. The researchers demonstrated that fat infiltration in muscle as a measure of muscle quality rather than muscle mass was a better predictor of muscle performance [69, 70]. Visser et al. [69] examined the composition of muscle using CT and its relationship to lower extremity performance score with the Health ABC cohort, including 2,979 participants aged 70 to 79 years. Among the Health ABC physical performance battery items, timed chair sit-to-stand test and walking speed were used to test lower extremity performance; each item is scored according to the quartiles of the Health ABC cohort (0 for the last quartile, 4 for the first quartile), less than 4 indicating poor lower extremity performance (LEP). They showed that both higher muscle mass and low fat infiltration as measured by DXA and CT, respectively, were associated with greater lower extremity performance. In other words, the participants who were in the highest tertile of muscle mass or the highest muscle attenuation (lowest fat filtration) had the greatest LEP test scores. In another study using only the Pittsburgh site of the Health ABC cohort consisting of 1,527 adults aged 70 to 79 years [70], higher fat infiltration in trunk muscle measured by CT was associated with lower test scores on lower extremity performance tests, including repeated chair sit-to-stand, OLS, and 6-meter walking speed. In this study, trunk and thigh muscle area were not significantly associated with PP in this population. However, either higher trunk or thigh fat infiltration was associated with poorer PP in lower extremities.

Although many studies support that muscle mass is a strong predictor of physical function in older adults, it is evident that lower fat infiltration in muscle, as a measure of muscle quality, could be also a good predictor of better PP. Since the role of infiltrated fat in muscle is still unknown, more studies are needed to investigate the effects of fat infiltration on PP.

3.2. Bone Mineral Density and Physical Performance. It is well established that PP is an independent predictor of the risk for falls and fractures [71, 72]. However, the relationship between PP and BMD is unclear, with conflicting conclusions from various research studies. With aging, loss of muscle and bone mass has significant implications on both physical function and health [18, 73–75].

Some studies support the notion that PP has weak or no association with BMD of various skeletal sites. A study with 47 older women (80.3 ± 7.0 years) who had previous hip fracture showed no association between walking speed and nonfractured leg and lumbar spine BMD [76]. Another study [40] with 104 community dwelling older adults investigated the relationship between femur BMD and handgrip strength, where a positive correlation was only observed in women ($r = 0.4$, $P < .001$), and not in men ($r = 0.27$, $P = .149$). There was also a significant correlation between body weight and handgrip strength in women ($r = 0.32$, $P = .006$); therefore, the latter was allometrically scaled with body weight to reduce the influence from other variables related to body dimension. Linear regression analyses showed that handgrip strength divided by body weight only explained 6% of variation in femur BMD, which was again shown only in the women. The Osteoporotic Fractures in Men Study [14] including 5,995 men aged 73.7 ± 5.9 years showed that only handgrip strength had a positive association with femoral and lumbar BMD measured by DXA. Accordingly, one standard deviation increase in handgrip strength (8.2 kg) showed significant increases in femoral and lumbar BMD (OR = 1.75[1.3, 2.2](%) and 1.74[1.3, 2.2](%), resp.) after adjustment for age, but these associations disappeared after adjusting for both age and weight (OR = 0.73[0.3, 1.2](%) and 1.05[0.6, 1.5](%), resp.). On the other hand, slower STS (3.3 seconds) was not associated with lower femoral and lumbar BMD (OR = $-0.05[-0.4, -0.5](\%)$, $-0.06[-0.5, -0.4](\%)$, resp.) in age-adjusted models, which appeared to be significant after adjusting for both age and weight ($-1.06[-1.5, -0.7](\%)$, $-0.85[-1.3, -0.4](\%)$, resp.). Walking speed however showed no association with BMD.

Conversely, other studies have shown positive associations between BMD of various skeletal sites and lower extremity PP measures [41, 77, 78]. Results of the study in 368 older men aged 78.8 ± 4.1 years living in a veterans' home in Taiwan [78] found that the calcaneus bone mass measured by Soundscan (quantitative ultrasound) expressed as broadband ultrasound attenuation was positively correlated with walking speed measured by a 6-minute walking distance. After adjusting for BMI, waist circumference, and hemoglobin level as a marker of nutritional adequacy and status, mean broadband ultrasound attenuation (BUA) values were significantly different among the groups, classified

according to the quartiles of 6-minute walking distance, showing that the lowest quartile had the shortest 6-minute walking distance. Similar trends were shown in the study with female subjects in Japan [77]. In this study which was conducted with 200 Japanese women 65 years and older, the relationship between walking parameters and bone health as measured by quantitative ultrasound bone densitometer expressed as stiffness index was examined. The results showed that higher stiffness index (SI) was positively correlated with faster usual and maximum walking speed. In multiple regression analysis with BMI, handgrip strength, and walking parameters, maximum walking speed had the strongest association with SI among women aged between 65 and 74 years. In the study with 606 Finnish older women aged 68.0 ± 1.8 years [41], hip BMD including femoral neck, trochanter, and total proximal femur and lumbar spine BMD were correlated with PP. After adjusting for age, BMI, hormone therapy use, years since menopause, smoking status, and use of oral glucocorticoids, multivariate linear regression analysis showed that the strongest relationship was between hip BMD and OLS, followed by handgrip strength and OLS. The relationship of spine BMD and both OLS and handgrip strength was weak but remained significant, however, not significant with walking speed or STS, separately.

The findings in previous studies that the PP related to a specific extremity is associated with bone mass of that same extremity are well supported. The results from the Study of Osteoporotic Fractures conducted in 5,405 older women of non-African origins aged 73.8 ± 5.3 years also showed that handgrip strength was positively associated with higher BMD of various skeletal sites, but particularly that of the forearm [44]. With an increase of 5 kg of handgrip strength, distal radius and femoral neck BMD increased by 3% and 1% after controlling for age and weight, respectively. Additionally, faster walking speed (0.2 m/s) was associated with an increase in 1% BMD of femoral neck, but not at other skeletal sites. Similarly, Lindsey et al. [43] conducted a study in 116 postmenopausal Caucasian women aged 68.3 ± 6.8 years examining the relationship between different skeletal sites and measures of functionality, including normal and brisk walking speed, step length, OLS, timed chair sit-to-stand test, and handgrip strength.

Results from multiple regression controlled for BMI, age of onset of menarche, total calcium intake, and total hours of physical activity showed that higher femoral neck, hip, and total BMD were significantly associated with faster walking speed, longer step length, and longer OLS time. On the other hand, stronger handgrip strength was significantly associated with all forearm BMD sites, but not with higher femoral neck BMD.

Notably, the relationship between handgrip strength and BMD of forearm was stronger than BMD of other skeletal sites in several studies. Another study with 2,619 community-dwelling older adults participating in the Health ABC study also investigated the correlation between handgrip strength and BMD of various skeletal sites [13]. Handgrip strength had the strongest positive correlation with upper limb BMD, followed by lower limb BMD or total and femoral neck BMD. Similarly, in another study [36] where bone mass was measured using an OsteoAnalyzer in 9,704 older women recruited from four clinical centers in the US, an increase in 5 kg of handgrip strength is correlated with a 3.5% increase in radius BMD (CI: 2.8, 4.3).

Other studies have examined handgrip strength from both hands, suggesting that nondominant handgrip strength could be a useful indicator to assess BMD. With 91 healthy active men and women living in Palo Alto, California, aged 70.0 ± 0.7 years [37], midradius and lumbar spine BMD were measured. In women, grip strength from both hands showed a significant relationship with spine and midradius BMD, especially BMD of the dominant hand. In men, only midradius BMD showed a significantly positive correlation with handgrip strength from both hands. On the other hand, in the study with 649 postmenopausal Caucasian women aged >65 years living in Southern California [42], handgrip strength from both the dominant and nondominant arm was examined in relation to BMD of upper limb, as measured by single-photon absorptiometry, and of spine and hip as measured by DXA. With dominant handgrip strength, BMD of the hip showed the strongest positive association followed by wrist and spine BMD after adjusting for potential covariates including age, BMI, thiazide use, smoking, regular exercise, arthritis, years since menopause, and estrogen use. With radius BMD, the positive trend was observed, but significance was not reached. However, with the nondominant handgrip strength, a positive association with BMD was observed for all skeletal sites measured, including hip, radius, wrist, and spine.

Notably, the study with the Health ABC study cohort including 3041 community-dwelling older adults [79] showed that the association between hip region BMD and PP was sex and race specific, with the strongest association in black women, followed by white women and men. In this study, ANCOVA results adjusted for age, study site, height, weight, medication (thiazides, corticosteroids, estrogen for women), smoking pack-years, and physical activity showed that the mean value of femoral neck and trochanter BMD was significantly different among groups classified according to the quartiles of performance measures including timed chair STS, 6-meter walking speed, and OLS. The graded associations between femoral neck and trochanter BMD and groups classified by all PP measures were significant among black women, showing a higher BMD with better PP ($P < .05$, except standing balance and femoral neck BMD; $P = .163$ for trend). In white women, there was a moderate trend observed between femoral neck BMD and STS only. In white and black men, there was graded association found in trochanter BMD among the groups based on STS quartiles, but the difference among the groups was not significant. Therefore, the conclusions drawn included that the association between BMD and PP measures was strongest in black women, followed by white women and men. Since the analyses already included physical activity, other factors like nutritional, hormonal, or environmental could be considered to further explain the differences under the genetic basis among races.

4. Discussion

In general, studies have shown that an increase in fat or decrease in muscle mass causes greater functional disability and lower PP. While muscle and fat mass have been considered an important factor of age-related decline in physical function, studies examining the relationship between fat/muscle mass and functionality have shown inconsistent results. Higher bone mineral density has tendency to correlate with better PP, although some studies showed that relationships depended on sex, race, and body compartment. Lorenzo [18] summarized several explanations of this inconsistency. First, because loss of muscle mass is inevitable with aging but also can occur due to weight loss from illness in the later stages of life, muscle mass may not be a good predictor of PP. Second, even though muscle mass is a good predictor of a muscle strength, it might not be as good of a predictor of physical strength as is muscle quality. Only a few studies have used CT to measure fat infiltration in muscle as a measure of muscle quality. Even though most studies selected in this review used DXA to measure body composition, each study used different ways to normalize or control for the absolute values of fat and muscle mass, which leads to different interpretation of data. For example, some studies used a fat index while others used the percentage of fat. Muscle mass was also normalized in several ways with height of stature or the leg for lower extremity. Finally, as mentioned above, the use of different instruments measuring PP can result in different outcomes. Even though handgrip strength was shown to be a good measure of overall PP, some studies also support that handgrip strength is more correlated with strength, body composition, and BMD of the upper extremity [13, 40].

Most of the studies are cross-sectional; so no long-term effects of the change in PP in different body composition categories have been investigated. Although functional capacity is known to dramatically decline with aging, most studies showed the correlations between body composition and PP without considering age and gender differences. Chronic diseases such as arthritis, back pain, and age-related vision decline which could affect walking speed were not considered as confounders in most studies. In addition, most studies included community-dwelling older adults, predominantly Caucasian, only two studies included African-American population [56, 80], and few studies were conducted in Asian populations [10, 77, 78]. Community-dwelling older adults might be healthier and more active than those living in long-term care facilities or nursing homes. Also, different races have different body composition and body size, which also might explain the differences in BMD among the racial groupings.

In conclusion, most studies showed a positive relationship between muscle mass and PP, especially in the lower extremities which are crucial for the mobility of the elderly. However, more studies regarding the relationships among obesity, adiposity, and PP are warranted. BMD has also shown a positive correlation with PP, where stronger relationships have been shown in women than men. Although body composition changes with aging process in the opposite way, preserving muscle/bone mass and reducing excessive fat mass may be beneficial to keep PP and reduce functional disability in older adults. Standardized measurement such as the CS-PFP to predict PP for older populations needs to be incorporated into future studies to avoid a "ceiling" or "floor" effect. Validation studies of different measurements of PP across the age, sex, and race and establishing reference values of each item would be useful to identify the risk of physical disability in the later life and recommendation of weight management for older adults.

Abbreviations

AFMI:	Appendicular fat mass index
ASMI:	Appendicular skeletal muscle index
BBS:	Berg balance scale
BIA:	Bioelectrical impedance analysis
BMD:	Bone mineral density
BMI:	Body mass index
BUA:	Broadband ultrasound attenuation
CS-PFP:	Continuous-scale physical-functional-performance test
CT:	Computed tomography
DXA:	Dual energy X-ray absorptiometry
The Health ABC PPB:	The health, aging and body composition study physical performance battery
HGS:	Handgrip strength
LEP:	Lower extremity performance
MRI:	Magnetic resonance imaging
OLS:	One-leg stance
QUS:	Quantitative ultrasound bone densitometry
SI:	Stiffness index
SLEPS:	Summary lower-extremity performance scores
SPPB:	The short Physical Performance Battery
PP:	Physical performance
STS:	Sit-to-stand
TUGT:	Timed up-and-go test
US PPT:	United states Physical Performance Test
WC:	Waist circumference
WHR:	Waist-to-hip ratio.

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Review Article

Physical Activity and Hip Fracture Disability: A Review

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Objective. The present paper examines pertinent literature sources published in the peer-reviewed English language between 1980 and November 1, 2010 concerning hip fractures. The aim was to highlight potential intervention points to offset the risk of incurring a hip fracture and its attendant disability. *Methods*. An in-depth search of the literature using the key terms: disability, epidemiology, hip fracture, prevention, and risk factors was conducted, along with data from the author's research base detailing the disability associated with selected hip fracture cases. All articles that dealt with these key topics were reviewed, and relevant data were tabulated and analyzed. *Results*. Hip fractures remain an important but potentially preventable public health problem. Among the many related remediable risk factors, low physical activity levels are especially important. Related determinants of suboptimal neuromuscular function also contribute significantly to hip fracture disability. *Conclusion*. Physical activity participation can help to reduce the prevalence and excess disability of hip fractures and should be encouraged.

1. Background to the Problem

In spite of much research, hip fractures continue to pose a serious health care problem as far as health policy makers and public health care organizations are concerned. Indeed, despite some evidence of declining hip fracture prevalence rates (e.g., [1, 2]), hip fractures remain a persistent cause of excessive morbidity, reduced life quality, and premature mortality among older adults [3, 4]. In addition, because the observed reversal of the hip fracture secular trend may not apply universally [5], it is likely the annual incidence of hip fractures will increase, rather than decrease over the next few decades [6].

Moreover, since hip fracture prevalence increases exponentially with age [7], as populations age and longevity increases worldwide [8], these injuries are likely to occur at accelerated rates [9]. This is important, because among those who sustain a hip fracture injury and survive, an increasing number continue to experience various degrees of subsequent disability, including the onset of painful disabling hip joint osteoarthritis, a high risk for falls, and further hip fracture injury. As a result, escalating and excessive monetary costs of care for this debilitating injury [8], which includes disability costs, nursing care, rehabilitation care, and surgical costs are predicted as well.

The aforementioned likelihood of an increase, rather than a universal decrease in hip fracture prevalence rates, along with their immense social, physical, and economic costs has recently endorsed the idea that continued vigilance plus the implementation of effective preventive strategies against hip fracture are essential [3, 8]. However, what should be screened for, and what strategies for prevention should be implemented, is uncertain. Indeed, without a better understanding of why hip fractures occur, just how debilitating these injuries are, and how subsequent treatment of these injuries might be better targeted to reduce their complications and to restore optimal function to the affected individual, progress in this area is likely to be very limited.

To examine why hip fractures occur and what is needed to reduce their immense deleterious impact and improve long-term outcomes, this paper sought to examine what factors continue to account for the marked susceptibility of aging adults to hip fracture disability. The specific aim was to provide recommendations for preventing hip fractures

and their complications based on this information. To this end, all relevant full-length published studies in the English language detailing the epidemiology and possible causes of hip fractures in the published data base over the time periods 1980–2010 were examined. Specific emphasis was placed on identifying changeable factors that heighten the risk for hip fracture and hip fracture disability. As well, an attempt was made to highlight the impact of this condition. Finally, a tentative framework for improving preventive directives against first and second hip fractures was developed based on the available evidence.

2. Methods

To achieve the goals of this paper, the relevant literature was sought through an in-depth environmental scan of all English language studies published in the PUBMED, Medline, and CINAHL data bases between 1980 and November, 2010 on the aforementioned topics. The key search terms used were disability, epidemiology, hip fracture, prevention, and risk factors. All related articles that reported on hip fracture surgical procedures or pathological fractures were excluded from this report. To achieve the goal of this paper, which was to obtain a comprehensive understanding of the magnitude and severity of hip fracture injuries, all 5 levels of evidence, categorized as ranging from I to V, or from excellent to poor, as defined by the Oxford Centre for Evidence-Based Medicine in the United Kingdom, and used to denote the quality of a research study, were deemed acceptable. That is, the present paper examined all peer-reviewed research articles reporting pertinent topical data, regardless of design quality or methodology, and scrutinized these with respect to three themes, the scope of the problem or hip fracture epidemiology, the key risk factors for hip fracture and hip fracture disability, and the associated recommendations for preventing hip fracture disability.

In addition, to better understand the need to continue to examine and intervene upon changeable risk factors underpinning this debilitating condition, prospective data obtained as part of a larger study on hip fractures and knee muscle function were reviewed. Several related observations on hip fracture outcomes and potential explanatory factors for these were also reviewed and reported. No systematic review was attempted due to the vast range of issues and limited numbers of level I related studies, and no rehabilitation studies were analyzed directly.

3. Results

3.1. Epidemiological Trends and Scope of Problem. Despite declining hip fracture incidence rates in some locations [10–13], a vast body of diverse research since the 1980s has generally shown the age-adjusted incidence of hip fractures is increasing or likely to increase in the next few decades [14–25]. Also predicted to increase are related health care expenditures [8]. Hip fracture incidence rates are not static however, and may vary, as a result of seasonality, the relationship between the community and health care system and extent of comorbidities, among other factors [26].

Yet, regardless of variations in hip fracture incidence, there is general consensus that hip fractures remain a major cause of excess mortality and substantial disability [25, 27, 28] and nursing home use [27] and this involves enormous medical and rehabilitation costs annually [29, 30]. Further, given that most hip fracture patients are elderly, report more signs of diseases than controls [23], and suffer comorbidities [31] that pose a high risk for complications at high rates, the direct costs of a hip fracture could be at least threefold higher than those basic estimates previously mentioned [32]. Moreover, as well as the excess mortality from a hip fracture of between 10 and 20 percent [33, 34], of those who survive, half will have longstanding disability [35], short-term hospital care stays of high duration [36, 37], and will generally occupy 20 to 25 percent of all orthopedic beds [36]. In addition, rehabilitation in this condition is slow [38], especially in the older patient [38], and of survivors, only two-thirds will return home [39], while 19 to 27 percent will require long-term institutional care [40].

Of further importance in the context of minimizing hip fracture disability is data showing hip fracture cases are commonly susceptible to multiple hip fractures. That is, a second hip fracture, which may be in the same location as the initial fracture with a tendency to greater displacement or instability is found to occur about six percent of the time and within a three- [14] to four-year postfracture period [41]. Further, Dolk [42] predicts the frequency of sustaining two hip fractures over the course of an individual's lifetime could reach 20 percent. In addition, because new hip fractures may occur on the same side as well on the opposite side to an initial fracture, it may be possible to sustain three hip fractures over time. According to Schroder et al. [43], the risk of incurring a third hip fracture per 1000 men is 8.6 and 9.8 per 1000 women, per year.

As a result of the magnitude and severity of a single hip fracture injury and its consequences, several studies have attempted to identify factors associated with a high risk of suffering both a first as well as a second hip fracture [44–47]. In the author's own work, it has been apparent that hip fracture survivors may incur substantive years of disability and unwarranted debility (see Table 1), and this universal problem demands more be done to alleviate the widespread suffering and costs.

3.2. Risk Factors for Hip Fracture. Risk factors can generally be categorized as those that cannot be changed readily or are nonmodifiable and those that can potentially be changed or modified.

3.2.1. Nonmodifiable Factors. Chief nonchangeable factors that heighten susceptibility to hip fracture include age, gender, race or ethnicities, and geography.

Gender and Age. Among research concerning the relationship between hip fractures and age, evidence shows aging

Table 1: Selected cases with a hip fracture history, their body mass indices, and their disability levels, showing only 25% of cases are underweight [48].

Age	Gender	Fracture history	Functional status-2000	Body mass index	Subsequent surgical history
**67	F	Sustained Sept 1998, underwent surgery, but hardware was removed because of infection, Oct 1998.	Nonambulatory for 12 months and in severe pain.	25	After various treatments in 1999 to reduce infection, the total hip arthroplasty previously inserted was removed and reimplanted.
***70	F	Sustained L hip fracture 1990, and developed avascular necrosis requiring total hip replacement	Ambulated min distance with crutch or cane.	25	Started to have pain in 2000, which progressed and was diagnosed as due to a loose L total hip replacement that required revision.
75	F	Initially sustained R hip fracture 1995.	<1 block with cane.	27	Failed hemiarthroplasty required revision with total hip arthroplasty because arthroplasty had worn down cartilage. Hospitalized for 14 days, then sent to rehabilitation center.
76	F	Sustained fracture following fall 1990, required surgery, but developed problems requiring revision after 3 months.	Min distance with cane due to pain.	22	Total hip replacement had failed and required revision. After 5 days could walk a max distance of 70 foot with support and was discharged to a Rehabilitation Center.
***77 ** *	F	Sustained R hip fracture 1983 followed by surgery, and R total hip replacement in 1987, then had L hip surgery in 1999 following a fracture on L.	Unable to walk due to pain.	29	L total hip replacement had failed and required conversion to total hip replacement. After 6 days could walk approximately 50 foot with rolling walker and supervision and was discharged to a rehabilitation center.
*83	F	Initially sustained R femoral neck hip fracture 1999.	Wheel chair bound.	27	Initially improved after surgical reduction, then deteriorated to point where she could not walk and required a total hip arthroplasty. After 8 day could walk 25 foot with crutches and supervision and was discharged home with physical therapy.
***85 ** *	M	Initially sustained a R hip fracture 1999 after a fall.	Able to walk max of 1 block with walker.	30	Original hardware consisting of pinning of the original fracture site required removal and conversion to total hip replacement due to pain. Was hospitalized for 8 days then sent to rehabilitation center.
90	F	Sustained R hip fracture that was pinned April 2000, but experienced failure of pin 2 months later and underwent hemiarthroplasty.	Unable to walk.	21	Diagnosed as having a malpositioned R hemiarthroplasty with a greater trochanteric fracture requiring removal and replacement with a new total hip replacement. After 7 days could walk a min distance with a walker and was transferred to a Skilled Nursing Facility for rehabilitation.

* Also has prior history of hip fracture on opposite side.
** Evidence of strength deficit of affected leg.
*** Diabetes.

adults, especially women, are more highly susceptible to hip fractures as they age compared to men [49–51]. Indeed, by age 90, one in four women compared to one in eight men will probably sustain a hip fracture [39], despite an observed trend break for New Zealand women [52] and Swedish women [53]. In Korea, however, this trend differs and between 2001 and 2004 hip fracture rates for women increased 4.7 percent [54]. In addition, in China Shenyang Province and in Turkey, where men do heavy physical labor, the normal female/male hip fracture ratio was reversed [17, 55].

Moreover, for very old women and men, the same risk of hip fracture exists in these countries [56], suggesting adults of both genders are highly susceptible to hip fractures as they age.

Ethnicity and Geographic Location. In terms of ethnicity, hip fracture rates are said to be greater among whites than among nonwhite populations [57–59] although this gap seems to be narrowing [60]. However, considerable variation within the nonwhite populations exists [21, 61]. In addition, in recent years comparable rates of hip fracture among Kuwaiti females have been observed relative to some European countries and rates for males that were equal to those of white males in the United States [62], suggesting aging adults of all ethnicities may be susceptible to hip fractures.

In terms of geography, research conducted within the United States shows a north-to-south gradient in rates of both hip fracture types exists among women, while no clear pattern exists for men. Similarly, in central Norway, there is a lower incidence of hip fractures in subjects who live in rural areas compared to those that live in urban areas [63]. In Poland, however, where hip fracture rates are amongst the lowest in Europe, the incidence rate in the 50–65 year age group was 50 percent higher for women than men [64]. Thus, no predictable geographic pattern exists, so it remains difficult to envision precisely where one should focus primary prevention efforts.

Impaired Cognition. In addition to the aforementioned factors, another relatively unchangeable intrinsic factor that can heighten falls risk plus the advent of a hip fracture is the presence of irreversible cognitive impairments [65–74], which can slow central integration processes and heighten the potential for inappropriately delayed or weakened muscular responses [65]. As well, a prevailing cognitive impairment, along with a visual impairment [75] may impact the effectiveness of postoperative rehabilitation strategies [76], as well as functional recovery following a hip fracture [28], refracture rates [14]. It is thus crucially important in the context of preventing hip fractures to recognize and minimize cognitive declines that occur with age, such as depression [77], which increases the risk for hip fracture [78]. In this regard, recent research shows physical stimulation [79] and physical rehabilitation [80] can be quite useful.

3.2.2. Modifiable Factors

Bone Mineral Density. Since a hip fracture is the most devastating consequence of osteoporosis [78], bone mineral density is often the organ targeted in efforts to minimize hip fractures. Yet, while bone density measures at the femoral neck have been found to be strongly predictive of hip fractures in both men and women in some cases [81], other studies have found a considerable overlap in bone densities between hip fracture patients and age- and gender-matched controls after the age of 70, or no clear independent risk [82–85]. In addition, Wei et al. [86] found the effect of risk factors for hip fracture among community-dwelling ambulatory elderly to remain the same, regardless of femoral neck bone mineral density. It has also been observed that bone mineral density is a weaker predictor of intertrochanteric hip fractures than femoral neck fractures [87], that osteoporotic indices were comparable between cases and controls [88], and that hip fracture patients were not more osteopenic than age and gender-matched controls [89]. Moreover, Asians, who have similar or lower bone mineral densities than whites and partake in diets low in calcium, have a low incidence rate of hip fracture, especially in women [17]. Mathematical models too cannot account for the exponential rise in hip fractures with age solely on the basis of bone density levels [90]. Further, individuals with osteoarthritis and higher bone density levels than the norm are not protected against hip fractures [91], and low bone density itself is not likely to cause most hip fracture injuries, given that falls seem to precede these. Such findings strongly suggest factors other than having a low bone mineral density and peak bone mass may contribute to the risk of fracturing a hip, including the extent of long-term physical loading [28]. Thus, even if preventable, an examination of factors unrelated to bone mass must merit consideration in establishing the causes of hip fractures.

These factors include those that increase the risk for falling, the mode of falling, the property of the fall surface, the degree of soft tissue covering the bone, the use of ambulatory aids, the prevailing degree of agility, motor function, and muscle weakness [56, 85, 92–98] (see Table 2). A further factor that may specifically lead to osteoporosis as well as to increases in the propensity to fall and fracture a hip is the adoption of consistently low levels of physical activity participation [98] although the effects of physical activity on bone mineral density and bone quality may not be sufficient to completely eliminate fracture risk [99].

Falls Risk. As observed more than a decade ago by Apple and Hayes [109], over 90 percent of hip fractures are associated with falls. As a result, understanding the risk factors for falls has become paramount in attempts to reduce hip fracture rates among older adults who are highly susceptible to falls. Among these fall-related mediators are intrinsic factors such as balance impairments [50, 104, 106, 110], neuromuscular and musculoskeletal impairments [111, 112], aberrant falls-related biomechanical responses [30, 113], visual deficits, muscle weakness [110], and depression [104]. In addition, cognitive impairments [104] and fear of falling [114], a serious disorder in older people, also increase the risk for falling and fracturing the hip [72]. Falls may also ensue as a result of age-associated declines in postural instability while turning [115], unanticipated interactions with environmental objects [116], perception, proprioception, transient circulatory insufficiencies [117, 118], impaired sensory integration or motor functioning [119], and/or "conservative movement performance" that reduces postural stability [119]. As such, preventing falls is highly challenging among the older population, and while highly desirable, falls are extremely difficult to predict and target uniformly. However, while most falls prevention programs thus pursue a multipronged intervention approach, a very strong and consistent

Table 2: Selected findings spanning a 20-year period describing various intrinsic factors *other* than age and bone mass as potential hip fracture determinants and showing a high percentage implicate neuromuscular factors*. (Level evidence: I–V refers to study quality as outlined by the Oxford Centre for Evidence-Based Medicine.)

Author and year	Type evidence	Level evidence	Hip fracture determinants
Cummings and Nevitt, [90], 1989	Expert opinion	V	Neuromuscular dysfunction*
Cummings et al. [84], 1995	Prospective study	II	Poor vision, weakness*
Sihvonen et al. [100], 1994	Theoretical model	V	Prior falls, low body mass
Lauritzen [56], 1997	Review	III	Deficient soft tissue covering hip falls, poor protective responses*
Slemenda et al. [93], 1997	Review	III	Neuromuscular impairment*
			Fall mechanics
Dargent-Molina et al. [94], 1999	Prospective study	II	Walking speed, poor mobility*
Fitzpatrick et al. [88], 2001	Case control study	III	Factors related to falls*
			Health perceptions
			Low mental health score
Nguyen et al. [92], 2005	Prospective study	II	Postural instability, muscle weakness*
			Falls history, prior fracture
Mussolino [78], 2005	Prospective study	II	Depression
Rojanasthien and Luevitoonvechki [101], 2005	Prospective study	II	Comorbidities, prior fracture
Holmberg et al. [102], 2005	Prospective study	II	Diabetes, poor self-rated health
Wilson et al. [103], 2006	Prospective study	II	Poor physical function inability to lift 10 lbs*
Has et al. [104], 2006	Prospective study	II	Instability, muscle weakness*
Abrahamsen et al. [105], 2007	Case-control study	III	Prostate cancer and therapy
Kulmala et al. [106], 2007	Cross-sectional study	III	Balance confidence/function*
Robbins et al. [107], 2007	Observational study	III	Poor health, prior fracture, smoking, diabetes self-reported physical activity*
Looker and Mussolino [108], 2008	Cross sectional study	III	Vitamin D insufficiency
Sihvonen et al. [100], 2009	Cross sectional study	III	Postural instability*
Lang et al. [96], 2010	Cross sectional study	III	Reduced amount of lean tissue of thigh muscle*
Jokinen et al. [98], 2010	Prospective study	II	Low functional mobility*

determinant of most falls is clearly the degree of physical activity participation, as well as the type of activity, an aging adult adopts or neglects to adopt over time.

Physical Activity Participation. In terms of falls and hip fracture prevention approaches, a multitude of studies conducted over the past 30 years have consistently concluded that inactivity increases hip fracture risk among the elderly, while physical activity, which helps to maintain mobility, physical functioning, bone mineral density, joint flexibility, and muscle strength and balance can assist in preventing falls and fractures among the elderly [99]. Some of these studies are shown in Table 3 and all consistently imply low physical activity levels, must be considered a key determinant of hip fractures, regardless of whether the study is conducted using a case control or a prospective design, as outlined by Michaëlson et al. [120], Suriyawongpaisal et al. [121], Coupland et al. [122], Lyritis et al. [36], Wickham et al. [82], and others [123–125]. Indeed, Cooper et al. [83] found a low degree of physical activity participation doubled the risk of fracturing a hip, as did Kujala et al. [126] and Coupland et al. [122]. Importantly, these increases in risk remained even after adjusting for body mass index, smoking, alcohol consumption, and dependence in daily activities.

Interestingly, while simply increasing the hours of physical activity adults usually pursue per week can protect against the risk of hip fracture among community dwelling older adults [91], one of the reasons why low physical activity participation rates may heighten the risk for falling and fracturing a hip is due to its detrimental effect on vitamin D exposure [108], which in turn influences neuromuscular function adversely [92]. In addition, the lack of optimal load-bearing activities, which can influence bone quality quite detrimentally, may be the most salient explanatory factor for the increasingly high hip fracture rates reported by developing countries, as well as first-world countries [93], given our increasingly sedentary societies.

As well as increasing falls risk, a lack of adequate physical activity leading to poor muscle strength and endurance, coupled with aging, can hasten the onset and/or the progression

Table 3: Over 20-years of research evidence showing degree of physical activity participation is a consistent predictor of hip fracture risk in the context of cross-sectional (Level III), case control (Level III), systematic reviews and prospective (Level II) studies as categorized according to Oxford Centre for Evidence-Based Medicine quality criteria.

Authors and year	Study design	Finding
Lau et al. [13], 1999	Case-control study of 400 Chinese men and women with hip fractures and 800 controls.	Daily walking outdoors, upstairs, uphill, or with a load protected against sustaining a hip fracture, as did higher levels of reported activity in middle life.
Cooper et al. [83], 1988	Case control study of 300 elderly men and women with hip fracture and 600 controls matched for age and sex.	Daily general and weight bearing activity protected against sustaining a hip fracture.
Coupland et al. [122], 1993	Population based, case-control study of 197 patients older than 50 years with hip fracture and 382 controls matched by age and sex.	Customary physical inactivity increased the risk for sustaining a hip fracture in the elderly.
Grisso et al. [123], 1997	Case-control study of 34 hospitals and 356 men with first hip fracture and 402 control men matched for age and geographic location.	Physical activity was markedly protective against sustaining a hip fracture.
Kanis et al. [125], 1999	Case-control study of 730 European men with hip fracture and 1132 age-stratified controls followed prospectively.	Decreased physical activity and exposure to sunlight accounted for the highest attributable risks for sustaining a hip fracture among a number of different risk factors.
Farahmand et al. [127], 2000	Population based case-control study of 1,327 women with hip fracture and 3,262 randomly selected controls.	There was a protective effect against sustaining a hip fracture of recent leisure-associated physical activity.
Suriyawongpaisal et al. [121], 2001	Case-control study of 187 Thai men over 51 years of age with hip fracture and 177 age-matched community controls.	Physical activity was independently associated with reduced risk of sustaining a hip fracture after controlling for confounding factors.
Englund et al. [128], 2010	Nested case-control study investigating associations between bone markers, lifestyle, and osteoporotic fractures that identified 81 female hip fracture cases that had reported lifestyle data before they sustained their fracture. Each case was compared with two female controls identified from the same cohort and matched for age.	An active lifestyle in middle age seems to reduce the risk of future hip fracture.
Wickham et al. [82], 1989	15-year prospective study of 1,688 community dwelling subjects.	Physical activity participation protected against hip fracture.
Gregg et al. [124], 1998	Prospective study of 9,704 nonblack women 65 years of age or older.	Among older community-dwelling women, physical activity is associated with a reduced risk for sustaining a hip fracture.
Kujala et al. [126], 2000	Prospective study of 3,262 men, 44 years or older followed for 21 years, or from age 50 for subjects initially younger than 50 years.	There is an inverse association between baseline physical activity and future hip fracture risk among men.
Høidrup et al. [129], 2001	Prospective study of leisure-time physical activity levels and changes in relation to risk of hip fracture among 1,211 men and women with first hip fractures.	Moderate levels of physical activity appear to protect against later hip fracture. Declining physical activity over time is an important risk factor for hip fracture.
Devine et al. [130], 2004	A population based sample underwent bone mass measures and answered surveys about their nutrition and physical activity practices.	A high level of physical activity and calcium consumption was associated with a higher hip bone mineral density.
Feskanich et al. [131], 2002	Prospective study to assess the relationship of walking, leisure-time activity, and risk of hip fracture among 51,200 postmenopausal women.	Moderate levels of activity, including walking, are associated with substantially lower risk of hip fracture.
Morita et al. [132], 2005	157 women with hip fractures were followed between 1989–1993; 216 were followed between 199–2000.	For prevention of hip fractures it is important to improve physical function to void falls.
Michaelsson et al. [120], 2007	Longitudinal, population-based study of 2,205 men.	Regular sports activities can reduce the risk of hip fractures in older men by one third.
Moayyeri [99], 2008	Meta-analysis of 13 prospective cohort studies.	Moderate to vigorous physical activity is associated with a hip fracture risk reduction of 45% and 38% among men and women.

Table 3: Continued.

Authors and year	Study design	Finding
Cawthon et al. [133], 2008	Prospective study of performance on 5 physical function exams among 5902 men 65 years of age or older.	Poor physical performance was associated with an increased risk of sustaining a hip fracture.
Trimpou et al. [134], 2010	Prospective study of hip fractures in 7,496 men aged 46–56 years.	High degree of leisure-time physical activity, high occupational class, and high BMI protected against sustaining a hip fracture. However, work-related physical activity was not protective.

of comorbid health conditions, another very important falls predictor. According to Hayes et al. [30], muscle weakness, which can reflect the degree and nature of physical activity participation especially increases the risk of fracturing a hip due to a fall because the intensity of the trauma may exceed the threshold to fracture more readily, regardless of bone strength. In addition, data suggest having weak muscles may also decrease the force required to fracture a hip [135] and a related decrease in the surrounding muscle mass [130] may imply a slower than normal reflex response and less protection of the underlying bone.

Low physical activity levels resulting in low levels of muscle strength also increases the chances of sustaining a hip fracture [83], because this can hasten bone demineralization [65], and diminish coverage of the underlying bone [72], thus impacting the magnitude of any prevailing fall-related force on the hip joint [131, 136]. Not surprisingly, an increased risk of falling, and possible hip fracture, has been specifically noted in association with neuromuscular impairments [93], declines in leg strength [110], low body and knee extensor strength [137], and the inability to rise from a chair without using one's arms [84]. In particular, the status of the neuromuscular systems at both the hip and knee, which is associated with physical activity participation, is shown to play a dominant role in determining hip fracture risk [94, 103].

The importance of being a physically fit adult across the lifespan is especially emphasized in the research presented by Parker and Palmer [138] and Myers et al. [139] who examined the relationships among prefracture status, the development of complications, and mobility outcomes at the time of discharge of the hip fracture patient. These researchers found prefracture status had a significant effect on these variables, particularly on ambulatory or mobility status [137]. As well as psychosocial factors [140], the ability to walk two weeks postoperatively [141], predicted return to the home environment, as did physical activity participation, and the ability to venture out and visit prior to the fracture.

Also, supporting the significance of prior physical activity participation in predicting posthip fracture outcomes is research by Fox et al. [142] who found that after adjusting for age, gender, race, and comorbidity, the patient's preexisting balance and summary mobility scores strongly predicted premature mortality. They also found poor balance, often linked to muscle weakness among other factors, frequently increased the need for hospitalization for up to 24 months post fracture. Further, cases with both poor balance and poor gait had increased odds of being placed in a nursing home or experiencing subsequent mobility problems and reduced independence.

Body Mass. In another series of studies, hip fracture risk has been deemed to be a product of the positive association between low body mass and fracture risk, especially among white men [143], after the age of 50 [144]. Yet, being underweight alone does not commonly lead to the development of a nonpathological hip fracture, suggesting other factors are involved [85]. Indeed, a hip fracture is much more likely to be attributed to the interaction of low body mass, low muscle mass, and muscle weakness leading to failure of protective responses, regardless of femoral bone density [35].

In addition, although most people who fracture their hips could be classified as being thin, Cumming and Klineberg [97] and Maffulli et al. [145] reported their patients with hip fractures tended to be overweight. Dretakis and Christadoulou [146] too noted similar rates of overweight and underweight hip fracture cases among their 373 patients. Similarly, when patients with severe dementia were excluded, Bean et al. [135] found thinness was not necessarily associated with hip fracture. However, their observations of differences in handgrip strength among hip fracture patients and controls of comparable body mass indices, suggested body mass in hip fracture cases might be constituted by a higher proportion of fat than muscle.

Thus, heavier individuals may not be immune to sustaining hip fracture injuries, despite their relatively higher proportion of body fat that can perhaps help dissipate a fall. This is because they may have restricted general mobility, their muscles may be constituted by a large fat mass, and the direct impact sustained by their high body weights may readily exceed the safety threshold of the underlying bone. These individuals are also be expected to have low levels of sex hormone-binding globulin, a finding among women with recent hip fractures [147], plus a high rate of comorbid conditions that are known risk factors for falling, such as hypertension, arthritis, diabetes and medical conditions associated with osteoporosis, such as cancer [105]. In this regard, much has been written about the significant impact of inactivity on rising obesity rates, and related conditions.

Chronic Illnesses. In addition to all the factors already mentioned, it is increasingly clear certain chronic illnesses, in particular, those that impair physical activity, such as arthritis and Parkinson's disease, substantially increase the risk

of falling, and hence of incurring a hip fracture [66, 67, 148]. As well, comorbid factors that impair physical activity participation such as arrhythmias, postural hypertension, pain, and peripheral neuropathies may increase the risk of falls and hip fractures [35], as may the presence of lower limb dysfunction, Alzeimer's type dementia [149] and other neurological conditions, such as stroke [150]. Diabetes mellitus [151], hyperthyroidism, which is linked to obesity [152], plus medical conditions associated with osteoporosis [153], as well as other forms of disability associated with an increased risk of falling [153, 154], the use of walking aids [154], and those that require prolonged immobilization [42] may similarly heighten the risk of a hip fracture. Rehospitalization after hip fracture may also be influenced negatively by comorbid clinical problems [155], which limit function [156], and the increased use of at least one psychotropic drug, can lead to a second hip fracture [157]. Since the numbers of comorbid diseases continue to rise among aging populations, along with increasingly poor levels of physical functioning, it can be anticipated that the prevalence of hip fractures will continue to rise. Another factor implicated in hip fractures along with poor health status and physical activity limitations [71], is impaired vision [72–76], which may be amenable to intervention.

Environmental Circumstances. Environment refers to all those factors extrinsic to the individual such as home environment, outdoor environment, and work environment that may pose a hip fracture risk to a susceptible individual. Although not always a changeable factor, certain environmental risk factors for hip fractures may be amenable to modification. However, as shown by Norton et al. [158] who investigated the circumstances of falls resulting in hip fractures among older adults in New Zealand prospectively, of the 85 percent of fractures involving a fall that occurred at home, only about 25 percent of these were associated with an environmental hazard. This finding led the authors to conclude that regardless of age or residential status, intrinsic factors such as balance, play a greater role than extrinsic factors, in causing falls that cause hip fractures. Further, while environmental factors may be one of several factors that contribute to falls [159], a recent study by Allander et al. [160], which found the correlation between the number of risk factors of the faller and the environment to be 0.07, suggested environmental hazards are of minimal importance in mediating hip fractures.

Parker et al. [116] who examined environmental hazards implicated in the aetiology of a consecutive series of 787 hip-fracture patients, found 51 different hazards were implicated in the falls experienced by 58% of patients. The author's conclusion was that given the nature of these environmental hazards, measures to reduce the risk of falls due to environmental factors are unlikely to lead to a significant reduction in the incidence of hip fractures.

In summary, as indicated in the prevailing data base, a variety of age-related physiological changes and other factors including medication status may mediate two crucial determinants of hip fracture, namely, femoral bone strength and the propensity to trauma. In particular, the anticipated decline in muscle function with aging and/or comorbid health conditions is likely to impact both of these key injury determinants, and hence the incidence of hip fractures [50]. Moreover, muscle strength and size and its influence on mobility, reaction time, balance, proprioception, fracture site coverage, and bone mass may explain or contribute towards subgroup variations in hip fracture incidence, presentation, and functional outcomes (see Table 3). The nature of the hypothesized relationship between these factors and the disability associated with hip fractures is elaborated upon in graphic form in Figure 1. The detrimental impact of hip fractures on well-being is emphasized in Tables 1 and 4, where some additional predictors of hip fracture disability are shown.

4. Preventing Hip Fractures and Hip Fracture Disability

Over 20 years ago, Cummings and Klineberg [97] advocated for a better understanding of the physical factors that underlie hip fractures, a generally increasingly prevalent disabling injury among older populations worldwide [170, 171]. In particular, they argued for the importance of the status of the neuromuscular system in mediating hip fractures. In this author's view, while many factors may be involved in the pathogenesis of hip fractures, physical activity defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" [172] is key to reducing the risk of falls and premature bone loss that lead to hip fracture. As such, it is increasingly apparent that efforts to promote physical activity across the lifespan, in addition to the identification and remediation of adults with deficient muscle function and bone mass is likely to be of paramount importance in continuing efforts to effectively reduce hip fractures incidence rates and hip fracture disability. This stated importance of having adults pursue adequate levels of physical activity participation across the lifespan seems reasonable owing to the role played by muscle in influencing: (1) bone structure, (2) balance capacity, (3) the effectiveness of protective reflexes, (4) the ability to attenuate impact at the hip joint, (5) general mobility, (6) proclivity to falls and falling mechanisms. That is, concerted efforts to offer comprehensive screening opportunities that can examine lifestyle factors, along with the presence of muscle-related deficits among vulnerable adults as they age, including muscle strength and responsiveness, proprioception, joint range of motion, and balance capacity are likely to improve most modifiable hip fracture risk factors or prevent these, including excess comorbidity, obesity, poor muscle strength, and balance capacity. To achieve this, individually tailored programs that are based on a comprehensive health assessment and thereafter encourage appropriate levels of physical activity or exercise, especially weight-bearing activities, are highly recommended (see Table 5 and Figure 2).

In addition, ensuring individuals in developing as well as developed countries have the resources and/or knowledge or skill to partake in physical activities and are able to do

Table 4: Studies over last 10 years describing poor outcomes after hip fracture, regardless of contemporary management and rehabilitation strategies, plus some common factors explaining outcomes.

Authors and year	Hip fracture population	Key findings concerning mortality and morbidity	Factors explaining outcome
Giaquinto et al. [161], 2000	58 cases, mean age 86.7 years.	12 patients died after complications of previous risk factors, on average survivors showed functional gains from admission to discharge, but most required supervision at discharge.	Age, type fracture, physical and mental health status, and fear.
Maggio et al. [162], 2001	42 cases.	The percentage of residents ambulating autonomously fell from 95–32 percent among those with fractures even though their prefracture mobility status was better than those who never fractured their hips.	Level of prefracture mobility or preserved autonomous mobility.
Davidson et al. [33], 2001	331 cases.	Twelve-month mortality was 26 percent. Followup of 231 surviving patients 12–24 months later showed 27 percent still had pain and 60 percent had worsened mobility.	Low Vitamin D levels, type of fracture and surgical repair.
Van Balen et al. [163], 2001	Prospective study of 102 elderly hip fracture patients mean age 83 years.	Mortality at 4 months was 20 percent. While 57 percent went back to original accommodations, 43 percent reached same level of walking ability, and 17 percent achieved same prefracture abilities of daily living, quality of life at 4 months was worse than the reference population.	Local complications, wound infection, age, number of comorbidities, cognitive state at one week after surgery.
Kirke et al. [164], 2002	Undertook a 2 year follow up of 106 older Irish women with hip fracture histories and 89 without hip fracture.	Mortality at 1 year was 16 percent, and 23.6 percent at 2 years. This occurred even though males or subjects with moderate or severe mental impairment were not included in the study. Hip fracture also had a marked negative effect on functional independence.	Poor mobility, multiple falls, and use of health and community services.
Empana et al. [166], 2004	Prospective study of 7,512 women over age 75 without hip fractures.	Within approximately 4 years, 338 women had a first hip fracture, and their postfracture mortality rate was 112.4 per 1,000 woman-years, compared with 27.3 per 1,000 woman-years for the 6,115 women who did not have any fracture ($P < .001$). After adjusting for age and baseline health status, women with hip fractures were more than twice as likely to die than women with no fractures.	Level of prefracture mobility.
Roche et al. [156], 2005	Prospective observational study of 2,448 consecutive cases.	Mortality was 9.6 percent at 30 days, and 33 percent at one year.	Chest infection and heart failure.
Haleem et al. [3], 2008	Reviewed all articles on outcome of hip fracture between 1,959 and 1,998.	The mortality rates at 6 and 12 months have remained essentially unchanged over the last 4 decades, and are approximately 11–23 percent at 6 months, and 22–29 percent at 1 year.	

Table 4: Continued.

Authors and year	Hip fracture population	Key findings concerning mortality and morbidity	Factors explaining outcome
Haentjens et al. [167], 2010	Prospective studies from 1957–2009 were examined, 22 women and 17 men.	Older adults have a 5–8 fold increased risk for all-cause mortality during the first 3 months after hip fracture. Excess annual mortality persists over time for both women and men.	Postoperative events, multiple comorbid conditions.
Juliebø et al. [168], 2010	Prospective observational study of 21 months duration, of 364 patients, mean age 83.4 years.	Six risk factors were identified for predicting mortality after hip fracture.	History of cardiovascular disease, male gender, low Barthel Index, low body mass, and use of diuretics.
Ho et al. [169], 2010	Retrospective study of prognostic factors for survival at one year over a 9-year period.	Overall survival rate was 86%.	Survival was lower in presence of comorbidities, those of higher ages, those with arthroplasties, and delayed surgeries.

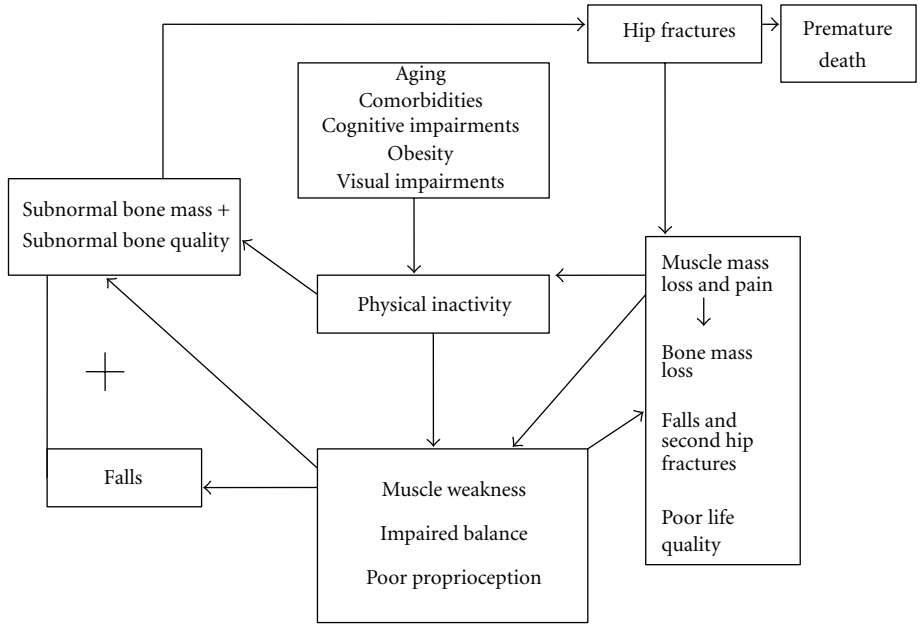

Figure 1: Model of key factors implicated in hip fracture injury.

so may foster the ability to maintain a healthy bone mass and optimal body weight across the lifespan as is indicated to offset unwarranted hip fracture disability. In this respect, adults with excessively low or high body weights, health conditions such as cancer or diabetes, cognitive or visual impairments, and those using steroids, benzodiazepines or other psychotropic agents should also be specifically targeted.

Other strategies that cannot be overlooked are the role of integrated bone and fall-related risk-factor assessment [158], the careful use of bone building supplements especially for hip fracture cases exhibiting difficulty performing effective physical exercise because of reduced walking ability [132], the reduction of remediable visual impairments and depression, and the avoidance of steroids, excessive smoking, caffeine and alcohol usage [84, 100]. Factors that may be especially useful to examine regularly during annual check-ups are listed in Table 5. Other areas warranting attention in future studies include the potential predictors outlined by Wilson et al. [103] such as health insurance status, educational level, and type of residence. In addition to multidisciplinary prevention programs for osteoporosis and falls, plus better in and after care for hip fracture cases as indicated by Alvarez-Nebreda et al. [26], more education about hip fractures and their serious health outcomes is needed. To avoid excessive functional deterioration among hip fracture survivors, including further bone and muscle mass loss, a fat gain of 11 percent [174], plus a high risk for postoperative failures or secondary fractures, the need for rigorous postoperative diagnostic evaluations and treatment of comorbid conditions, especially in the male hip fracture patient, has been emphasized [175]. In addition, comprehensive and protracted rehabilitation interventions including pain control [173], bone-enhancing physical and/or pharmacologic interventions, sunlight exposure, and carefully

Table 5: Representative commonplace assessments and related checklist that could be used in primary care or community settings during regular examinations as well as among those receiving surgical interventions for a first hip fracture to identify those at high risk for first and secondary hip fractures and poor outcomes, as well as associated potential intervention areas.

Measures	Results		
Physical			
Body weight	Underweight	Normal	Overweight
Bone density status, bone scan, and ultrasound [94]	Normal		Low
Cardiac status and cardiogram	Normal		Subnormal
Blood pressure	Normal	High	Low
Pain (visual analogue scale) [173]		0 1 2 3 4 5 6 7 8 9 10	
Physical activity (yale physical activity survey) [173]	Normal		Sedentary
Smoker	yes		no
Musculoskeletal			
Arm muscle circumference and triceps skinfold thickness [85]	Normal		Subnormal
Balance capacity, single-leg stance test, and berg balance scale [106]	Normal		Subnormal
Functional independence measure (FIM) [94]	Normal		Subnormal
Muscular strength and manual knee extensor muscle test	Normal		Subnormal
Sensorimotor reflexes, sensation, joint position sense	Normal		Subnormal
Clinical			
Mental health status—Folstein minimental state exam	Normal		Subnormal
Drug usage—medication check list	0–3	4–6	7+
Fear of falling—survey	yes		no
Nutritional status—dietician	Normal		Subnormal
Medical conditions—check list-physician	0	1–3	3+
Previous falls history—survey	yes		no
Visual status	Normal		Impaired
Environmental			
Home hazards, visiting nurse, or occupational therapist	yes		no
		List number of risk factors: ___	

designed physical activities are strongly indicated and need to be investigated in rigorous trials.

5. Conclusions

In 1987, Melton and Cummings [176] stated that in spite of a general impression to the contrary, the risk factors for age-related fractures were poorly understood. Almost 25 years later, while the key risk factors have been quite well studied, with few exceptions, it is difficult to pinpoint precisely what should be targeted in preventive efforts against hip fractures, as well as where this should take place, because the incidence rates for hip fracture vary widely [101]. In addition, while falls-related trauma and suboptimal bone strength appear to be key factors influencing hip fracture occurrences [177], neither factor alone sufficiently explains the exponential increase in hip fracture incidence rates that occur with aging [90]. However, as was reviewed more than ten years ago by Joakimsen et al. [178], it seems clear the extent of lifelong physical activity participation is especially important. This may be because physical activity participation potentially determines health status, plus the propensity to falling and fracturing a hip owing to its effect on neuromuscular as well as bone physiology. Cummings and Nevitt, 1989 [90] proposed that four conditions must be satisfied in order for a fall to cause a hip fracture: (a) the faller must be oriented to impact near the hip, (b) protective responses must fail, (c) local soft tissues must absorb less energy than necessary to prevent fracture, and (d) the residual energy of the fall applied to the proximal femur must exceed its strength. All of these events become more likely with aging and low physical activity levels and might explain the presently observed exponential rise in the risk of hip fracture with advancing age, despite bone building medication availability. Thus, a combination of targeted physical activities along with appropriate calcium intake, minimizing caffeine intake, maintaining a normal body weight, and avoiding long-term psychoactive medications and other interventions that prevent falls as outlined by Gillespie et al. [179] may prove to extremely efficacious for reducing the risk of hip fracture as outlined by Cummings et al. in 1995 [84].

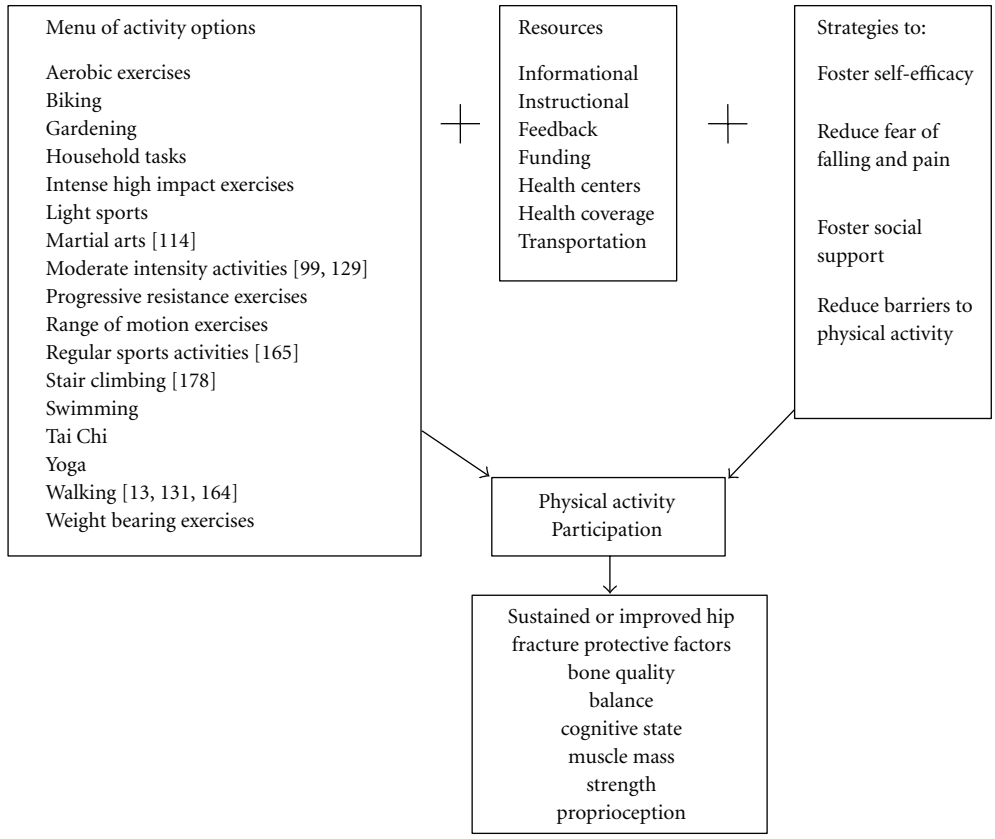

Figure 2: Selected modifiable factors that might facilitate physical activity participation among adults across the lifespan.

However, to offset the high mortality as well as high morbidity rates associated with hip fracture, this approach is more likely to succeed if implemented early on in adult life, rather than later on, when physical activity levels are likely to be quite low [91]. As well, since the propensity to fall, an important factor in the pathogenesis of hip fracture [180] may be related to excess alcohol consumption, medical comorbidities and visual problems [84], as well as physical fitness correlates, these at risk individuals should be targeted early on as well. Since muscle function and structure and its influence on bone quality and integrity can undoubtedly influence the impact of trauma on the structural properties of the hip joint, regardless of age, physical activity participation is key to preventing a fair majority of hip fractures due to slips, trips and falls, as well as osteoporosis, excessive depression, and a host of other chronic diseases that increase hip fracture risk, such as diabetes and cancer [132]. Cognitive status is usually affected favourably as well by physical activity participation, as is blood pressure, both health issues that heighten hip fracture risk as reported in the literature. Outdoor activities such as walking that expose older people to sunlight and vitamin D and enable them to weight bear in variable contexts may yield the benefits of both improving muscular function as well as bone structure.

To further prevent hip fracture disability and enhance hip fracture surgical outcomes, high-intensity strengthening and balance related exercises, plus activities that promote early weight bearing after surgery, and prolonged followup strategies are strongly indicated. To specifically reduce hip fracture morbidity and mortality rates associated with second hip fracture, those with comorbid conditions, cognitive disorders, visual impairments, and osteoporosis and those using psychotropic drugs should be strategically targeted.

As stated by Devine et al. [130], if the whole population followed a high physical activity lifestyle with adequate calcium consumption, it is likely the population risk of hip fractures could be reduced significantly. However, even though isolated high activity in later life provided similar protection to that of high physical activity participation in early adulthood [127] or by regular sports participation [134], rather than applying this approach belatedly to the older population, to achieve maximum protection, young adults everywhere need to be apprised of their future risk for hip fracture in later life and encouraged to be follow healthy active lifestyles.

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Review Article

Treatment and Prevention of Osteoarthritis through Exercise and Sports

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Osteoarthritis (OA) is a degenerative joint disease with a high prevalence among older people. To date, the pathogenesis of the disease and the link between muscle function and OA is not entirely understood. As there is no known cure for OA, current research focuses on prevention and symptomatic treatment of the disorder. Recent research has indicated that muscle weakness precedes the onset of OA symptoms. Furthermore, several studies show a beneficial effect of land-based aerobic and strengthening exercises on pain relief and joint function. Therefore, current research focuses on the possibility to employ exercise and sports in the prevention and treatment of OA.

1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disorder having a significant economic impact on our health system world wide. Osteoarthritis is known to be most frequent in the lower extremity, especially the knee joint, where pathological joint impact and shear forces as well as posttraumatic risk factors cause early cartilage degeneration and "joint aging" [1]. The predominant symptoms are pain, a decreased joint range of motion (ROM) and stiffness, periarticular muscle weakness and atrophy, joint effusion and swelling, and physical disability. Despite the high prevalence of the disease, the pathogenesis and the reasons for progression are not entirely understood: primary OA versus secondary OA, as by, for example, inflammatory diseases and posttraumatic entities. Commonly, OA is characterised by structural changes of the entire joint. Partial to full thickness loss of articular cartilage, subchondral bone sclerosis, osteophyte formation, and thickening of the capsule are the typical clinical and radiological signs. Although radiological changes of OA constantly progress with age, clinical features do not necessarily correlate with radiological findings [2]. As there is no cure for OA, besides different symptoms-reducing drugs as well as joint preserving and replacement surgery, potentially amenable factors in the prevention and treatment of the disease such as muscle function are investigated. It is generally accepted that muscle weakness in OA is due to its atrophy, which is believed to be secondary to joint pain (arthrogenic muscle inhibition) [3, 4]. Recent studies, however, suggested that age-related decrease of muscle volume is a risk factor for OA [5–11]. Thus, as muscle weakness could be targeted by a strengthening program, the question has been raised whether exercise and sports can be used to prevent and symptomatically treat OA.

2. Muscular Dysbalance and Atrophy as a Cause of OA

Muscles play an important role in joint biomechanics as they produce movement, absorb loading, and provide dynamic joint stability, and thus they are involved in the joint adaptation and degeneration process of OA [6, 7, 12–16]. Several studies have investigated the effect of muscular weakness and imbalance on the induction of OA [5–11, 17]. It is commonly accepted that, due to age or previous trauma, muscles are less intensively used. Such weak muscles do not only fatigue more rapidly, but they also display a slower

voluntary and reflex motor control. Thus, once the protective muscular control is lost, excessive joint movement and instability with pathological shear and peak joint forces occur. As a consequence, stress-induced microtrauma to the articular cartilage leads to cartilage degeneration, pathological subchondral pressure increase, consequent subchondral bone sclerosis, and consequent joint collaps with axis maldeviation leading to the typical pathobiomechanical OA vicious circle. Herzog and Longino investigated the relationship of muscular dysfunction and the development of OA in a rabbit model [18]. In their study, knee extensor muscles of rabbits were injected with Botulinum type-A toxin causing a substantial reduction in muscle strength while maintaining functionality, thereby reproducing the clinical picture seen in patients with quadriceps weakness. Histological analyses of joint sections revealed signs of joint degeneration in two out of five animals sacrificed 4 weeks after injection with BTX-A, indicating that even a short period of muscle weakness might be a risk factor for OA. In the development of knee joint OA, quadriceps weakness has been suggested to be a risk factor [5–7]. In this regard, a prospective study was carried out by Slemenda et al. investigating the occurrence of OA in women in a specified timeframe. His results showed that women developing OA had reduced knee extensor strength when compared to unaffected participants of the study [7]. A recent investigation by Valderrabano et al. reported similar results in patients with unilateral ankle OA. The authors were able to show that patients with ankle OA display a reduced calf circumference and had reduced mean electromyography frequencies of lower leg muscles on the affected side [4]. A recent followup study carried out in our institution included MRI analyses of lower leg muscle size. Here, it was determined that it were specific muscle groups which showed signs of OA muscle atrophy (unpublished data).

To determine the cellular abnormalities of muscle weakness and atrophy in OA, several histological and histochemical studies have been carried out [4, 19, 20]. Human muscle biopsy studies have shown that immobilisation in the healthy individual leads to atrophy of mainly type 1 fibres. In knee-OA patients, however, Nakamura and Suzuki found a type 2 fibre atrophy in the vastus lateralis [20]. In contrast to the slow-twitch type 1 fibres, these type 2 fibres are fast-twitch type fibres containing high levels of glycogen and enzymes and thus allow for more sustained tension. A recent study by Fink et al. also investigated the structural changes of the vastus medialis muscle in OA of the knee. Consistent with previous data by Nakamura, he found an atrophy of type 2 fibres in all specimens. Interestingly though, he also showed an additional type 1 fibre atrophy in 32% of patients [19]. As we all know, both type 2 and type 1 muscle fibres have been shown to increase in diameter upon muscle training [21–24]. Thus, the authors strongly believe that exercise programs and sports activity may be able to prevent or counteract muscle atrophy and thus prolong the onset of OA.

Lately, age-related muscle atrophy, namely sarcopenia, has been frequently discussed in literature. This multifactorial disease has been recognised as an important geriatric syndrome [25]. It is characterised by a generalised loss of skeletal muscle mass leading to a significant decrease in strength and can be distinguished on a cellular level from disuse muscle atrophy [26–28]. Various mechanisms such as endocrine dysfunctions, neurodegenerative disease and inadequate nutrition but also muscle disuse and immobility are thought to contribute to its onset and progression. Although sarcopenia mainly affects older people, it has also been found in younger adults. Current treatment concepts include exercise programs to recover some muscle mass and increase strength [25–28]. As patients with sarcopenia display reduced muscle mass and strength and thus are less able to control joint motion, it is likely they have a high risk for developing OA.

To date, many questions regarding the pathogenesis of OA remain open. However, muscular weakness and in some cases even muscular atrophy, either preceding or accompanying the OA disease, is frequently observed. As muscle increases in size upon exercise, atrophy might not only be a result of joint stiffness and pain but also by age-related sarcopenia and physical immobilisation and reduction of sports activity. Since no cure is available for OA, current research should focus on the prevention of this age-related joint disorder. Muscle weakness and atrophy contribute to the OA process, and thus the question has been raised whether exercise and sports could be employed to prolong time to pain onset or relieve pain and improve quality of life in symptomatic patients.

In summary, a strong correlation between muscle atrophy and osteoarthritis has been found on many occasions. It is currently believed that muscle atrophy regardless of causative pathomechanism is a major contributing factor for the development of OA. As exercise increases muscle mass and improves muscle function, it might play a crucial role in the prevention and treatment of OA.

3. Exercise and Sports in the Treatment of OA

As there is no cure for OA, treatments currently focus on management of symptoms. Pain relief, improved joint function, and joint stability are the main goals of therapy. Studies conducted within recent years provided data that supports the assumption that muscle weakness and muscle atrophy contribute to the disease process [5–11]. Thus, rehabilitation and physiotherapy were often prescribed with the intention to alleviate pain and increase mobility. However, as exercise has to be performed on a regular basis in order to counteract muscle atrophy, continuous exercise programs are recommended in people with degenerative joint disease. Therapeutic exercise regimes either focus on muscle strengthening and stretching exercises or on aerobic activity which can be land or water based. To verify the effectiveness of such physical activity, several studies [29–35] as well as a few meta-analyses [36–42] have been carried out. No major difference in effectiveness was reported between land-based aerobic and strengthening exercise [40–42]. Concerning the beneficial effects of aquatic-based exercise, controversial data exists. In one study, aquatic exercise has been shown to be less efficient in reducing pain and improving muscle function than land-based exercise [32]. A review by

Bartels analysed data from four different studies and could show short-term improvement of OA symptoms in knee OA patients supposedly due to an increase of strength of the muscles around the knee. However, long-term effects could not be verified [36]. A recent study by Cadmus reported beneficial effects of aquatic-based exercise only for obese patients but not for nonobese [29]. Due to the buoyancy of water, it is possible to exercise without experiencing full body weight allowing for relatively pain-free motion. Thus, aquatic-based exercise might be a good way to introduce disabled and obese patients to sports. A frequently raised question concerns the intensity of exercise. After reviewing several aerobic exercise studies, Brosseau concluded that both low- and high-intensity aerobic exercise was beneficial in patients with OA [37]. Jan et al. investigated the effects of high and low resistance training and the effects of weight-bearing versus nonweight-bearing exercise in patients with OA of the knee. He determined that both low- and high-resistance type training led to reduced pain and improved function. A recorded increased walking speed on uneven terrains led the authors to speculate that both types of resistance training improved balance and proprioception. Albeit not statistically significant, high resistance training also demonstrated consistently higher functional performance and greater reduction of pain [31]. Furthermore, when comparing the effects of weight-bearing and non-weight-bearing exercises, an improved position sense was found in addition to decreased pain scores and increased muscular strength [30]. A recent study investigated the effects of Tai Chi in treating OA of the knee. This traditional Chinese mind-body exercise combines strength, balance, and flexibility training. When compared to a wellness education and stretching program, the overall outcome showed a greater improvement of pain and physical function in patients attending the Tai Chi training [35].

In conclusion, literature shows clear improvement of OA symptoms in patients undertaking exercise programs. Decreased pain and increased muscle function have been reported for both strengthening and aerobic exercises. However, these effects do not persist if exercise programs are discontinued. Thus, the motivation of the patient to start and continuously practice exercise is of crucial importance. Many patients suffering from OA refuse to start exercising due to joint pain. In such cases, the use of painkillers during the first weeks of an exercise program might not only facilitate joint movement but can also drastically improve patient compliance. Furthermore, in case of severe joint pain or in obese patients, the authors believe that an initial period of water-based exercise is helpful. As swimming or aqua jogging provides a muscle workout without joint loading, further pain and weight-related joint destruction is avoided. Although many studies investigated the effect of different exercise types, hardly any study can be found investigating the effect of different kinds of sports on OA. Current knowledge supports practicing sports which avoid sudden peak stresses but improve muscle function and contribute to the stabilisation of the affected joints. Sports that fulfil these criteria and are regularly recommended to people suffering from OA are low-impact sports, as cycling, nordic walking, and aquajogging. However, data on the short- and long-term effect of theses types of sport in OA are scarce, and therefore further studies are urgently needed. When it comes to exercise programs, both low- and high-resistance training with or without weight bearing has been shown to have beneficial effects. Patients unable to participate in exercise or sport programs should be encouraged to continue carrying out activities of daily life such as walking the dog, gardening, or biking to work. However, it is the authors' opinion that exercise and sports can and should be practiced at any stage of OA although the intensity has to be adjusted to the individual capability.

4. Exercise and Sports in the Prevention of OA

Exercise has been shown to improve pain and function in OA [38] and is recommended by the Osteoarthritis Research Society International (OARSI) for the management of hip and knee OA [43]. However, to date, very little research has been conducted to investigate whether exercise and sports can also be used to prevent the onset of OA. It is widely recognised that physical activity is beneficial to cardiovascular health and is considered an integral component of a healthy lifestyle [44]. Furthermore, regular exercise facilitates weight loss and prevents weight gain. As obesity is a recognised risk factor for knee OA [45, 46], exercise is thought to have a beneficial effect on the OA disease progression. However, OA is not only found in obese patients and not all joints are affected equally by weight increase [47]. Thus, other disease-related factors have been investigated. Muscle weakness and muscle atrophy have been reported to occur even before the onset of symptomatic OA [6]. As muscle weakness usually results from disuse of muscles, the question has been raised whether exercise and sports could be employed to prevent or counteract muscle weakness and therefore prevent or delay the onset of OA. Recently, two studies have been published on the protective effect of exercise and of quadriceps strength in the prevention of cartilage loss at the tibiofemoral joint [48, 49]. Amin et al. [48] showed that there was no association between a decrease in quadriceps strength and cartilage loss in a 30 months trial. However, he also determined that participants of the study with greatest quadriceps strength displayed the least cartilage loss at the lateral compartment of the patellofemoral joint indicating that a strong quadriceps muscle had protective cartilage effects. In the study by Otterness et al. [49], the effects of daily exercise on cartilage degeneration in hamsters were investigated. Hamsters were undergoing either 3 months of daily exercise or 3 months of sedentary living. Histologic analyses of the femoral articular cartilage of the exercising hamsters showed a smooth surface similar to that of young control animals. In contrast, signs of cartilage degeneration were seen in sedentary hamsters. Furthermore, cartilage composition in these animals showed a reduced proteoglycan content and synovial fluid volume. This data indicates that at least in hamsters early cartilage degeneration is not a result of exercise but rather of inactivity and decreased muscle function. Thus, it can be argued that inactivity not only

promotes muscle weakness and thereby joint instability but also makes cartilage more prone to damage by altering its structure. As the data by Otterness was derived in a hamster model, it was questionable whether the same cartilage change would occur in humans. A literature search revealed a study in human in which the effects of moderate exercise on cartilage were analysed in knees prone to develop OA [50]. The study participants had all undergone partial medial meniscectomy 3 to 5 years previously and were either asked to complete a 4-month exercise program or remain at their current physical exercise level. At the end of the study, 68% of the exercise group reported an increase in activity level. Furthermore, glycosaminoglycan levels which were measured by T1 relaxation time on MRI scans were clearly increased, indicating that exercise also has a beneficial direct effect on cartilage structure in human. The exact mechanism that causes chondroprotection upon exercise however is not entirely understood. A recent study discovered an increase in IL10 levels of synovial fluid after acute resistance exercise in patients with OA of the knee [51]. IL10 is an anti-inflammatory cytokine with chondroprotective properties. It has been shown to suppress the release of inflammatory cytokines by macrophages and activates chondrocytes and synoviocytes and, thereby, is interfering with important steps in the pathogenesis of OA [52, 53]. One could speculate that during regular exercise, IL10 levels would be constantly elevated, thus reducing inflammation in the joint and hence reducing pain. As a result, physical activity can be undertaken more frequently, thus increasing muscle mass and thereby providing more joint stability. However, to confirm this hypothesis a lot more research is needed.

In summary, investigations on the effectiveness of exercise in the prevention of OA have revealed some interesting facts. Animal studies and clinical trials clearly showed a protective effect of exercise on joint cartilage, thus perhaps reducing the likelihood for developing OA. Furthermore, an anti-inflammatory environment was found in OA knee joints upon exercise. Assuming that the same environment exists in a healthy joint under the same conditions exercise might be very effective in preventing the onset of disease. However, to fully understand the protective effects of exercise on the development of OA, further clinical and molecular studies are needed.

5. Conclusions

As overall conclusion, OA is a multifactorial disease with a pathogenic link to muscle function and volume that is not entirely understood. Over the last decade, research has provided data supporting the hypothesis that exercise is not the reason for OA but rather delays onset and alleviates symptoms of the disorder. Furthermore, several studies have shown that muscle weakness is a predisposing factor for OA and that muscle atrophy is a common finding in OA. Changes in cartilage structure have also been investigated, and it was determined that in order to remain firm a certain amount of muscle exercise was needed. Taken into account all the above mentioned data, this would argue that exercise and sports should be used in the prevention and also in the treatment of OA and aging people. To determine which type of exercise would be most appropriate, various studies were carried out. It was shown that aquatic exercise was beneficial only in the beginning and in obese people whereas land-based aerobic and strengthening exercises had a continuous effect for as long as they were carried out. Once exercise is discontinued, all the beneficial effects that come with it vanish as well. Thus, the authors strongly believe that any additional measures that help to motivate patients to continue sports, such as training schedules, group exercises, or instructional sessions with physiotherapists are of crucial importance. To date, many studies have been carried out investigating the effect of exercise on the progression of OA. Although alleviation of pain has been shown to occur upon regular exercise, the minimal intensity of training necessary for such a positive effect still needs to be determined. Therefore, one of the biggest challenges still remains to understand the pathogenesis of OA in order to prevent the onset or find further treatments for this debilitating disorder.

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Review Article

Benefits of Exercise in Rheumatoid Arthritis

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This paper aims to highlight the importance of exercise in patients with rheumatoid arthritis (RA) and to demonstrate the multitude of beneficial effects that properly designed exercise training has in this population. RA is a chronic, systemic, autoimmune disease characterised by decrements to joint health including joint pain and inflammation, fatigue, increased incidence and progression of cardiovascular disease, and accelerated loss of muscle mass, that is, "rheumatoid cachexia". These factors contribute to functional limitation, disability, comorbidities, and reduced quality of life. Exercise training for RA patients has been shown to be efficacious in reversing cachexia and substantially improving function without exacerbating disease activity and is likely to reduce cardiovascular risk. Thus, all RA patients should be encouraged to include aerobic and resistance exercise training as part of routine care. Understanding the perceptions of RA patients and health professionals to exercise is key to patients initiating and adhering to effective exercise training.

1. Background

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease, and the most common form of chronic joint inflammation, affecting 0.5–1% of the UK population. RA is most prevalent in individuals aged 40 years or older with the risk of developing RA being up to 5 times higher in women [1]. As a consequence of their disease RA patients typically suffer severe joint pain, reduced muscle strength, and impaired physical function [2]. Although outcomes of the disease have improved with modern approaches to drug treatment, using agents such as methotrexate and biologics, the disease is still a progressive one with long-term joint damage and disability the expectation rather than the rule.

A major feature of the disease is severe inflammation of the synovium where there is a 3–100 times elevation of proinflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and C-reactive protein (CRP) [3]. The course of RA is typically one of exacerbations and remissions but, even during inactive phases of the disease, systemic levels of cytokines remain dysregulated when compared to those without rheumatoid arthritis [4]. RA also results in downregulation of anabolic factors for muscle, for example, muscle levels of insulin-like growth factor I (IGF-1) [5]. The circulating levels of cytokines reflect disease activity and level of inflammation present and also may play a significant role in the systemic effects of the disease, such as vascular disease [4] and rheumatoid cachexia [6].

In addition to the articular features of the disease, RA is associated with increased morbidity and mortality from cardiovascular disease (CVD) [7, 8]. The relative risk of myocardial infarction is estimated to be double in women with RA relative to those without [8], and CVD events typically occur a decade earlier and to a greater extent in patients with RA relative to healthy controls; sometimes even before the fulfilment of all criteria of RA [9]. A recent meta-analysis of 24 studies, comprising 111,758 patients with 22,927 cardiovascular events, reported a 50% increased risk of CVD deaths in patients with RA compared with the

general population [10]. This increase in CVD in RA patients appears to be independent of traditional cardiovascular risk factors [11]. Given that chronic low-grade inflammation is thought to play an important role in the underlying cause of CVD, atherosclerosis [12], it seems reasonable to hypothesize that systemic inflammation contributes to elevated CVD in persons with RA [9].

Most RA patients also suffer from an accelerated loss of muscle mass, a condition known as "rheumatoid cachexia". This loss contributes to disability and has a significant impact on an individuals' quality of life [13]. Rheumatoid cachexia has been reported in two thirds of all RA patients, including patients with stable RA [5, 14]. Roubenoff and colleagues [6] proposed that rheumatoid cachexia is caused by the cytokine-driven (principally TNF-α) hypermetabolism and protein degradation. However, poor nutrition [15] and low physical activity levels [16] are also believed to contribute.

Low physical activity is an important and reversible characteristic of RA. It has been demonstrated that RA patients do less exercise than their healthy counterparts; more than 80% of RA patients are physically inactive in some countries [17], whilst in the UK it is believed that approximately 68% of RA patients are physically inactive [17]. The extreme physical inactivity of RA patients' becomes a vicious circle in terms of health and disease progression. Thus it has become apparent that encouraging physical activity is an important and essential part of the overall treatment of RA.

The purpose of this paper is to highlight the importance of exercise in patients with RA and to demonstrate the multitude of beneficial effects that a properly designed exercise intervention has in this population. In order to present this aim, this paper has been organised into separate sections. Firstly, a brief explanation of the background of RA and the benefits of exercise in the general population is presented. Secondly, the benefits of exercise in RA are highlighted, focusing on the areas of cardiovascular disease, musculoskeletal and joint health, and overall function. Thirdly, the perceptions of RA patients regarding exercise are discussed and finally exercise prescription for RA is reviewed. This expert review has been derived from a combination of systematic reviews and other research papers focusing on randomised controlled trials, published guidelines, the recent literature, and also making use of our own specialised experience. It is not within the scope of this review to discuss the benefits of standard low-intensity physiotherapy techniques such as range of motion, stretching, and/or specific joint strengthening. The review, however, does encompass a range of physical activity and physical exercise. We broadly define physical activity as any bodily movement produced by skeletal muscles resulting in energy expenditure above resting levels and physical exercise ("exercise" or "exercise training") to be a subset of leisure time physical activity that pertains to planned, structured, and repetitive bodily movements, aimed at improving or maintaining fitness, physical performance, or health [18]. We have based our definition of functional ability from the disablement process in RA as described by Escalante and Del Rincon (2002) of pathology, impairment, functional limitation, and disability [19].

Overview of the Benefits of Exercise in the General Population: Older Adults. It is widely acknowledged that regular exercise/physical activity provides multiple health benefits for the general population and patients with chronic diseases. This includes improvements in cardiovascular health and reducing the risk of coronary artery disease, stroke, and type 2 diabetes by attenuating hypertension and dyslipidemia, improving insulin sensitivity and reducing adiposity [20]; reducing the risk of colon and breast cancers [21]; increasing muscle strength and mechanical properties and bone mineral density [22, 23]; improving balance and reducing the incidence of falls [24]; facilitating psychological well-being [25]. By engaging in recommended exercises older adults can help reduce the risk of chronic disease (e.g., of developing CVD by about 30%–50% [26]), premature mortality, functional limitation, and disability [27].

Basic recommendations from the American College of Sports Medicine (ACSM) suggest for health benefit that every adult should accumulate at least 30 minutes of moderate-intensity physical activity on most days of the week. ACSM have issued a separate set of guidelines for older adults, that is, men and women aged 65 years and above and adults aged 50–64 years with clinically significant chronic conditions such as RA. These guidelines are similar with additional importance stressed on muscle strengthening exercises and exercises to improve balance and flexibility [27].

2. Benefits of Exercise in RA

Apart from the general effects of exercise previously mentioned in the general population, exercise has been shown to have specific health benefits in people with RA. In fact, as evident from past research, including findings from randomised controlled trials [5, 28–41], exercise is considered to be fundamentally beneficial for RA patients. The reported benefits of properly designed physical exercise programs include improved cardiorespiratory fitness and cardiovascular health, increased muscle mass, reduced adiposity (including attenuated trunk fat), improved strength, and physical functioning, all achieved without exacerbation of disease activity or joint damage. Furthermore, when comparing the effectiveness of high and low intensity exercise training in stable RA, it is found that the former was more effective in increasing aerobic capacity, muscle strength, joint mobility, and physical function with no detrimental effect on disease activity in patients with controlled [5, 36] and active RA [37].

2.1. Cardiovascular Disease and Exercise. A goal for any RA treatment regime should be to reduce cardiovascular comorbidity, in line with the overall aim of prolonging and improving quality of life. The benefits of physical activity, exercise training, and cardiorespiratory fitness in primary and secondary cardiovascular disease prevention are well established [42, 43]. Low aerobic fitness is strongly associated with all-cause and cardiovascular disease mortality in apparently healthy men and women, those with comorbid conditions (obesity, hypertension, and type 2 diabetes mellitus) and those with known coronary artery disease [44].

In general, patients with RA are less physically active and have aerobic capacities, the measure of cardiorespiratory fitness, 20 to 30% lower than age-matched healthy controls [45, 46]. Furthermore, in a cross-sectional study of 65 RA patients (43 females), Metsios et al. [47] observed that physically inactive RA patients had a significantly worse cardiovascular risk factor profile (higher systolic blood pressure and elevated total cholesterol, and low-density lipoprotein levels) when compared with physically active RA patients.

Exercise training and increased physical activity reduces cardiovascular events in the general population. Meta-analyses of exercise-based cardiac rehabilitation estimate a reduction in mortality of around 20 to 30% [48]. Given that the main cause of reduced life expectancy in persons with RA is CVD related, the probable cardioprotective benefit of exercise training and regular physical activity to RA patients cannot be ignored. To date, however, most studies of the beneficial effects of exercise training in RA have focused on improvements in functional ability and other RA-related disease outcomes. In a recent Cochrane review, moderate evidence for a positive effect of short-term dynamic exercise on aerobic capacity in RA patients was found [49]. It is worth noting, however, that none of the 8 studies reviewed reported any other cardiovascular risk factors. A wider review of 40 studies of exercise in RA [50] observed that none investigated exercise interventions in relation to CVD in RA. Clearly, future studies are required to specifically investigate the effect of exercise training and cardiorespiratory fitness on CVD risk in RA.

Summary of CV Health and RA. (i) RA patients have an increased CV risk factor profile; (ii) RA patients have been shown to be less active and have poor aerobic fitness; (iii) the relationships between physical activity, aerobic fitness, and CV risk in RA patients requires more research; (iv) reducing CV risk through exercise could have an enormous impact in patients with RA.

2.2. Musculoskeletal Health and Exercise

2.2.1. Rheumatoid Cachexia and Skeletal Muscle Function. As mentioned previously, approximately two thirds of RA patients suffer from cachexia (i.e., significant muscle wasting) [5, 14]. "Rheumatoid cachexia" is defined as a loss of body cell mass which predominates in skeletal muscle. Unlike the cachexia associated with conditions such as HIV-AIDS, cancers, COPD, and frail old age, rheumatoid cachexia is usually characterised by stable bodyweight as the decrease in muscle mass is masked by a concomitant increase in fat mass [51]. These detrimental changes in body composition not only causes muscle weakness and increased disability, but also contribute to fatigue and augmented risk of diabetes and CVD [5, 6, 47]. It has been proposed [6] that cachexia occurs in RA due to the excess production of proinflammatory cytokines, principally TNF-α, which is catabolic and thought to alter the balance between protein degradation and protein synthesis in RA. However, it is unlikely that this is the only cause as specifically blocking TNF-α has proved unsuccessful in reversing muscle loss in previously untreated RA patients [52]. Thus the precise mechanism by which rheumatoid cachexia occurs is not known but reduced insulin action, muscle IGF-I levels, testosterone, and low habitual physical activity are likely to be contributing mediators [5, 53, 54]. Furthermore, the use of high-dose steroid therapy to control disease activity can exacerbate muscle atrophy in RA [55]. In addition, the symptoms of the disease, for example, pain and fatigue, also result in RA patients being less physically active; decreasing physical activity then becomes part of the viscous circle of further decreasing muscle mass and has detrimental effects on other aspects of skeletal muscle health [56].

Loss of strength, of up to 70%, is a common finding in RA patients in comparison to healthy counterparts [57]. Loss of muscle mass is the main contributor to loss of muscle strength; however, it is not the only factor responsible [23, 58]. With RA, the loss of muscle mass, decreased physical activity, and immunologic factors may combine with alterations in skeletal muscle properties that could result in decreased muscle strength. Lower strength and power then lead on to functional limitation in RA. A summary of these pertinent factors and how they are interlinked with other RA disease-related factors that result in functional limitation are shown in Figure 1. Although there was a suggestion that RA patients have a lower activation capacity [59], recent studies have shown that in stable RA quadriceps muscle recruitment, strength, and other skeletal muscle properties are not compromised [60, 61]. However, a case study in active RA indicates that these parameters might be negatively affected during increased disease activity and especially in the presence of an effusion, which adversely affects mechanical joint and muscle function. Quadriceps wasting, as well as a dramatic loss of force production, which was not due to pain or impaired muscle quality, was observed [62]. This needs to be further investigated in larger studies with active RA. If muscle physiological properties are impaired during times of disease flare, it is likely that this would impact on the length of recovery time needed after flare. This would thereby further emphasise the importance of early and persistent exercise training in these patients and early treatment of joint effusions to avoid possible reflex inhibition and altered joint geometry caused by the effusion that may interfere with exercise training.

The impaired physical function that is characteristic of RA is strongly correlated with the diminished muscle mass [13], but to date there is no standard treatment for rheumatoid cachexia.

High intensity resistance exercise has been shown to safely reverse cachexia in patients with RA and, as a consequence of this restoration of muscle mass, to substantially improve physical function and reduce disability in RA patients [5, 28, 63, 64]. For example, a 24-week high-intensity progressive resistance training (PRT) program produced significant increases in lean body mass, reduced fat mass (notably trunk adiposity), and substantial improvements in muscle strength and physical function in RA patients [5]. It is notable that the low-intensity range of movement exercises performed by an age-, sex- and disease-matched group of patients as the control condition elicited no changes in body composition or physical function. This

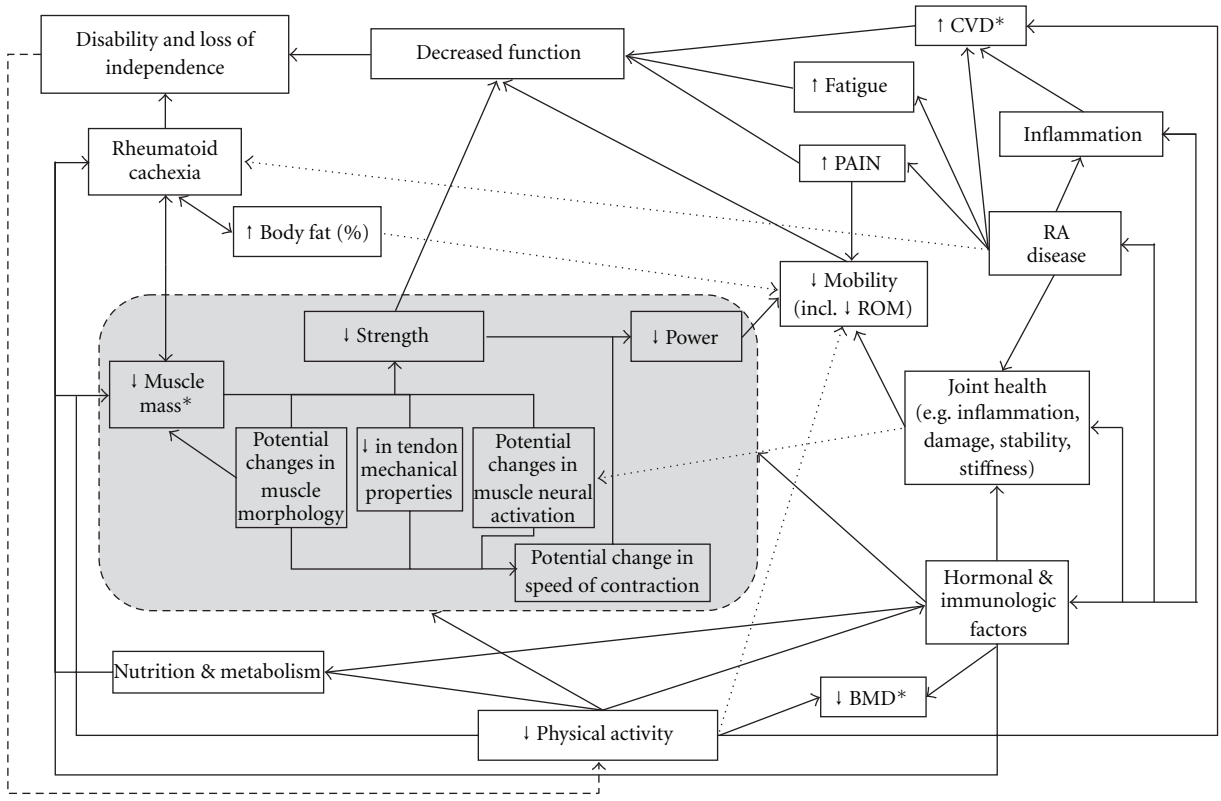

Figure 1: A summary of the influence of skeletal muscle properties on the factors affecting functional limitation, disability and loss of independence in RA. Note: not all of the skeletal muscle properties have been routinely demonstrated with RA (e.g., [60, 61]). BMD: bone mineral density, CVD: cardiovascular disease, ROM: range of motion. *Factors that are adversely affected by medications.

investigation also revealed increases in previously diminished muscle levels of IGF-I- and IGF-binding protein-3 following PRT suggesting a probable contributing mechanism for rheumatoid cachexia. Other exercise training programs have also been suggested to induce an anti-inflammatory effect, specifically relating to TNF-α production [57]. However, immune function (including TNF-α and IL-6) was unaltered following 12 weeks of high-intensity PRT [65].

In terms of the magnitude of hypertrophic and strengthening effects of PRT observed in RA patients [5, 63, 64] these are similar to those reported for healthy middle-aged or older subjects (e.g., [23, 57, 66–68]). The study by Hakkinen and colleagues [64] in fact provides a direct comparison of training response. They identified almost identical body composition changes (increased thigh muscle cross-section and reduced thigh fat thickness) and comparable strength increases in female RA patients and age-matched healthy women following completion of the same resistance exercise program. Furthermore, a range of skeletal muscle parameters (force, muscle architecture, coactivation of antagonist muscles, contractile properties, etc.) were observed to be no different between well-controlled RA and their healthy counterparts, resulting in similar muscle quality (muscle force per size) between the groups, even in cachetic RA patients [60, 61]. Consequently it is now clear that patients with RA are not resistant to the anabolic effects of exercise as previously suggested [69]. These findings are important to health professionals and those involved in prescribing exercise for people with RA as rheumatoid muscle should respond to exercise training in a similar way to that of muscle in healthy individuals. In fact now much research is promoting the fact that there are more detrimental effects if exercise is not undertaken [70].

As high-intensity PRT performed by RA patients, with both newly diagnosed and long-standing disease, has proved to be efficacious in increasing muscle mass, strength, and improving physical function, whilst being well tolerated and safe, it is advocated that such programs are included in disease management to counteract the effects rheumatoid cachexia [5, 56, 57, 71, 72]. PRT can also benefit other health aspects, for example, improving coordination and balance which RA can detrimentally affect. It is also important to maintain normal muscle strength in order to stabilise the knee joint, preventing joint angulation, and later osteoarthritis [73]. Further health benefits are detailed below.

Summary of Rheumatoid Cachexia and Musculoskeletal Health and Exercise Types for Treatment. (i) At least 50% RA patients suffer loss of lean mass; (ii) intensive progressive resistance training can increase lean mass, reduce fat mass, increase strength and improve function; (iii) PRT is the most effective exercise to improve skeletal muscle size and strength; (iv) PRT, even performed at high intensity, is safe in RA.

2.2.2. Bone Mineral Density. In people with RA, not only does the typically sedentary lifestyle put them at greater risk of lower bone mineral density (BMD), but the disease itself (systemic inflammatory activity and high-dose oral steroid medication when used as part of RA treatment) results in radiological changes including bone loss (especially peripherally) [74, 75]. Lower BMD has been shown to occur at the femoral neck, distal forearm, and hip, but not the spine, in RA when compared with controls [74, 76]. Lower BMD in RA is found in patients on glucocorticoid treatment, and those with lower strength (handgrip and quadriceps) and physical capacity [74, 77, 78]. Thus highlighting how physical activity that involves muscle strengthening may assist in mitigating the bone loss in people with RA.

Loss of BMD with age is difficult to mitigate and requires long-term weight "loading" on bone (either by repetitive weight-bearing and/or strengthening exercises) [78]. Several studies have reported no change in BMD with exercise training programmes in people with RA. However most of these investigations have either been too short in duration to detect changes, have featured low participant numbers, or did not include sufficient weight loading stimulus [56, 79]. The Rheumatoid Arthritis Patients in Training program (RAPIT) study observed a reduced rate of BMD loss in the hip, but not the spine, during 2 years of high-intensity weight-bearing exercise training [77]. This mitigation of BMD loss was associated with increases in both muscle strength and aerobic fitness. The authors concluded that there is an essential role for the combination of high-intensity, weight- and impact-bearing exercises in improving bone mineral density in RA patients [77].

Summary of Exercise Types for Bone Health. (i) Load-bearing exercise, PRT and/or weight bearing, is required to increase BMD; (ii) combination of PRT and weight/impact-bearing exercises may be required to improve BMD.

2.3. Joint Health and Exercise. The role of exercise in promoting the joint health of a person with RA is of great importance, especially as this is the most pronounced and invariant element of the RA disease pathology [80]. The health of the joint involves a combination of factors, as detailed below.

Tendons are extensible structures that transmit forces from muscle to bone and reversibly deform under mechanical loads, with stiffer tendons providing more efficient force production. RA causes synovial inflammation of tendon sheaths, leading to synovial hypertrophy and sometimes infiltration of synovial tissue within the tendon. The raised circulating inflammatory cytokines also affect collagen, leading to damage and disorganisation of the tendon structure. In addition, tendons gradually lose their elasticity and stiffness as they age and in persons who do not engage regularly in physical activities or following disuse [23, 81, 82]. Only recently have tendon properties been investigated in RA, with tendon stiffness in stable established RA being lower than that of matched healthy controls (manuscript in preparation). In the case study example described above [62], lower patella tendon stiffness that was observed only in the effused knee during the acute phase was found in both knees 1 year later, despite maintenance of regular physical activity. Local effects of the joint effusion are likely to be responsible for the acute decrease in tendon stiffness whilst the systemic inflammatory processes of RA could be responsible for the long-term effects. Tendon stiffness can be increased, however, following strength training in older people [23] and with endurance training [83]. Potential beneficial exercise training effects in tendons of RA patients are to date unknown and warrant further investigation.

The ligament forms another essential component of the joint, with the main function being to passively stabilise and guide the joint through its normal range of motion [84]. Similar to the research surrounding tendons and the effects of exercise, it is known that exercise strengthens ligaments and that even relatively short periods of immobilisation weakens them [85, 86]. Thus, it may be suggested that regular physical activity for the RA patient is essential in order to maintain normal ligament and, consequently, overall joint health and function.

The primary function of cartilage within the synovial joint is to protect the bone from damage by helping to minimise friction between adjacent bones during movement [87]. It is known that periods of compression and decompression, which can be achieved through the mechanical forces and regular cyclic loading of an exercise bout, are required to prevent cartilage tissue from becoming fragile and dysfunctional [88–90]. Furthermore, it is known that cartilage responds in a site-specific way to this loading [88].

For many years, intensive dynamic and weight-bearing exercises were considered inappropriate for people with RA due to concerns that such activities may exacerbate disease [36]. Furthermore, research has revealed that patients are concerned about whether such exercise can cause damage to the structure of the joint [91]. Research by de Jong and colleagues [28, 77, 92, 93] has shed light on this area of concern. They investigated the effects of a high-intensity exercise program in the RAPIT study. This involved biweekly participation in a 1.25-hour exercise session including aerobic, muscle strengthening, joint mobility, and an impact-delivering "sport" or "game" sessions for 2 years. When compared to patients receiving usual care, it was concluded that exercise did not cause an increase in the rate of damage to either large [28] or the small joints of the hands and feet [77]. Although initially there was a suspicion that those large joints which were badly damaged prior to the start of the study deteriorated more rapidly in the exercise group than controls [93], results from a follow-up study led the authors to retract this conclusion [92]. At 18 months following the cessation of the exercise program, there was no significant difference in the rate of damage of the large joints between those patients available at follow-up who were still exercising and those who had discontinued exercise [92]. Another finding from the RAPIT study indicates that there was no significant change in cartilage oligomeric matrix protein (COMP) level, a measure of cartilage damage, in patients after 3 months of exercising [94].

Range of movement and flexibility are also improved as a result of exercise, reducing movement limitation [95].

For example, Van Den Ende et al. [37] found that joint mobility increased as a result of a short-term intensive exercise programme in RA patients with active disease. Joint proprioception has also been reported to improve after physical activity and deteriorate after immobilisation or joint disease [96, 97]. Whilst yet to be determined in the RA population [98], elderly people who regularly practiced tai chi showed better proprioception at the ankle and knee joints than sedentary controls [99]. It may also be that joint lubrication is enhanced as a result of physical activity, further acting to promote the health of the RA joint. More specifically, after resting for long periods, synovial fluid is squeezed out from between the two surfaces of joint, resulting in contact between the areas of cartilage. When movement is resumed, the mechanism of fluid film lubrication is reactivated [100].

A study by Lynberg et al. [39] is typical of findings that PRT does not exacerbate joint inflammation (synovitis, joint swelling, joint tenderness, periarticular tenderness, and range of motion were all clinically assessed). Furthermore, in patients with moderate disease activity a reduction in the number of clinically active joints after vigorous exercise has sometimes been observed [36, 101].

RA is also characterised by an increase in blood flow (synovial hyperaemia) and vascularisation of the synovium [102, 103]. Whilst the links between this process and joint destruction are poorly understood, it is thought that proliferation of the joint synovium and the action of cytokines such IL-1 and TNF-α act to break down the superficial layers of joint cartilage [104]. This matrix degeneration potentially leads to joint failure, functional limitation, and disability [105]. However, some evidence suggests that intermittent cycles of raised intra-articular pressure during dynamic exercise might increase synovial blood flow, suggesting a beneficial effect of dynamic exercises in joint inflammation [106]. Using a quantitative method, ultrasonography, recent research has suggested no acute effect of handgrip exercise on synovial hyperaemia of the wrist joint in RA patients [107]. In summary, adequate strength and endurance of the muscles alongside tone and elasticity of the connective tissues promotes optimal joint stability, alignment and attenuation of impact and compressive forces [89, 108].

Summary of Exercise Types for Joint Health. (i) Resistance training increases tendon stiffness and strengthens connective tissue; (ii) cyclic loading (e.g., walking, cycling, strength endurance exercises) enhances cartilage integrity and joint lubrication; (iii) mobility exercises increase range of motion.

2.4. Improving Overall Function. Patients with rheumatoid arthritis usually suffer from disability, severe pain, joint stiffness, and fatigue which impair physical function [109]. Even after controlling for the disease with development of powerful disease-modifying antirheumatic drugs (DMARDs), patients still suffer from functional limitation, often leading to work disability [110]. However, exercise has been shown to significantly improve some or all of these symptoms, especially function as well as psychological well-being [5, 56, 63, 111, 112]. For example, a two-year strength training program resulted in improvements in subjective patient assessments of disability by the Health Assessment Questionnaire (HAQ) [45]. Similarly, Marcora and colleagues [63] found a significant inverse correlation between increases in leg lean mass following 12 weeks PRT and the perceived difficulty in performing activities of daily living (ADLs). However, this beneficial effect on subjective measures of function is not universal. For example, an intensive PRT program failed to improve modified HAQ scores in a group of RA patients despite significant improvements in muscle mass and strength [5]. It was concluded that patients involved in this program had relatively low disability and that the modified HAQ was not sensitive to change in a low disability group.

Another factor common in RA that limits overall function is fatigue. Fatigue is frequently experienced in RA with 42% of RA patients experiencing severe fatigue [113]. Often patients report fatigue as one of the most annoying symptoms [114]. However, an internationally accepted definition of fatigue in RA currently does not exist, and its aetiology still remains a mystery. Fatigue can be described as a subjective experience, a feeling of "extreme, persistent tiredness, weakness or exhaustion which can be both mental and physical" [115]. Identifying ways to reduce fatigue and improving overall quality of life are very important. So far few methods have shown to be effective, however, recent research suggests that fatigue can be reduced by performing exercise [116]. A systematic review which explored the effectiveness of nonpharmacological interventions for fatigue [112] also concluded that both aerobic and resistance exercise interventions reduce RA fatigue.

Summary: It Is Important to Note the Following. (i) Exercise can reduce pain, morning stiffness, and even reduce fatigue in RA; (ii) exercise can improve functional ability and psychological well-being; (iii) exercise has not been shown to exacerbate disease activity.

3. Perceptions of RA Patients Regarding Exercise

Whilst there are numerous reasons why exercise is considered to be of fundamental benefit, it is apparent that the RA population is less physically active than the general population. Therefore, it is important for those involved in the care of RA patients to be aware of factors that may positively and negatively affect the uptake of and compliance to an exercise prescription.

The perceptions of people with RA may provide reasoning for the lower physical activity levels of RA patients when compared to the general population [17]. Thus, understanding the perceptions of RA patients regarding exercise is salient to the role of the health professional [91].

The Obstacles to Action study (New Zealand) [117] investigated factors influencing exercise participation for individuals with self-reported arthritis who were defined as "nonexercisers", "insufficiently active", and "regular exercisers". Their qualitative analysis of focus group discussions revealed that active people with arthritis believed more

strongly in the benefits of physical activity, reported significantly higher levels of encouragement from others, and had greater overall levels of self-efficacy when compared with the less active participants. Arthritis, fatigue, and discomfort were ranked by both groups as the top three barriers. However, the active participants reported significantly lower impact scores for these barriers than the inactive group, and these findings persisted after adjusting for occupational status, body mass index, and comorbidities [117].

Other barriers suggested to affect the successful uptake of exercise recommendations in arthritis patients have also been revealed. Physical barriers have included pain, fatigue, and physical capabilities, alongside the additional complications of further comorbidities. Psychological aspects such as a lack of enjoyment, motivation, and confidence have been identified as negative influences. However, receiving assistance from instructors and the opportunity for social interaction have been highlighted as factors encouraging patients to exercise. Especially prevalent in those on a limited income, environmental barriers such as cost and a lack of adequate insurance have also been revealed as barriers among nonexercisers. It has also become clear that a lack of transportation can be a major hindrance. Time constraints brought about by lifestyle and other commitments is a factor common to both the general and patient population, often further compounded by the distance necessary to travel to an exercise facility [40, 91, 117–120]. It is also important to consider patient perceptions and potential barriers when promoting the maintenance of an exercise program. For example, working towards strengthening patient beliefs that they are able to continue exercise outside of the healthcare environment may be valuable [121].

As previously identified in OA patients [122], worry that exercise may have detrimental effects on joint health was also present in RA patients. Additionally, these patients had specific apprehensions regarding the effects of impact and repetitive exercises [91]. Joint pain has also been highlighted as a definitive barrier and has also been perceived as a prominent factor in determining the patients' exercise behaviour [120, 123]. In contrast, however, qualitative research suggests that patients *feel* that their joints benefit from exercise, with quotes indicating that joints are "lubricated" as a result of movement and patients feel more agile [124]. Similar perceptions indicating feelings of reduced pain have also been established [120]. However, evidence suggests that whilst patients with arthritis believe exercise to be an important factor in treatment, uncertainty about which exercises to do, and how to do them without causing harm, deters many patient from exercising at all [125]. Within the Obstacles to Action study [117] "insufficient advice from a healthcare provider" was a theme for the insufficiently active individuals, with queries relating to the type, frequency, and intensity of appropriate exercise.

Due to their condition RA patients are in frequent contact with their health professionals and this contact influences their perceptions about the role of exercise as part of their treatment. Moreover, because patients are constantly making decisions about treatment due to the fluctuating nature of RA, it is important for patients to understand how to modify their exercise according to their symptoms [126, 127]. The perceptions and behaviour of the rheumatologist is an important consideration when working towards a successful exercise prescription. Research by Iversen et al. [126] found that discussions about exercise were four times more likely to occur when the rheumatologist initiated exercise discussion, with discussions strongly impacting on the likelihood that a patient received an exercise prescription. Furthermore, although high-intensity exercise is now considered to provide the greatest benefit, the outcome expectations of patients, rheumatologists, and physiotherapists for high intensity exercise have been found to be significantly less positive than those for a conventional exercise program [128], with rheumatologists reporting their most negative attitudes towards aerobic exercise [127]. It is also interesting to note that, when examining the predictors of exercise behaviour in RA patients 6 months following a visit with their rheumatologist, Iversen et al. [126] found that if a patient's rheumatologist was currently performing aerobic exercise, the patient was more likely to be engaged in exercise.

A further issue relating to the health professional is their own assertion and certainty when prescribing exercise to those with RA. In the study by Iversen et al. [126], only 51% of rheumatologists reported they felt confident that they knew when exercises were appropriate for their patients with RA. Correspondingly, recent research has revealed that patients perceive uncertainties within the health profession regarding the impact of exercise on pain and joint health. In particular, this was in relation to whether the sensation of exercise discomfort or pain equated to actual joint damage and the effects of different types of exercise on the health of their joints [91]. These concerns pose a further challenge to RA patients [38, 45, 93, 129, 130].

Despite these reservations, patients have demonstrated an awareness of the advantages of exercise in terms of improving strength, mobility, and function and reducing pain [91]. However, due to the effects of RA and considering the aforementioned issues, if the perception of exercise as a positive feature of RA treatment is to supersede the apparent negative connotations, continual emphasis of the benefits of exercise in this population is of great importance [40, 77, 131]. This also means that clear exercise guidelines and prescription is necessary to attend to the fact that RA patients are currently faced with ambiguous and incomplete information. In addition to the pivotal role of the rheumatologist in influencing exercise prescription [126, 127], these recommendations are also relevant to the other health professionals involved in the treatment and care of RA patients (i.e., nurse specialists, physiotherapists, and occupational therapists) and significant others such as the patient's family and friends.

Key Recommendations for Health Professionals and Significant Others in the Improvement of Patient Perceptions Regarding Exercise. (i) Impart better advice regarding the effects and benefits of exercise; (ii) clarify specific exercise recommendations; (iii) consider methods of overcoming individual barriers to exercise.

4. Exercise Prescription for RA

The benefits of dynamic exercise in improving outcomes for patients with RA were highlighted following a systematic review by Van Den Ende et al. (1998) [72]. However, this early meta-analysis [72] was limited to six studies. In the intervening decade, numerous studies of varying quality have investigated the effects of aerobic and/or muscle strengthening exercise training programs for RA patients. This growing body of evidence, which is the subject of a number of systematic reviews [49, 50, 132–135], strongly suggests that exercise is effective in management of patients with RA, and does not induce adverse effects. Current guidelines now advise that exercise is beneficial for most individuals with RA (e.g., NICE guidelines, 2009). However, whilst the exercise benefits for RA patients are widely recognized, further studies are required to investigate the most effective exercise prescription (intensity, frequency, duration, and mode), the optimum modes of exercise delivery, and how adherence to training can be facilitated. A summary of exercise types and recommendations for individuals with RA based on current evidence is depicted in Table 1. Typically exercise interventions have focused on effects of aerobic training, strength training and a combination of aerobic training and strength training.

4.1. Aerobic Training. The aerobic activities most often included in exercise interventions are walking, running, cycling, exercise in water, and aerobic dance. Walking is a good mode of exercise as it is inexpensive, requires no special skills, is safe, and can be performed both indoors and outdoors. Regular brisk walking, even in short bouts, improves aerobic fitness and reduces aspects of CVD risk in healthy adults [136]. Cycling is also an excellent mode of aerobic activity that works the large muscle groups of the lower extremity. Cycling, in line with the guidelines in Table 1, improves aerobic capacity, muscle strength, and joint mobility (e.g., by 17%, 17%, and 16%, resp., [36]) with no exacerbation of disease activity. Water-based exercise has also been studied in RA. Hydrotherapy (the use of water) has been shown to be very effective for RA sufferers. As little as two 30-minute sessions for 4 weeks have been shown to significantly reduce joint tenderness, improve knee range of movement, and improve emotional and psychological well-being [137]. Dancing is another form of aerobic exercise which has reported improvements in aerobic power and resulted in positive changes in depression, anxiety, and fatigue, with no deterioration in disease activity in RA patients [41]. See Table 1 for aerobic exercise types and recommendations for individuals with RA.

4.2. Resistance Training. With a loss in muscle mass, and subsequent functional limitation and burgeoning disability a characteristic of the disease, RA patients should be encouraged to perform exercises which elicit muscle hypertrophy and strengthening. Several studies have demonstrated the beneficial effects for RA patients of performing muscle strengthening exercises, in particular PRT. These improvements include increases in muscle mass, reduction in fat mass, and substantial improvements in physical function [5, 63, 64]. Exercises that involve the large muscle groups of the upper and lower extremities as well as hand strengthening exercises have been shown to be effective [5, 63, 111]. The effects of a two-year dynamic strength training program in early RA patients [45] found significant improvements in muscle strength (19–59%) along with reductions in systemic inflammation, pain, morning stiffness, and disease activity. These findings suggest that long-term dynamic strength training can significantly improve the physical well-being of RA patients without exacerbating disease activity. Muscle strength gains from PRT programmes can also be maintained over several years of continued training at sufficient intensity [56, 92]. These examples have assisted in recommendations for strength training being developed, a summary of which is presented in Table 1.

Table 1: Summary of general exercise guidelines for RA. This information is derived from ACSM exercise management guidelines [140] and the research literature.

Benefit	Type of Exercise	How best to Achieve
Improve CV health	Cycling	60–80% HR max
	Walking	30–60 mins/session
	Swimming	3–5 days/week
	Dance	Increase duration, then intensity over time
Increase muscle mass & strength	Free weights	60–80% 1RM
		8–10 exercises (large muscle groups)
	Weight machines	8–12 reps/exercise
	Therabands	2-3 sets
		2-3 days/week
		Increase intensity over time
Increase ROM & flexibility for enhanced joint health	Stretching	10–15 minutes
	Tai Chi exercises	2 days/week
	Yoga/Pilates	
Improve balance*	One leg stance	On a regular basis
	Stability ball	
	Strengthening core muscles	

* The effects of balance training alone in RA patients to enhance functional capacity through increased proprioception and coordination and to reduce the risk of falls have yet to be conducted [98]. Thus the effectiveness and safety of balance training are unclear.

4.3. Combination of Aerobic and Strength Exercises. The optimum exercise program for RA patients would include both aerobic and resistance training. With poor cardiovascular health being the main cause of death in RA and with RA patients tending to have poor cardiorespiratory fitness, the requirement of aerobic exercise as part of treatment is crucial. Whilst the addition of strengthening exercises helps to mitigate rheumatoid cachexia and other musculoskeletal and joint health issues, and induces substantial improvements in physical function and the ability to perform ADLs. Both

types of exercises may need to be required for maintaining BMD [77].

4.4. General Exercise Guidelines. Exercise programs for RA patients should be initially supervised by an experienced exercise professional so that the program can be tailored to individual aspirations and adapted to the disease activity, joint defects, and symptoms of patients [93]. Following on from moderate to high intensity PRT or combined programs, RA patients have been shown to have high adherence rates to exercise in "real life" situation that help maintain improvements [56, 92]. Although, continuation of both high-intensity and high-frequency sessions may be required for maintenance of training gains in aerobic fitness, muscle strength, and functional ability [92], but evidence is still required regarding the minimum maintenance regimen. Home-based exercise programs have also been investigated and have been shown to improve quality of life and functional status [138]. However, due to the difficulties in ensuring that exercise of sufficient intensity is performed these exercises often fail to elicit significant increases in muscle strength or aerobic fitness. Although the minimal exercise dose for functional improvements and health maintenance is unknown, even regular training performed once weekly has been shown to improve function assessed subjectively by HAQ scores and health status [139].

As many RA patients have below average physical capacity, exercise training should be initiated at a lower intensity. Evidence of exercise prescription in RA patients with severe disability (Functional classes III and IV) is still lacking [57, 93]. Even so, strengthening exercises are recommended for all stages of RA [134]. Exercise programs, even over long periods and at high intensities, have been found to be safe as well as effective [92]. However, little is known as to whether exercise, particularly strength training, should be continued through inflammatory "flares" and further research should be conducted on the effects of exercise on joints that are already severely damaged. For continued training adaptation (i.e., increased fitness) a progression of the exercise dose (i.e., duration and/or intensity) is required.

Unfortunately, studies have also shown that most of the beneficial muscle adaptations are also lost after cessation of the exercise training [56]. Thus, as with healthy individuals, the beneficial effects of exercise (PRT, aerobic, mobility) are lost if training is discontinued.

5. Conclusions

The importance for the inclusion of exercise training in the treatment of RA is now clear and proven. Exercise in general seems to improve overall function in RA without any proven detrimental effects to disease activity. Thus all RA patients should be encouraged to include some form of aerobic and resistance exercise training as part of their routine care. More research is still required on the optimal dose and types of exercises, especially when combining types, as well as how best to incorporate exercise into the lives of RA patients across the variable course of the disease.

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Research Article

Physical and Leisure Activity in Older Community-Dwelling Canadians Who Use Wheelchairs: A Population Study

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Background. Physical and leisure activities are proven health promotion modalities and have not been examined in older wheelchair users. *Main Objectives*. Examine physical and leisure activity in older wheelchair users and explore associations between wheelchair use and participation in physical and leisure activity, and wheelchair use, physical and leisure activity, and perceived health. *Methods*. 8301 Canadians ≥60 years of age were selected from the Canadian Community Health Survey. Sociodemographic, health-related, mobility-related, and physical and leisure activity variables were analysed using logistic regression to determine, the likelihood of participation in physical and leisure activity, and whether participation in physical and leisure activities mediates the relationship between wheelchair use and perceived health. *Results*. 8.3% and 41.3% older wheelchair users were physically and leisurely active. Wheelchair use was a risk factor for reduced participation in physical (OR = 44.71) and leisure activity (OR = 10.83). Wheelchair use was a risk factor for poor perceived health (OR = 10.56) and physical and leisure activity negatively mediated the relationship between wheelchair user and perceived health. *Conclusion*. There is a need for the development of suitable physical and leisure activity interventions for older wheelchair users. Participation in such interventions may have associations with health benefits.

1. Introduction

Canadians aged 65 and older are 4 times more likely to use a wheelchair compared to those who are younger [1]. Previous estimates suggest that approximately 4.6% of adults aged 65 and older in the community [2] use a wheelchair for mobility. With predicted population estimates suggesting a two-fold increase in the number of adults aged 65 and older by 2020 [3], a substantial increase in the number of older wheelchair users is expected.

Both aging and wheelchair use are associated with deteriorations in physical functioning, which can lead to physiological deconditioning that is associated with numerous health risks, morbidity, and early mortality [4]. Lack of physical activity seemingly exacerbates physiological deconditioning, which can result in further accumulation of functional limitations and disability over time [5]. In fact, physical inactivity has been named the greatest health risk factor for older adults by the World Health Organization [6] and the 4th highest attributable risk of death in the USA [7]. It has been suggested that interventions which promote or maintain physical activity behavior among older adults with disabilities might provide an effective strategy for lessening the health risks of functional decline [8].

Physical activity, defined as bodily movements produced by skeletal muscles that result in energy expenditure [6], is a proven modality of health promotion. Physical activity interventions may optimize physical functioning and slow the spiralling effects of deconditioning in adults with chronic conditions [9] and disabilities [10]. The benefits of physical activity include associations with decreased morbidity and early mortality risk for older adults [7], improved stamina and muscle strength in individuals with chronic and disabling conditions, reduced anxiety and depression, and improved mood and general feelings of well-being [11]. Similarly, physically active adults with mobility impairments

are healthier than their less active peers and have decreased mortality risk [12] and younger physically active wheelchair users have improved functioning and less risk of early mortality risk compared to their inactive peers [10, 12].

General improvements in health and well-being for older individuals with a disability are also highly associated with participation in leisure activities. In fact, participation in leisure activities, defined as a nonobligatory activity that a person is engaged in during discretionary time [13], has been shown to be the primary predictor of well-being after stroke [14]. Participation in active leisure pursuits, which may include long walks, attending entertainment venues, and gardening, may also fit the definition of physical activity. Therefore, participation in active leisure pursuits may provide health benefits similar to those of participation in physical activity.

Previous findings have suggested that most of the association between physical impairment and lower well-being are explained by disability [14]. Adults with chronic conditions [15], older adults with arthritis [16] who participate in physical activity, and older adults after stroke who participate in leisure activity [17], report having better perceived health than those who do not participate in physical or leisure activity. Furthermore, participation in both physical and leisure activities has been shown to improve general well-being for individuals with disabilities [11, 18]. Due to the associations of perceived health with objective health measures [19], health care costs, and mortality [20], improved perceived health due to increased physical activity is arguably just as important as the physical benefits [21].

The benefits of participation in physical and other leisure activities would be similar for older adult wheelchair users, but the likelihood of participation for people with disabilities is low [14, 22]. The lack of participation may be a result of the numerous unique barriers faced by wheelchair users and the limited number of interventions that specifically address their complex needs. Physical activity participation levels among individuals with disabilities are affected by a complex set of barriers and facilitators that are unique to this population. These barriers and facilitators include the environment, emotional and psychological barriers, equipment barriers, information-related barriers, professional knowledge and training issues, attitudinal barriers, and availability of resources [23, 24]. Since older wheelchair users are a heterogeneous group, with varying disabilities, functional limitations, and a diverse range of likes and dislikes, current physical activity models provide few choices given the environmental barriers that wheelchair users face. Finding suitable durations, frequencies and types of physical activity for wheelchair users also poses a complex challenge due to the variations in ability and in ways of moving [25]. Strategies that incorporate methods for enhancing self-efficacy along with the promotion of physical and other leisure activities have been suggested as a means of improving quality of life among older adults who have a disability [8, 17].

The association between wheelchair use and participation in physical activity and other leisure activities has not been documented to date. A better understanding of the prevalence of physical activity in older community-dwelling wheelchair users and its association with perceived health may provide insight and rationale for the development of appropriate physical and leisure activity interventions, which forms the purpose of this study.

The primary objectives of this study were to (1) examine participation in physical and leisure activity in older wheelchair users and (2) determine if there is an association between wheelchair use and participation in physical and leisure activity. The secondary objectives were to (1) examine perceived health in older wheelchair users and (2) determine if participation in physical and leisure activity mediates the relationship between wheelchair use and perceived health. The primary hypotheses were (1) wheelchair users would report lower levels of participation in physical and leisure activity compared to older adults who do not use a wheelchair and (2) wheelchair use would be a significant risk factor for reduced participation in physical and leisure activity. The secondary hypotheses were (1) older wheelchair users would have lower perceived health than older adults who do not use a wheelchair and (2) participation in physical and leisure activity would negatively mediate the relationship between wheelchair use and perceived health in older wheelchair users.

2. Methods

2.1. Design, Data Collection, and Subjects. Findings from this study were based on data collected for Canadian Community Health Survey (CCHS) Cycle 3.1, which were collected by Statistics Canada between January and December 2005. The CCHS cycle 3.1 was the third cross-sectional survey in a series of larger national surveys designed to estimate health determinants, health status, and health system utilization of Canadians. Subsample 1 of CCHS 3.1 was chosen as it was specifically designed to provide additional estimates for the Health Utility Index, which included questions related to functioning and mobility, including wheelchair use. Details of the CCHS, including a methodological overview have been previously published [26].

The target population of the CCHS was Canadians aged 12 and over. Individuals living on Indian Reserves and on Crown Lands, institutional residents, including nursing homes and long-term care facilities, full-time members of the Canadian Forces, and residents of certain remote regions were excluded from the sampling frame. A total of 32,153 Canadians were surveyed. For the purposes of this study, responses from all adults aged 60 and older ($n = 8301$) were included in the analyses. This subgroup was further divided into three categories: wheelchair users, nonwheelchair users who required some form of assistance to walk, and non-wheelchair users who did not require any assistance to walk. The data were collected by Statistics Canada under the authority of the Statistics Canada Act. Access to the data was granted by Statistics Canada based on a peer-reviewed proposal for the study. While the research and analysis are based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.

Table 1: The questions used to calculate the Physical Activity Index. Respondents were asked: "Have you participated in the following physical activities for at least 15 minutes during the past 3 months".

Physical activity	
Walking	Bowling
Gardening/yard work	Baseball or softball
Swimming	Tennis
Bicycling	Weight training
Popular/social dance	Fishing
Home exercises	Volleyball
Ice hockey	Basketball
Ice skating	Soccer
In-line skating/roll	Other (#1)
Jogging or running	No physical activity
Golfing	Other (#2)
Exercise class/aerobics	Other (#3)
Skiing/snowboarding	

2.2. Classification of Wheelchair Use. Wheelchair use was identified using the Health Utility Index module of the CCHS. Respondents were initially asked, "Do you walk without difficulty or without support". Responses were coded dichotomously as "yes/no". If their answer was "no" or "unsure", respondents were asked, "Do you walk with assistance from another person" and "Do you walk with assistance using an assistive device". For the purposes of this study, responses from these two questions were collapsed into one variable, "walk with assistance", which was coded dichotomously as "yes/no". In addition, those who responded they required assistance to walk were also asked, "Do you require a wheelchair for mobility". If the respondent used a wheelchair, and could walk with assistance, they were classified as a wheelchair user in this study, and the responses were coded dichotomously as "yes/no". Two subgroups of older adults who did not use a wheelchair were identified (walk without difficulty or without support, and walk with assistance) for comparisons with older wheelchair users, and both were coded dichotomously as "yes/no".

2.3. Dependent Variables. Participation in physical and leisure activities were assessed using two questions from the Physical Activity module of the CCHS. The Physical Activity Index provided an indication of the amount of participation in physical activity through estimates of overall energy expenditure from physical activity. This was calculated using the type of physical activity, and frequency and duration of each physical activity session, as well as the MET (metabolic equivalent) values for each physical activity. Respondents were asked which physical activities they participated in for at least 15 minutes during the past 3 months from a preset list determined by Statistics Canada, which included activities such as going for a walk, gardening, and/or lifting weights. If the list did not include a specific activity, the respondent was given the option to respond "other". The "other" option was able to be selected up to three times by the respondent, thus capturing physical activities that were not necessarily included on the list. The response option, "did not take part in any physical activity for at least 15 minutes during the past 3 months" was also available to respondents. A complete list of the questions used to calculate the Physical Activity Index is shown in Table 1.

The MET is the energy cost of the activity expressed as kilocalories expended per kilogram of body weight per hour of activity, doing a physical activity during the past 3 months, the number of times, and time spent on each activity. The derived Physical Activity Index [27] resulted in three categories, including "Active", "Moderately Active", and "Inactive". "Active" corresponded to an average of 3.0+ kcal/kg/day of energy expenditure, or the amount of exercise required for cardiovascular health benefits. "Moderately Active" corresponded to energy expenditure of 1.5–2.9 kcal/kg/day, or some health benefits but little cardiovascular benefit. "Inactive" corresponded to energy expenditure below 1.5 kcal/kg/day or little to no health benefits. Although the Physical Activity Index included 3 questions which asked the respondents whether they participated in "other" physical activities during the past 3 months, it is not clear how the METs were calculated for these variables. For the purposes of this study, the three categories were recoded into dichotomous outcomes as "active (active/moderately active)/inactive". All nonresponses for this variable were coded as "inactive".

Participation in leisure activity was measured using one question on the CCHS, which asked whether or not respondents participated in leisure activities during the last 3 months. The responses were coded dichotomously as "yes/no". Leisure activities included playing cards or other games, listening to radio or music, doing crafts or other hobbies, visiting with family and friends, and attending events or entertainment. Leisure activities did not include reading a book or watching television.

Perceived health was assessed using the self-rated health variable, which is indicative of the respondent's health status at that point in time based on personal judgment. Self-rated health was assessed using a 5-point ordinal scale (poor, fair, good, very good, excellent), and responses were recoded as dichotomous outcomes for "poor-fair/good-excellent" for the purposes of study.

2.4. Independent Variables. Sociodemographic (age, sex, marital status, education, income) and health-related (body mass index (BMI), tobacco use, alcohol consumption, having a chronic condition) covariates were included for analyses. Age was collected as a continuous variable and sex was coded dichotomously as "male/female". Marital status was included in this report as a proxy measure of social support. It was originally coded using a 5-point ordinal scale (married, common law, widowed, divorced, single), but for analyses purposes it was collapsed into dichotomous variable ("married-common law/widowed-divorced-single"). Education level was reflective of whether or not the respondent graduated from high school or not. Household income was originally collected as a continuous variable, but was collapsed and coded dichotomously as "CAD < 14999/CAD > 15000".

Self-reports of height and weight were used to calculate BMI as a continuous variable. Respondents were asked to indicate their current tobacco use on a 3-point ordinal scale (daily, occasional, never), which was recoded dichotomously as "daily-occasional/never". Alcohol use was originally coded using a 4-point ordinal scale (regular, occasional, former, never), which was recoded dichotomously as "regular-occasional/former-never". The existence of one or more chronic conditions was assessed by whether respondents had been diagnosed by a healthcare professional as having a disease or other health condition that had lasted for, or was expected to last for, 6 months or longer. Responses were coded dichotomously as "yes/no".

2.5. Statistical Analysis. The raw data were obtained from the Statistics Canada Research Data Centre, University of British Columbia, Vancouver, British Columbia. As suggested by Statistics Canada, bootstrapping methods were used to apply sampling weights to estimate the variance of all point estimates based on 500 replications for each model in order to correct for unequal probabilities of selection in calculating variances.

The sample groups were described using summary statistics based on their group status.

Primary Objectives

Prevalence of wheelchair use in adults aged sixty and older was calculated using frequency counts.

Participation in physical and leisure activity (Physical Activity Index, participation in leisure activity) was compared between older adults who do and do not use a wheelchair using percent concordances.

Wheelchair use as a risk factor for decreased participation in physical activity was assessed using multivariate logistic regression, while controlling for sociodemographic and health-related variables. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for each variable to determine the differences in participation in physical and leisure activities between each group (older wheelchair users, older adults who could walk with support) and to examine the association between wheelchair use and participation in physical and leisure activities.

Secondary Objectives

The perceived health of older wheelchair users was compared to the perceived health of older adults who do not use a wheelchair using percent concordances.

The association between participation in physical and leisure activity and poorer perceived health in older wheelchair users was estimated using 2 multivariate logistic regression models. The initial model produced ORs and 95% CIs for each variable to estimate risk factors of poor perceived health in wheelchair users. Physical and leisure activity were then added to the model 250 to examine if participation in physical and leisure activity mediated the relationship between 251 wheelchair use and perceived health. All data were analyzed using SPSS (Version 13.0, Chicago, IL, USA) software.

3. Results

Weighted estimates suggested that the population of community-based Canadians aged 60 and older was approximately 5,362,000 and the estimated prevalence of wheelchair use within this population was approximately 100,000. The average (SD) age of the subsample of wheelchair users was 76.4 (9.5) years, of which 62% were female. The estimated proportions for the sociodemographic and health-related variables are described in Table 2.

3.1. Physical and Leisure Activity. Approximately 8.3% of community-based wheelchair users aged 60 and older reported being physically active, compared to 16.5% and 48.8% of older adults who walked with and without assistance, respectively. Participation in leisure activity was higher in all groups, with approximately 41.3% of community-based wheelchair users compared to 64.6% and 88.9% of older adults who walked with and without assistance, respectively, reporting they took part in leisure activities (Table 2).

3.2. Predictors of Participation in Physical and Leisure Activity. After controlling for sociodemographic (age, sex, marital status, income) and health related (BMI, tobacco use, alcohol consumption) variables, multivariate logistic regression showed that older adults who walked with assistance (Odds Ratio (OR) = 2.96, 95% CI 2.16, 4.04) were less likely than older adults who walked without assistance to participate in physical activity. Likewise, wheelchair users were even less likely to participate in physical activity compared to older adults who could walk (OR = 44.71, 95% CI 0.02, $3.31e^6$).

Tobacco use and higher BMI were significant risk factors for reduced physical activity, while increasing age was a slight risk factor for reduced participation in physical activity. Predictors of being physically active included being male, graduating from high school, and consuming any alcohol. Marital status, income, and having a chronic condition were not significant risk factors for reduced participation in physical activity. See Table 3 for detailed information of this model.

Both older wheelchair users (OR = 10.83, 95% CI 5.84, 20.05) and older adults who walked with assistance (OR = 4.24, 95% CI 3.08, 5.84) were less likely than older adults who could walk without assistance to participate in leisure activity, after controlling for sociodemographic and health-related variables. Tobacco use was a significant risk factor for reduced participation in leisure activity, while alcohol consumption had a protective association. Age, sex, marital status, education, income category, BMI, and having a chronic condition were not significant predictors of participation in leisure activities.

See Table 3 for detailed information of this model.

Table 2: Description of Canadian Community Health Survey 3.1 subsample 1 respondents aged 60 and over.

	Walk (n = 7217)	Walk with assistance (n = 935)	Wheelchair user (n = 149)
Population estimates	4738248 (88.4%)	523577 (11.3%)	99992 (1.9%)
Sociodemographic variables			
Age mean (SD), range	69.6 (7.4), 60–100	76.8 (8.7), 60–98	76.4 (9.5), 60–93
Sex (%)			
Male	47.4	34.9	38
Female	52.6	65.1	62
Marital status (%)			
Married/common law	68.5	45.6	49.2
Single/widowed/divorced	31.5	54.4	50.8
Graduated high school (%)			
Yes	51.7	38.3	46.7
No	48.3	61.2	53.3
Income (%)			
CAD < 14999	8.3	85	81.4
CAD > 15000	91.7	15	18.6
Health-related variables			
BMI† (m/Kg^2), mean (SD)	26.1 (4.3)	27.4 (5.9)	26.6 (5.9)
Smoker type (%)			
Daily/occasionally	12.6	12.6	15.1
Never	87.3	87.4	84.9
Alcohol consumption (%)			
Regular/occasional	72.8	56.4	57.4
Former/never	27.2	43.6	42.6
Has a chronic condition (%)			
Yes	88	97.9	100
No	12	2.1	—
Dependent variables			
Physical activity index (%)			
Active/moderately active	48.4	16.5	8.3
Inactive	51.6	83.5	91.7
Participate leisure activity (%)			
Yes	88.9	64.6	41.3
No	11.1	35.4	58.7
Self rated health (%)			
Poor/fair	18.1	56.8	74.2
Good/very Good/excellent	81.9	43.2	25.8

Note: results are weighted to provide proportional representation of the Canadian population.
†Body mass index.

3.3. Risks Factors for Poor Perceived Health. Approximately 74.2% of community-based wheelchair users aged 60 and older reported having poor perceived health, compared to 56.8% and 18.1% of older adults who walked with and without assistance, respectively (Table 2).

Multivariate logistic regression suggested that using a wheelchair (OR = 10.56, 95% CI 5.90, 18.92, $P < .001$) and requiring assistance to walk (OR = 4.18, 95% CI 3.05, 5.75, $P < .001$) were significant risk factors for poor perceived health compared to older adults who walked without assistance. Having a chronic condition, smoking, and having an income of less than 14,999 CAD were also significant risk factors for poor perceived health, while graduating from high school and consuming alcohol had a protective effect. Age, sex, and BMI were not significant predictors of poor perceived health in older adults.

See Table 4 for detailed information of this model.

When participation in physical and leisure activity was added to the model, logistic regression analyses showed that both reduced participation in physical activity (OR = 1.64,

Table 3: Association of wheelchair use, sociodemographic and health-related variables on physical and leisure activity in older Canadian adults.

Sociodemographic variables	*Physical activity index*			*Participates in leisure activities*		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)	1.03	1.02, 1.05	<.001	1.02	1.00, 1.04	.02
Sex						
Male	0.72	0.61, 0.84	<.001	1.16	0.93, 1.44	.18
Marital status						
Married/common law	0.98	0.83, 1.16	.83	1.08	0.86, 1.36	.52
Education						
Graduated from high school	0.62	0.52, 0.73	<.001	0.61	0.49, 0.76	<.001
Income						
CAD < 14999	1.05	0.81, 1.34	.74	1.14	0.86, 1.51	.37
Health related variables						
BMI (m/Kg^2)	1.07	1.05, 1.09	<.001	1.04	1.01, 1.06	<.001
Type of smoker						
Regular/occasional	1.95	1.51, 2.52	<.001	1.81	1.33, 2.46	<.001
Alcohol use						
Regular/occasional	0.74	0.61, 0.89	<.001	0.54	0.43, 0.69	<.001
Has a chronic condition						
Yes	1.12	0.086, 1.46	.41	7.60	3.20, 18.03	<.001
Wheelchair use						
No (walks with support)	2.96	2.16, 4.04	<.001	4.24	3.08, 5.84	<.001
Yes	44.71	0.002, $3.3e^6$	.51	10.83	5.84, 20.05	<.001

95% CI 1.29, 2.07) and leisure activity (OR = 1.67, 95% CI 1.24, 2.26) were significant risk factors for poor perceived health. Adding participation in physical and leisure activity to the model reduced the Odds Ratio for both older wheelchair users (OR = 6.94, 95% CI 3.81, 12.65, $P < .001$) and older adults who could walk with assistance (OR = 3.63, 95% CI 2.64, 4.99, $P < .001$). The other sociodemographic and health-related variables were not influenced by the addition of participation in physical and leisure activity to the model (Table 4).

4. Discussion

The prevalence of wheelchair use in adults aged 60 and older adults living in the community was estimated to be approximately 100,000. Although this estimate corresponded with previous estimates of wheelchair users aged 65 and older by Shields [1] ($n = 81300$) and Clark and Colantonio [2] ($n = 88300$), it is thought to be an underrepresentation of the actual number of Canadian wheelchair users aged 60 and older. Despite efforts to account for unequal sampling probabilities, the small CCHS subsample only includes community living individuals and not those who live in Indian reserves or in institutions.

The overall purpose of this paper was to examine participation in physical and leisure activities in older wheelchair users and to examine the association of wheelchair use and physical and leisure activity on perceived health. As hypothesized, wheelchair users were significantly less likely to participate in leisure activities compared to those who walked with or without support and wheelchair use seemingly increased the likelihood for reduced participation in physical activity. Wheelchair use was also a significant risk factor for poor perceived health, and participation in physical and leisure activity were shown to have a negative mediating effect on the associations between wheelchair use and perceived health.

Although recent findings suggest the number of physically active older adults is slowly increasing [28], there is still a large portion of the population who are not active enough to receive health benefits [9]. Findings from this study suggest this is particularly true for older adults who use wheelchairs, as only 8.3% of wheelchair users reported participating in physical activity compared to 48.8% of older adults who walked without support. Due to the collapsing of the "moderately active" and "active" variables within the Physical Activity Index, being physically active within this sample represented an energy expenditure of 1.5 to greater than 3 kcal/kg/day. Therefore, the percentage of individuals who meet the recommended 1000 kcal/kg/day [29] is likely much smaller than the reported findings in this study values with respect to prevalence of physical activity.

A larger proportion of the population reported participating in leisure activity. Since some of the leisure activities reported may be active leisure pursuits, it is likely that a portion of the 41.3% of older wheelchair users who reported taking part in leisure activities would be participating in

Table 4: A Summary of risk factors for predictive models of perceived health in older Canadian adults.

Sociodemographic variables	*Perceived health (model 1)*			*Perceived health (model 2)*		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)	1.02	1.01, 1.04	<.001	1.02	1.00, 1.03	.05
Sex						
Male	1.15	0.92, 1.43	.21	1.20	0.96, 1.50	.11
Marital status						
Married/common law	1.0	0.80, 1.25	.98	1.00	0.80, 1.25	.35
Education						
Graduated from high school	0.56	0.46, 0.70	<.001	0.61	0.49, 0.76	<.001
Income						
CAD < 14999	1.13	0.85, 1.50	.40	1.14	0.86, 1.51	.37
Health related variables						
BMI (m/Kg^2)	1.04	1.01, 1.06	<.001	1.03	1.00, 1.05	.04
Type of smoker						
Regular/occasional	1.89	1.38, 2.59	<.001	1.72	1.26, 2.36	<.001
Alcohol use						
Regular/occasional	0.52	0.41, 0.66	<.001	0.55	0.43, 0.70	<.001
Has a chronic condition						
Yes	7.60	3.21, 18.07	<.001	7.48	3.18, 17.57	<.001
Wheelchair use						
No (walks with support)	4.18	3.05, 5.75	<.001	3.63	2.64, 4.99	<.001
Yes	10.56	5.90, 18.92	<.001	6.94	3.81, 12.65	<.001
Physical Activity Index						
Inactive	—			1.64	1.29, 2.07	<.001
Participates in leisure activities						
No	—			1.67	1.24, 2.26	<.001

Model 1: impact of wheelchair use on perceived health, controlled for sociodemographic and health-related variables.
Model 2: impact of wheelchair use on perceived health after adding physical activity behaviours to the model, controlled for sociodemographic and health-related variables.

more physical activity than if they were not participating in those leisure activities. It is possible that physical activity levels in older wheelchair users may have been underestimated by the Physical Activity Index alone. However, findings from a recent study suggest that individuals with disabilities are limited to more passive leisure activities, due to limited mobility, loss of function, and fatigue [17]. Regardless, it is clear that wheelchair users take part in less leisure activity compared to 64.6% of older adults who walk with support and 88.9% of adults who walk without support. This is an important finding as participation in leisure activities has been shown to have similar health benefits as participation in physical activity for older adults, including contributions to successful aging by reducing the risk of premature death [30], and improving overall function [31].

Logistic regression analyses suggest that wheelchair use may be a risk factor for reduced participation in physical activity (OR = 44.71) and is a significant risk factor for reduced participation in leisure activity (OR = 2.96). Although the odds ratios suggest that wheelchair use increased the likelihood of not participating in physical activity, the extremely large variance of these estimates suggests these findings must be interpreted with caution. Despite the large variance in this point estimate for the Physical Activity Index, it is clear that a large portion of older wheelchair users are not physically active and are not receiving the benefits of physical activity. The other protective factors in the logistic model for physical activity and leisure activity are supported by previous findings of older adults [9], which showed that males who graduated from high school and consumed alcohol were more likely to take part in physical activity behaviour.

Wheelchair use (OR = 10.56) was also found to be a significant risk factor for poor perceived health compared to those who did not use wheelchair. Similar to previous findings, having a chronic condition [7, 32], smoking [33], and having a higher BMI were also significant risk factors for poor perceived health, while graduating from high school and consuming alcohol [9] had a protective effect on perceived health.

Reduced participation in physical activity (OR = 1.64) and leisure activity (OR = 1.67) was also a significant risk factor for poor perceived health. Moreover, when physical activity behaviours were added to the model, using a wheelchair (OR = 6.99) was reduced somewhat, but was still a significant factor in predicting poor perceived health.

These findings suggest that regardless of sociodemographic and health-related variables, participation in physical activity behaviours can significantly reduce the risk of having poor perceived health in older wheelchair users. This is supported by previous findings which showed that participation in leisure time physical activity had a graded and continuous association with better self-rated health in older adults [34]. Furthermore, this study also suggested that even small amounts of leisure-time physical activity are related to a better health status, which can be summarized and linked to the clinical and public health recommendations that "even a little is good; more is better" [35].

The health benefits of physical [6, 7, 10, 36] and leisure activity [14, 17, 18, 24] are well documented. Findings from this study suggest that participating in physical and leisure activity is associated with improved perceived health, which may also be associated with improved quality of life for older wheelchair users. Furthermore, ratings of perceived health have been shown to be highly predictive of mortality [32]. While the benefits of exercise are well known, it is likely that wheelchair users who are quite sedentary may benefit from small increases in physical and leisure activities that require more bodily movement than what is normally done. The findings from this study highlight the need for targeted surveys of older wheelchair users that incorporate appropriate, accessible, and desired physical and leisure activities, and indentify the need for the development of interventions that include a broad range of physical and leisure activities.

The cross-sectional nature of this study imposed inconclusive findings regarding the causality and direction of the relationships of the variables studied. It can only be concluded that there are associations between wheelchair use and participation in physical and leisure activity and between participation in physical and leisure activity and poorer perceived health.

Also, the pre-defined structure of the questions imposed some uncontrollable limitations to the findings of this study. The study variables (i.e., physical and leisure activity) were challenging to define due to the structure of the questions on the CCHS. The broad questions asked about physical and leisure activity left some uncertainty about the activities the respondents participated in. Due to the challenges with defining physical and leisure activity, the results must be interpreted with caution. The types of physical activities asked of the respondents and the uncertainty of the methods used for calculating energy expenditure for the "other" categories of the Physical Activity Index may not have provided an ideal assessment of participation in physical activities for older wheelchair user, which may include wheeling or other physical activities that can be done in a wheelchair. The inclusion of participation in leisure activities in the models must also be interpreted with caution, as there is uncertainty as to which specific leisure activities the respondents took part in. However, since some leisure activities fit the definition of physical activity, and because there are some similar health benefits of both physical and leisure activity, it was felt that examining the associations between wheelchair use and participation in leisure activity was important for gaining a comprehensive understanding of participatory behaviours of older wheelchair users. It should also be noted that activities of daily living and occupational activities, both of which may include activities that fit our definition of physical activity, were not included in our analyses. Therefore, it is likely that our findings underrepresent the amount of physical activity that older wheelchair users take part in. Despite the exclusion of activities of daily living and occupational activities, our findings do suggest that very few older adult wheelchair users participate in enough physical and leisure activities to receive health benefits.

5. Significance

Findings from this study suggest that older wheelchair users are not as physically or leisurely active as those who do not use a wheelchair; current physical activity measurement tools are not appropriate for older wheelchair users; there is a need for the development of accessible physical and leisure activity interventions. Interventions that focus on promoting physical and leisure activities may lead to increased participation in physical and leisure activity, which is associated with improvements in perceived health for older wheelchair users. Appropriate interventions for this target population should focus on counselling for behaviour change and should include suitable and accessible activities that are appealing to older adult wheelchair users.

6. Conclusion

Wheelchair use is associated with reduced participation in physical and leisure activity, and both wheelchair use and reduced physical and leisure activity are significantly associated with poor perceived health. Perceived health is correlated to objective health measures, both of which may be improved through interventions that target health-related behaviours changes, such as participation in physical and leisure activity. Participation in such interventions may be associated with health benefits.

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Review Article

Physical Activity and Telomere Biology: Exploring the Link with Aging-Related Disease Prevention

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Physical activity is associated with reduced risk of several age-related diseases as well as with increased longevity in both rodents and humans. Though these associations are well established, evidence of the molecular and cellular factors associated with reduced disease risk and increased longevity resulting from physical activity is sparse. A long-standing hypothesis of aging is the telomere hypothesis: as a cell divides, telomeres shorten resulting eventually in replicative senescence and an aged phenotype. Several reports have recently associated telomeres and telomere-related proteins to diseases associated with physical inactivity and aging including cardiovascular disease, insulin resistance, and hypertension. Interestingly several reports have also shown that longer telomeres are associated with higher physical activity levels, indicating a potential mechanistic link between physical activity, reduced age-related disease risk, and longevity. The primary purpose of this review is to discuss the potential importance of physical activity in telomere biology in the context of inactivity- and age-related diseases. A secondary purpose is to explore potential mechanisms and important avenues for future research in the field of telomeres and diseases associated with physical inactivity and aging.

1. Introduction

Aging is a complex biological phenomenon and the factors governing the process of aging and longevity are only beginning to be understood. Physical inactivity increases the risk of several age-related diseases such as cardiovascular disease (CVD), hypertension, osteoporosis, stroke, and type 2 diabetes [1]. Becoming or remaining physically active in old age has been shown to reduce the risk of morbidity and mortality from these age-related conditions [2, 3]. Moreover, multiple reports have revealed the lifespan extending potential of physical activity (PA) [4–7]. Consistently performed PA appears to slow the rate of cellular and molecular damage accumulation and blunt the decline in physiological function that is characteristic of the aging process [8, 9]. Despite these findings, the causal molecular and genetic links between PA and the reduction in age-related disease risk remain elusive.

A potential link between aging and increased disease risk is shortened and/or dysfunctional telomeres. The role of telomeres in several diseases associated with physical inactivity and aging has recently been elucidated [10] and recent epidemiological and experimental evidence points to PA as being able to influence telomere biology [11–13]. It should be noted that telomeres are also associated with other diseases, such as neurodegenerative diseases and cancer; however, this review will focus primarily on organ systems involved in diseases associated with physical inactivity and aging such as blood cells and cardiovascular and musculoskeletal systems. In the present review, we will (1) discuss the recent evidence of telomere modulation in physical inactivity- and age-related diseases, (2) describe the relationships observed between telomeres and PA, and (3) explore possible mechanisms underlying these relationships and suggest future research directions.

2. Telomeres in Aging

Many hypotheses of aging have been proposed and tested, but no single hypothesis fully explains the complex intricacies of biological aging. A popular model is the "telomere length hypothesis" of aging that is set within the context of

cellular senescence. Telomeres are repeated DNA sequences (5′-TTAGGG$_n$-3′) found on the ends of linear chromosomes that protect the ends of DNA from damage during replication. Telomeres also act as a "mitotic clock" [14], shortening with every cell division until cellular senescence occurs (i.e., critically short telomeres lead to senescence, where a cell is metabolically active but unable to repair damage or divide). As the senescent population of cells in a tissue increases with advancing age, the function of the tissue becomes impaired and displays an aged phenotype [15]. Thus, telomeres and their length are considered at minimum an important aging biomarker but may also act as a critical mechanism for age-related decline [10, 16–18]; however, whether short telomeres are cause or consequence of typical physiological aging and age-related disease is yet to be determined. Beyond aging, shortened telomeres are implicated in genetic syndromes such as dyskeratosis congenita [19, 20], Werner syndromes [21, 22], and aplastic anemia [23]. Also several studies have identified gene variants in the telomere-related proteins that are associated with altered telomere lengths [24–27]; their role in the predisposition to age- and disease-related traits is unclear at this time.

Telomere length is highly variable among mammalian species and among tissues within a species [28]. Human telomeres are typically 5–12 kilobases in length [29], while mouse and rat telomeres are much longer (up to 150 kilobases depending on inbreeding status and strain) [28]. This is important to consider when interpreting telomere data from animal studies, as telomere length dynamics between mice and humans are different, though mouse models with shorter telomeres are an important resource in the study of comparative telomere biology [28, 30]. In humans, tissue-specific telomere length is detectable at birth with a rate of attrition estimated at 30–150 base pairs per year in leukocytes and fibroblasts [31, 32]. Telomeres shorten during DNA replication due to the end-replication problem, in which the DNA polymerase enzyme cannot fully copy the end of the DNA strand during DNA replication associated with mitosis and cell division [31].

In certain cells with high mitotic activity (e.g., germ line and progenitor cells; immune cells), the end-replication problem is overcome by the enzyme telomerase that maintains telomere length homeostasis by adding 5′-TTAGGG-3′ repeats to telomeres following DNA replication [33]. Telomerase is a ribonucleoprotein complex consisting of an enzymatically active protein component (TERT) and an RNA template (TERC) [34]. Telomerase knockout mice (both *Tert* and *Terc* knockouts) have been developed and used as models for several age-related diseases, with *Tert*$^{-/-}$ animals identified as a model of CVD [35]. A recent study has shown that TERT reactivation in aged TERT-deficient mice was able to alleviate signs of aging showing the importance of the telomere system in tissue health and aging [36] and providing further evidence for telomere shortening as a likely factor in age-associated organ decline and disease risk [36–38]. Though telomerase typically has low activity in postmitotic cells, telomerase is activated along with the expression of other oncogenes (e.g., MYC, RAS) in most cancers and immortalized cell lines. This results in a paradoxical role for telomerase, with critical functions in both health and disease depending on the cell type [39, 40].

Telomeres are protected by a six-protein complex termed "shelterin", which functions to monitor telomere length and protect DNA telomere ends from being recognized by DNA damage response proteins and nucleases [41]. Shelterin is also involved in cell cycle regulation and is important for maintenance of cell viability [41]. Shelterin consists of six key proteins bound to chromosome ends, including three components that interact directly with telomere DNA: telomere-repeat binding factors 1 and 2 (TRF1 and TRF2) and protection of telomeres 1 (POT1). In addition, shelterin includes three additional proteins that each interact with the three telomere DNA-binding proteins. The regulation of telomere length by telomerase and shelterin components is critical in determining cellular fate.

Recent studies have associated various aspects of telomere biology (e.g., telomere length and expression of telomere-related gene products) to diseases of aging, including but not limited to CVD and CVD risk factors, diabetes phenotypes, and musculoskeletal diseases. Many of these same diseases and risk factors have also been associated with an inactive lifestyle. Physical activity and exercise training have been associated not only with prevention and improvement of disease symptoms but also with telomere length, indicating a possible role for PA influencing telomere biology as a potential mechanism for prevention or delay of age-related disease. Figure 1 presents an overview of the major factors in the regulation of telomere biology as related to both age-related diseases and cancer. The research described below shows a clear association of shortened telomere length with diseases associated with aging and inactivity, though future research is needed to determine if telomere shortening is an etiology of these diseases.

3. Telomeres and Age- and Inactivity-Related Diseases

3.1. Telomeres and Cardiovascular and Metabolic Disease Risk Factors. Cardiovascular disease and its risk factors represent a major proportion of the population's disease burden during aging and PA is a potent means of reducing the risk of developing CVD. Thus, CVD and other CVD risk factors are considered diseases of both physical inactivity and aging. Several studies have associated shortened telomere length in peripheral blood mononuclear cells (PBMCs) and other tissues to hypertension and other CVD risk factors. A common hypothesis is that leukocyte telomere length reflects the overall systemic burden of oxidative stress and inflammation, which are two key risk factors for CVD, thus providing a potential physiological link between telomeres and CVD [42].

For example, Jeanclos et al. [43] showed a relationship in twins that telomere length was inversely related to pulse pressure. Aviv et al. [44] showed that abdominal aorta cells displayed telomere shortening as a function of age indicating an age-dependent loss of vascular cell function. Benetos et al. showed over multiple studies in

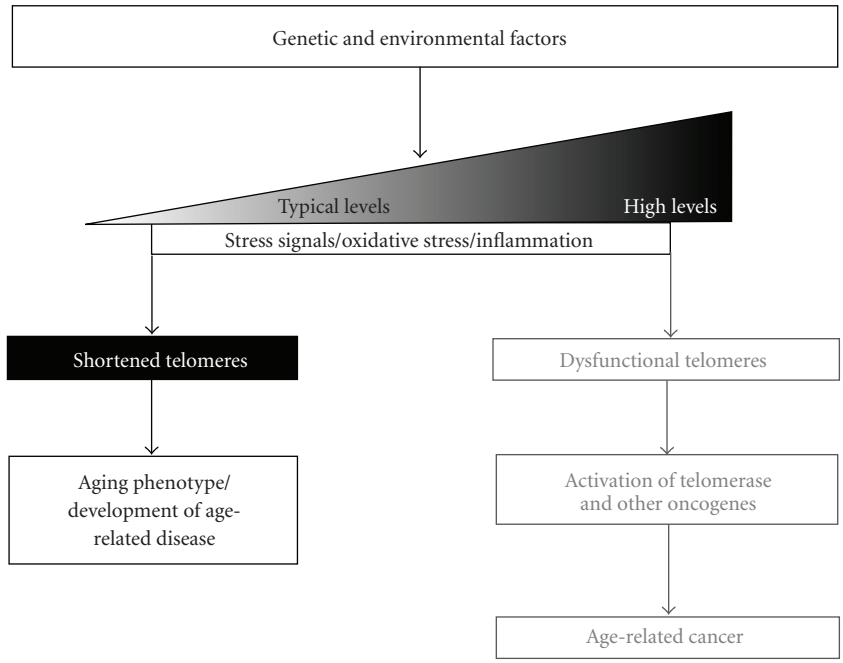

Figure 1: The major factors leading to age-related disease or cancer phenotypes are shown. Interaction of genetic and environmental factors can lead to varying levels of DNA damage, oxidative stress, and inflammation, all of which can contribute to shortened or dysfunctional telomeres, depending on the extent of damage. Typically-shortened telomeres can result in cell cycle arrest, tumor suppression, and loss of functional tissue via senescence or apoptosis/necrosis and an aging phenotype. At the extreme, DNA damage (e.g., gene mutations) and subsequent activation of oncogenes, such as TERT and telomerase activity, can lead to age-related cancer. Becoming or remaining physically active may prevent or delay the onset of many age-related diseases and even some cancers, potentially through protection of telomeres.

men that higher pulse wave velocity and pulse pressure [16], carotid artery plaques [45], and plasma aldosterone levels [46] were associated with shorter telomeres. Patients with chronic heart failure have also been observed to have shorter leukocyte telomere lengths [47]. In the Framingham Heart Study and the Cardiovascular Health Study shorter telomere lengths were associated with increased oxidative stress, insulin resistance, and hypertension [48, 49]. In two other studies by the Aviv group in the Framingham Heart Study shorter telomeres were associated with increased renin-aldosterone ratios and to carotid artery thickness in men [50, 51]. In an interesting study of the inheritance of telomere length, Brouilette et al. [52] measured telomere length in the healthy offspring of both coronary artery disease (CAD) patients and nondiseased controls. The results revealed shorter leukocyte telomere lengths in the offspring of CAD patients compared to the offspring of healthy controls. The authors showed that offspring telomere length was significantly associated with parental telomere length and that the telomere length difference between the two groups represented the equivalent of 17 years of telomere length attrition [52]. Brouilette et al. [53] also showed that statin use significantly reduced telomere shortening in CVD patients and that telomere length may be a good predictor of successful statin treatment. In a cross-sectional study of young and older men, the angiogenic CD31+ cell fraction of PBMCs were isolated and characterized for telomere length, telomerase enzyme activity, and various cellular function phenotypes. The results showed that older men had shorter CD31+ telomere lengths and were more susceptible to apoptotic stimuli compared to the younger men [54]. This study provides an important link between telomeres, angiogenic cells, aging, and risk for CVD by showing decreased stress resistance and cellular function concordant with reduced telomere length. Interestingly, Ornish et al. [55] showed that a lifestyle intervention including exercise and low-fat diet was able to lower LDL cholesterol levels and increase telomerase activity in leukocytes. Though preliminary, these data indicate that lifestyle intervention, through a reduction in systemic oxidative stress and inflammation, may increase telomerase activity and telomere maintenance.

Two recent longitudinal studies in separate cohorts of CVD-affected individuals have confirmed the cross-sectional findings described above, but with an unanticipated complexity [10, 56]. Farzaneh-Far et al. demonstrated that the most potent predictors of telomere shortening in CVD patients were age, male sex, and increased waist-to-hip ratio [10]. Surprisingly, only a portion of the patients showed the expected telomere shortening, and telomere length was shown to be maintained or even lengthened with advancing age in some individuals, showing that *in vivo* telomere dynamics are more complex than a simple, predictable shortening of the mitotic clock [10, 56]. Vasan et al. [42] and Kuznetsova et al. [57] also recently observed longer leukocyte telomere length in individuals with left ventricular hypertrophy. The groups speculate that longer

telomere lengths in diseased patients may be due to an increased reserve potential of angiogenic progenitor cells in individuals with left ventricle hypertrophy, since left ventricle hypertrophy is highly dependent on angiogenesis, or altered levels of growth factors (e.g., IGF-1) and activation of telomerase. The unexpected findings in longitudinal studies that telomeres can take three different trajectories (expected shortening, maintenance, and lengthening) deserve special attention. Designing studies to elucidate the underlying factors associated with the different telomere trajectories and the cellular outcomes will provide insight into our understanding of whether telomere dynamics are cause or consequence in the progression of CVD.

Multiple studies have also associated telomere length with the presence of type II diabetes and diabetes-related phenotypes (e.g., insulin resistance and impaired glucose tolerance). Risk factors for and symptoms of type II diabetes, including impaired glucose tolerance, increased levels of glycosylated hemoglobin, and increased adiposity, have been associated with shorter telomeres in leukocytes [58–61]. Al-Attas et al. showed that higher HOMA-IR values in males and reduced serum levels of adiponectin in females were the best predictors of shortened telomere length in leukocytes [62]. In subjects with CAD but with or without metabolic syndrome, it was observed that telomere length and telomerase enzyme activity were lower and oxidative DNA damage (8-oxo-deoxyguanine) higher in endothelial progenitor cells from those CAD patients with metabolic syndrome [63]. In a cohort of women, Epel et al. [64] associated stress arousal and CVD risk factors to lower telomerase enzyme activity and shorter telomeres. Specifically lower telomerase enzyme activity was associated with higher fasting glucose, poor lipid profile, increased abdominal adiposity, and a composite metabolic syndrome variable. Shorter telomeres were also associated with increased levels of circulating stress hormones (cortisol and catecholamines).

In two studies by Tarry-Adkins et al. [65, 66], the researchers showed in two different tissue types that poor maternal nutrition can influence telomere length of the offspring. Since poor maternal nutrition and the subsequent "catch-up growth phase" are associated with increased risk of CVD and type II diabetes, the authors tested the hypothesis that telomeres would be shorter in offspring of nutritionally deprived mothers. They observed that telomere length was shorter in aorta and pancreatic islets in the offspring of animals with poor maternal nutritional status that were undergoing catch-up growth compared to control offspring. More recently Salpea et al. [67] showed that individuals with type II diabetes had shorter telomere lengths than controls and telomere length was positively correlated with total antioxidant levels in patient leukocytes. Oxidative stress, which is known to shorten telomeres and to be higher in type II diabetics, may provide a link between disease and telomere length. These data indicate that altered metabolic status induced by type II diabetes and related traits is associated with shorter telomeres, though, similar to CVD, whether or not losses of telomere length are a cause or consequence of metabolic disease is unclear.

3.2. Telomeres and Musculoskeletal Diseases Associated with Physical Inactivity and Aging. The losses of bone mineral density and skeletal muscle mass with advancing age have important consequences for morbidity and mortality in older men and women. Fewer studies of telomere biology have been performed in these tissues, but the results generally indicate a similar association to that observed for CVD and metabolic disease. For example, several studies have associated reduced bone mineral density and shortened telomere length in both men and women [68, 69]. In a longitudinal study of 84 men, researchers observed a positive correlation between age-adjusted leukocyte telomere length and distal forearm bone mineral density [68]. Other studies have not observed an association between telomere length and markers of bone health, including a Health ABC study in which telomere length was not associated with markers of bone health over a five-year period [70, 71]. The cell type examined in those studies (leukocytes) may, however, confound the results in that bone tissue telomere length or bone progenitor cell telomere length may be a better indicator of bone health. For instance, chondrocytes of aged or diseased (osteoarthritic) individuals near the osteoarthritic lesions had shorter telomere lengths and exhibited increased evidence of cell senescence than cells farther from the lesions [72].

Few studies have examined telomere length in sarcopenia or other skeletal muscle phenotypes. Skeletal muscle is unique in that it consists of multinucleated muscle fibers and multiple niche populations of singularly nucleated cell types, the most well-characterized being satellite cells [73]. Skeletal muscle is also considered to be postmitotic, with only the satellite cells actively dividing when new nuclei are needed within the skeletal muscle fiber. When skeletal muscle satellite cells are activated to divide and incorporate into muscle fibers as new myonuclei, the fibers' average telomere length is reduced [73, 74]. The newly added satellite cell nuclei represent the nuclei with the shortest telomeres since these newly added nuclei would have been actively dividing over time [73, 74]. Minimum telomere length in skeletal muscle is thus thought to represent the replicative history of satellite cells [75]. As such, over time skeletal muscle telomere length can change despite its postmitotic condition [73, 76, 77].

Thus, when measuring skeletal muscle telomere length, mean and minimum telomere length (i.e., the shortest of the lengths observed in a tissue sample), representing fiber telomere length and satellite cell telomere length, respectively, must be analyzed and interpreted correctly [73]. A recent investigation showed that skeletal muscle telomere length was reduced in elderly individuals compared to young controls, as well as a modest trend for shorter skeletal muscle homogenate telomere lengths in sarcopenic compared to nonsarcopenic individuals [78]. Other studies in skeletal muscle have focused on the replicative potential and regenerative capacity of satellite cells rather than skeletal muscle per se. For example, Wernig et al. studied the regenerative capacity of satellite cells and showed a slight decrease in mean telomere length with age in those cells, corresponding to reduced regenerative capacity [79]. Data

from several different muscular dystrophies indicate shortened satellite cell and skeletal muscle homogenate telomeres and telomere-related dysfunction associated with the muscle degradation and atrophy [77, 80, 81]. When considered together, these studies indicate that skeletal muscle telomere length can change and moreover that using diseases such as muscular dystrophies as extreme skeletal muscle remodeling models may provide an avenue to understand the complex skeletal muscle telomere biology landscape [82]. The role of telomeres and telomerase in skeletal muscle and satellite cells was reviewed recently [73].

4. Telomeres and Physical Activity

As shown in Table 1, several reports, including one from our laboratory, have associated PA or exercise training with alterations in telomere length and/or the network of proteins that interact with telomeres [11, 12, 73, 76, 83–85]. These results provide evidence of a link between PA and aging at the cellular level and indicate the possibility of a mechanistic link between the influences of PA in the attenuation of age-related diseases.

Collins et al. [76] were the first to demonstrate an association of telomere length with physical activity when they reported excessive telomere shortening in skeletal muscle of endurance athletes with severe fatigued athlete myopathic syndrome (FAMS) compared to age- and training volume-matched athletes. In a follow-up study by the Collins group, shorter minimum telomere lengths were observed in those endurance athletes with the highest number of years and hours spent training [85]. These results indicate that long-term endurance training by highly trained athletes may be a significant stressor to skeletal muscle and/or satellite cell telomeres, as indicated by the shorter minimum telomere lengths.

Beginning in 2008, a number of groups began to study the association of typical, moderate physical activity with telomere length in humans. Ponsot et al. [86] investigated skeletal muscle telomere length in physically active and inactive men and women in two age groups, young and old, and observed that telomere length was similar within an age group regardless of activity level, indicating that moderate PA is not detrimental to skeletal muscle telomere length. In epidemiological studies by Cherkas et al. [11] and Ludlow et al. [12] a positive association between PA and leukocyte telomere length was observed up to moderate levels of typical PA, while high levels of PA were associated with shorter PBMC telomere lengths [12]. These results were not fully replicated in a large cohort of older Chinese individuals (~72 yr old), though telomere length tended to be lowest in the group with the lowest PA level ($P = 0.09$) [88]. Whether that study was impacted by a "ceiling" effect by examining only older individuals is possible. Nevertheless, these studies provided the first evidence of a potential benefit of moderate PA on telomere biology.

Additional evidence for a role of PA in telomere biology has emerged in more recent studies. For example, a recent study reported that physically active women had longer leukocyte telomere lengths compared to sedentary individuals, which the authors hypothesized was related to PA diminishing the potential influence of perceived psychological stress [94] on leukocyte telomere length [90]. In addition, a study investigating telomere length and PA in adolescent males and females observed that African American females who spent more time performing vigorous PA had significantly longer telomeres than less active peers [91]. LaRocca et al. [84] showed that leukocyte telomere length was longer in older endurance exercise-trained individuals compared to sedentary age-matched controls and was not different from young-trained individuals and that telomere length was related to maximal aerobic exercise capacity [84]. Finally, Song et al. [92] reported that lifestyle factors (e.g., exercise level, smoking, body mass index) correlated with newly defined biomarkers [95] of DNA damage and telomere dysfunction in blood cells.

Other investigations have attempted to associate telomere alterations to resistance exercise. Kadi et al. [87] studied competitive powerlifters compared to recreationally active individuals and both average and minimum telomere lengths of vastus lateralis muscle in the powerlifters were shown to be longer compared to the controls. In contrast, within the group of powerlifters minimum telomere length was inversely associated to personal records in the squat and deadlift, indicating that the greater the weight lifted in a maximum effort, the shorter the minimum telomere length. It should be noted that resistance training and unfamiliar lengthening contractions are known to cause cellular damage to skeletal muscle [96] and activate satellite cell proliferation for regenerative purposes [97, 98]. One would assume that this would result in telomere shortening of the satellite cell telomeres due to cell proliferation, with the new nuclei incorporated into the muscle fiber representing the shortest telomeres in the regenerated muscle fiber; however this was apparent only in the strongest powerlifters [87]. Though speculative, the long-term training in the powerlifters seems to have resulted in a protective effect on telomere length in skeletal muscle, while excessive training associated with elite-level performance may result in accelerated telomere shortening.

Animal models have also provided evidence of a role of physical activity in modifying telomere biology. Although rodents tend to have significantly longer telomeres compared to humans [28], the associated proteins and overall telomere biology between the species are similar, thus providing useful insights into possible regulatory mechanisms. Werner et al. [13] recently showed that the cardioprotective effects of voluntary wheel running on cardiomyocytes were conferred by an exercise-induced increase in telomere binding proteins (shelterin) and telomerase enzyme activity mediated by the presence of telomerase protein component TERT as well as IGF-1 and eNOS. Exercise was also shown to decrease markers of apoptosis and reduce gene expression of several cell cycle associated genes, showing that exercise induces an antiapoptotic environment thus preserving functional tissue and delaying an aged phenotype [13]. Cardiomyocyte telomere length itself was not different between exercise and sedentary groups but was different with age (3 months versus 18 months), indicating age-related telomere shortening. In

Table 1: Summary of studies investigating physical exercise and telomere-related traits.

Study	Major findings
Human skeletal muscle	
Collins et al. [76]	Shorter telomeres in VL of subjects with Fatigued Athlete Myopathic Syndrome (FAMS)
Ponsot et al. [86]	Equal VL telomere length between sedentary and active individuals
Kadi et al. [87]	Longer VL telomeres (mean and minimum) in powerlifters compared to sedentary men
Human leukocytes (WBC unless otherwise noted)	
Cherkas et al. [11]	Longer telomeres in more active individuals
Ludlow et al. [12]	Longer PBMC telomeres in moderately active individuals compared to both sedentary and high active
Woo et al. [88]	No difference in telomere length between active and sedentary individuals
Shin et al. [89]	No difference in telomere length in obese middle age women who underwent 6 months of aerobic exercise training compared to sedentary controls
Werner et al. [83]	Longer PBMC telomeres in older athletes compared to older sedentary individuals
Puterman et al. [90]	Longer telomeres in active individuals with lowest psychological stress levels
Zhu et al. [91]	Longer telomeres in active adolescent African American females compared to less active peers
LaRocca et al. [84]	Longer telomeres in older active individuals compared to sedentary peers
Song et al. [92]	Longer telomeres positively correlated with lifestyle factors such as PA level, BMI and smoking status
Rodent Tissues	
Radak et al. [93]	No change in telomerase activity with chronic (8 weeks) swimming in rat skeletal muscle or liver
Werner et al. [13]	Increased telomere protection and reduced apoptotic signaling in myocardium after VWR; elucidation of possible mechanisms
Werner et al. [83]	Increased telomere protection and reduced apoptotic signaling in aorta tissue after VWR; confirmation of possible mechanisms observed in Werner et al. [13]

VL: vastus lateralis; WBC: white blood cells; PBMC: peripheral blood mononuclear cells; PA: physical activity; BMI: body mass index; VWR: voluntary wheel running.

a follow-up study in aortic tissues of mice and mononuclear cells of humans, Werner et al. [83] again showed that exercise training increased telomerase enzyme activity, increased telomere binding protein and mRNA expression, and decreased levels of Chk2, p16, and p53 in mouse aorta. These gene expression changes were again shown to be mediated by TERT and eNOS in the aorta. Similar to the cardiomyocyte data, aortic telomere length was not altered by 3 weeks or 6 months of voluntary wheel running but demonstrated age-related shortening (3 months versus 18 months). In the human arm of the study, the authors investigated young sedentary, young athletes, aged sedentary, and aged athlete groups for telomere-related outcomes. Mononuclear cell telomere length was preserved in the aged athletes and was shortest in the aged sedentary individuals, and telomerase activity was greater in young and aged athletes compared to the age-matched sedentary individuals. Telomere-repeat binding protein 2 (TRF2) expression was increased in the athletes compared to sedentary individuals, while cell cycle genes (e.g., p16, p53, Chk2) were reduced in the athletes compared to the inactive groups [83].

In summary, these human and animal experimental and epidemiological results, most notably the papers by Werner and coworkers, indicate that exercise training is a potent stimulus to the telomere biology system, though influences on telomere length itself may not be seen unless the training is for a long duration. The data also indicate the possibility that moderate PA may provide the greatest positive influence on telomere biology while higher levels of exercise training may have a negative effect.

5. Possible Mechanisms of Physical Activity-Induced Modifications of Telomere Biology

Few studies have defined direct cellular and molecular mechanisms of the effect of PA on the biology of aging, though as outlined above a slowing of telomere degradation may act as one potential mechanism. The direct signaling pathways by which PA interacts with the telomere are not clearly delineated, though the work of Werner et al. has provided some initial insights. In general, regular PA is thought to prevent and delay inactivity- and age-related disease through multiple mechanisms, with reductions in either oxidative stress [6] or inflammation [99] or both being key potential mediators. These same pathways can be linked to changes in telomere biology, providing potential mechanisms by which

PA influences telomere biology with downstream influences on disease development and progression.

For example, exercise training increases antioxidant capacity via an increase in antioxidant enzyme activity [100–102]. Telomere shortening is exacerbated in numerous cell types due to oxidative stress [103–106]. Besides proliferation, telomeres can also shorten due to unrepaired damage from such oxidative stress, which could explain telomere shortening in postmitotic tissues such as neurons, myocardium, and skeletal muscle [13, 103, 107, 108]. Thus, telomere length may be maintained in moderately physically active individuals due to reductions in oxidative damage occurring to the telomere. Telomerase is also responsive to oxidative stress and may be key to protecting cells from stress insults [109, 110]; so this component of the telomere system may also benefit from the reduction in oxidative stress associated with PA.

In the studies by Werner et al. [13, 83], a role for endothelial nitric oxide synthase has been described, such that the presence of eNOS, and assumed nitric oxide (NO) bioavailability, is critical for the exercise-induced alterations to the telomere binding proteins in cardiomyocytes and aortic tissue in mice. These findings indicate that exercise, mediated by the beneficial effects of NO, is able to confer oxidative stress resistance and reduced apoptosis in multiple tissue types via genome stabilization by an increased expression of telomere binding proteins and telomerase by activation of cell survival pathways. Nitric oxide signaling via cGMP is able to activate several prosurvival protein kinases including phosphatidylinositol 3′ kinase (PI-3K) and protein kinase B (AKT) [111]. These studies by Werner et al. also showed a role for IGF-1 in the activation of telomerase. Recent epidemiological evidence indicates that older individuals with low circulating IGF-1 and free of overt disease have shorter leukocyte telomere lengths [112]. Since acute exercise stimulates expression of IGF-1 from both skeletal muscle and liver [113], IGF-1 may be playing a role in the augmentation of telomere biology by exercise. How the "exercise signal" is transmitted via prosurvival pathways to the telomere-related genes has not been defined; however, these recent findings have highlighted possible molecular underpinnings of the beneficial effects of exercise training on vascular phenotypes.

Exercise of all types can activate AMP-activated protein kinase (AMPK) [114, 115] and mammalian target of rapamycin (mTOR) [116, 117]. Both of these pathways regulate gene expression of several genes, are energy sensitive, and are involved in cellular aging [118, 119]. Interestingly, these pathways are involved in insulin signaling, protein synthesis (mRNA translation), and cell growth and survival, which makes these pathways important targets to consider when studying telomeres. For instance, telomerase has been shown to be associated with altered levels of AMPK [120]. These pathways deserve special attention with regard to the linkages between exercise, telomere biology, and cellular aging.

Stress hormones such as cortisol and stress responsive pathways such as those of the mitogen-activated kinases (MAPK) have also been implicated in telomere biology [121, 122]. For instance, Spallarossa et al. [122] demonstrated that p38 MAPK was involved in the regulation of *Trf2* gene expression in response to doxorubicin treatment in cardiomyocytes. Acute exercise is known to activate MAPK signaling, though the effects of exercise training on MAPK are less clear [123]. So acute exercise may result in a repression of telomere binding protein expression, which is consistent with longer telomeres [124]. The MAPK pathway should be investigated as a possible mechanism by which exercise can influence telomere biology.

In addition to oxidative stress-related pathways, short telomeres may contribute to the chronic inflammatory phenotype associated with aging, as demonstrated recently in a study showing shortened telomeres implicated in the regulation of interferon-stimulated gene 15 (ISG-15) [125]. Lou et al. used a customized microarray analysis of cells with short, normal, and artificially elongated telomeres to elucidate genes differentially expressed in human skin fibroblasts and ISG-15 was clearly differentially expressed in relation to telomere length. Several studies have linked the expression and secretion of ISG-15 to inflammation through its stimulation of the proinflammatory interferon, IFNγ [126, 127]. These results point to a possible mechanism whereby shortened telomeres are causing an increase in inflammation (a condition associated with many age-related diseases), thus contributing directly to the disease process. A recent study using $mTert^{-/-}$ cells with shortened telomeres showed enhanced toll-like receptor 4 (TLR4) expression [128]. TLR4 mediates the inflammation process by stimulating the expression of NF-κB, which initiates the transcription of several proinflammatory genes such as Il-6, COX2, and TNF-α. Thus, shortened telomeres have been linked to a proinflammatory cellular environment.

In contrast, acute and chronic moderate exercise training is associated with beneficial changes in inflammatory makers [129, 130], pointing to a possible protective effect of PA against telomere shortening through reduced inflammation-related gene expression. Several inflammatory cytokines have been shown to be augmented in age-related diseases (e.g., TNF-alpha), and PA may blunt these age-related changes in inflammatory cytokines [131]. Short telomeres may initiate a feed-forward mechanism resulting in the expression of both inflammatory and oxidative stress pathways that could accelerate telomere shortening and enhance age- and inactivity-related disease phenotypes. Thus, PA may be exerting its antiaging effects by protecting telomeres from shortening by improvements in antioxidant capacity and chronic inflammation.

Determining whether or not telomere shortening is causing cellular dysfunction and age-related disease or if telomere length is simply a bystander reflecting the hostile cellular environment associated with age-related disease is a challenge. The phenotypes of early generation $Tert^{-/-}$ and $Terc^{-/-}$ knockout mice do not display telomere shortening as expected, but later generations of these animals have shortened telomeres and overt phenotypes such as CVD, indicating a direct link between telomere shortening and disease [132, 133]. These and other knockout animal models may provide insights into whether or not shortened telomeres

are responsible for diseases of aging and inactivity. Other possibilities include engineering tissue-specific knockout animals for components of the shelterin complex. Whole-body knockouts for *Trf1* and *Trf2* have been attempted but have not survived past the embryonic stage [134, 135], showing vital roles for these proteins in development. In contrast, tissue-specific shelterin component knockout mouse strains produce viable offspring that display aging phenotypes and cancer [124, 136]. Tissue-specific knockout animals could be exposed to PA intervention studies to further elucidate the role of PA in telomere biology.

6. Conclusions and Future Directions

The majority of existent literature concerning telomere length in human epidemiology to date has focused on a sample of convenience, namely, white blood cells or more specifically PBMCs. Peripheral blood mononuclear cells are easily obtained via venipuncture and simple isolation procedures. The main reasons these cells have become a staple in human telomere research are their ease of acquisition and, as immune cells, they are a cell type active during the disease process and thus demonstrate telomere shortening. These cells have related limitations, however, in that immunological cells may be a better marker of systemic inflammation rather than of age-related disease itself [137] and may not be representative of the telomere length trajectory of other tissues. Thus future studies would be improved by studying tissue- and cell-specific telomere biology in relation to disease by obtaining biopsy specimens, or working in established animal or cell culture models of disease, to elucidate specific pathways, signals, and environmental stimuli contributing to age- and inactivity-related disease traits.

The evidence for a modification of telomeres in several inactivity- and aging-related diseases is clear. The possible mechanisms for these alterations in telomere biology are multifactorial and include oxidative stress, growth- and stress-related hormones and their associated pathways, and inflammation, though the direct mechanistic pathways have yet to be identified with each disease. The connection between the exercise-induced changes in telomere biology and age- and inactivity-related diseases has yet to be elucidated, but considerable indirect evidence indicates the potential for PA to improve cellular conditions and thus reduce disease risk through impacts on telomere biology.

Future studies should focus on telomere dynamics in response to acute, moderate, and long duration (life-long) exercise trials in animal models and where possible in humans to clarify potential mechanisms, with emphasis on longitudinal study designs with repeated measures of telomere length and other age- or disease-related outcomes. Exercise of different intensities should also be explored at various time points across the life span, as some literature indicates differential influences on telomere biology depending on intensity. Human trials will necessarily involve long durations to allow measurement of telomere length changes, though examination of telomere-related components can be studied with shorter durations. The factors responsible for the exercise-induced alterations in telomere binding proteins are yet to be fully elucidated, which offers an open avenue of research. Exercise is known to prevent or delay many age-related diseases such as CVD and type II diabetes, which in turn have been linked to telomeres. The question of whether or not telomeres and associated proteins are causing the disease progression or are simply altered as a result of disease-related processes is open for debate. What is clear is that exercise slows or prevents symptoms of age-related diseases and is also able to alter telomere biology. Deciphering the role of exercise in altering telomere biology in inactivity- and age-related disease progression holds promise for continued understanding of exercise training as a critical tool for the prevention and treatment of these diseases.

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Research Article

Effects of a Flexibility and Relaxation Programme, Walking, and Nordic Walking on Parkinson's Disease

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Symptoms of Parkinson's disease (PD) progress despite optimized medical treatment. The present study investigated the effects of a flexibility and relaxation programme, walking, and Nordic walking (NW) on walking speed, stride length, stride length variability, Parkinson-specific disability (UPDRS), and health-related quality of life (PDQ 39). 90 PD patients were randomly allocated to the 3 treatment groups. Patients participated in a 6-month study with 3 exercise sessions per week, each lasting 70 min. Assessment after completion of the training showed that pain was reduced in all groups, and balance and health-related quality of life were improved. Furthermore, walking, and Nordic walking improved stride length, gait variability, maximal walking speed, exercise capacity at submaximal level, and PD disease-specific disability on the UPDRS in addition. Nordic walking was superior to the flexibility and relaxation programme and walking in improving postural stability, stride length, gait pattern and gait variability. No significant injuries occurred during the training. All patients of the Nordic walking group continued Nordic walking after completing the study.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases with a prevalence of 100–200/100000 people worldwide [1–3]. The risk of developing PD increases with age. The clinical manifestation is characterised by specific motor deficits: bradykinesia, tremor, rigidity, and postural instability. While the UK brain bank criteria require the presence of bradykinesia combined with at least one of the other symptoms [4, 5] for diagnosis of Parkinson's disease, others do not consider that bradykinesia has to be always present and make the diagnosis of Parkinson's disease when two of these symptoms are present [6, 7].

The pathological definition of PD includes the loss of dopaminergic cells in the substantia nigra pars compacta with the subsequent lack of the neurotransmitter dopamine [8–12] and the presence of Lewy bodies [13]. Medical and surgical treatments provide symptomatic relief, but even with optimal therapy there is no cure for the disease and symptoms progress further [14]. PD patients tend to adapt a sedentary lifestyle very early in the course of the disease [15, 16] and have lower levels of strength [17, 18] and functional ability. This is caused by a combination of physical impairments, such as walking and balance problems, cognitive dysfunction with focus on executive dysfunction, depression, fatigue, and pain. Therefore, physical treatment gained in importance. A review on the effectiveness of exercise in PD has shown that exercise is effective at improving physical functioning, health-related quality of life (HRQL), leg strength, walking and balance [19, 20]. However, there have not been sufficient data regarding dose, type and components of exercise programmes, and stage specific effects. Despite the interest in this area, only a few randomized clinical trials comparing different approaches of sports therapy are published so far.

We selected from our data base 500 PD patients who participated in sports. To choose appropriate sports activities for the study, we asked this group to complete a questionnaire.

According to the patients replies, they liked the social aspects of sports activities and wanted to improve their health, fitness and mobility. Complex and difficult sport activities with an increased risk of falls were not preferred. Walking, Nordic walking, gymnastics, biking, and dancing were most popular. Nordic walking is a physical activity consisting of walking with poles similar to ski poles. It has evolved from an off-season ski training. The poles are designed for the purpose of activating the upper body during walking. The poles are equipped with rubber or spike tips and the walking itself resembles Nordic style skiing.

Patients are asked to walk in an upright position, not leaning forward or backward. The head should be up and looking forward and the poles are held close to the body. When the leading foot is moving forward, the opposite arm swings forward to waist height. The opposite pole strikes the ground level with the heel of the leading foot. The patients were reminded not to plant the pole in front of their feet. The poles remain pointing diagonally backward and the pole is pushed as far back as possible. The arm straightens and the hand is opening off the grip by the end of the arm swing. Nordic Walking is not expensive and can be performed round the year. Compared to walking, there is a stronger involvement of the upper body in Nordic Walking which might burn more calories [21, 22]. Furthermore, by using the poles, the muscles in the upper body can be activated, and the length of each step taken is supposedly increased, resulting in a faster gait [23, 24]. The aim of the present study was to evaluate the effects of two aerobic training programmes, Nordic walking and walking and the effects of a combined flexibility and relaxation programme without aerobic components and the adherence to the allocated sports programmes after completion of the study period. The first hypothesis of the study was that all exercise programmes, irrespective of the mode of the training programme, improve (a) walking speed, (b) gait pattern, (c) balance, (d) symptoms of Parkinson's disease, and (e) cardiovascular parameters at maximal and submaximal intensity.

The second hypothesis was that the effects of Nordic walking are superior to those of the walking and the flexibility and relaxation programme.

2. Patients and Methods

2.1. Subjects. 90 PD patients, 45 men and 45 women (UK brain bank criteria) [4], and a Hoehn & Yahr stage II and III [25] were included in the study. Exclusion criteria were severe concomitant diseases, which limit physical performances, and a second neurological disease. All patients were assessed by a movement disorder specialist (IR, SM). Medical treatment was optimised prior to the study. It was aimed at keeping medication stable during the study. Demographic data included age, body length, body weight (patients were weighed at the beginning and end of the training programme), body mass index (BMI), duration of disease, weekly sports activity, smoking habits, and concomitant diseases (hypertension, chronic obstructive pulmonary disease, thyroid disease, diabetes mellitus, hypercholesterinaemia, osteoarthritis).

2.2. Design (Figure 1). Prior to the training patients underwent a medical examination [26] including a cardiovascular exercise test. A medical history was taken, and patients were screened for coronary heart disease, hypertension, pulmonary function, cardiopulmonary diseases, diabetes and osteoarthritis. Patients kept an activity log one week prior to the training programme and during the last week of the training period. Time spent sitting, doing light, moderate and heavy work was recorded.

Patients did not participate in other sports programmes during the study but were allowed to continue physiotherapy and participated in family leisure activities. These activities were recorded.

Patients were randomly allocated to one of the three training groups. Randomisation was conducted by using a computer-generated sequence. One training group performed Nordic walking (NW) training, 3 times per week for 6 months. Each session lasted 70 minutes and consisted of a warming up including some flexibility and strength exercises with and without the poles. One session per week was dedicated to practising NW technique, the other sessions focused on endurance training. Patients were encouraged to increase the intensity of the training by walking faster or uphill and to increase the distance walked. Each training session finished with a cooling down programme. Training sessions took place in a park and a forest near to the university hospital. Technical performance was assessed by video recording. In addition, NW instructors used a checklist for assessment of the technical skills (i.e., diagonal sequence, opening of the hands, and planting of the poles).

The second training group conducted a walking training. Training sessions were performed three times per week over 6 months. The training session also lasted 70 min and consisted of a warming up, technique training, endurance training and a cooling down. Instructors emphasised on arm swing and coordination of upper and lower limbs. One session per week included walking uphill to improve muscle strength.

The third group performed flexibility exercises and a relaxation training. The training took place in a gym. Each session lasted 70 min. The training focused on stretching, improving balance and range of movements. The flexibility and relaxation programme did not include aerobic exercises, while aerobic fitness and endurance were additionally addressed by walking and NW training. Nordic walking is thought to be a more vigorous exercise than walking. Thus, the training programmes differ in the amount of aerobic exercises included. Three physiotherapists who were trained as NW instructors conducted the training sessions of the three groups.

The Borg scale was applied as a measure [27] for exertion to estimate the intensity of the training.

Since training should also help patients to adapt a more active life style, partners were offered six training sessions of the training programme, which was allocated to the patient.

Primary outcome measures were maximal walking speed on a treadmill ergometer, a 12-m and 24-m walking test, stride length and gait variability, assessed at different walking speeds, specific PD disability on the UPDRS

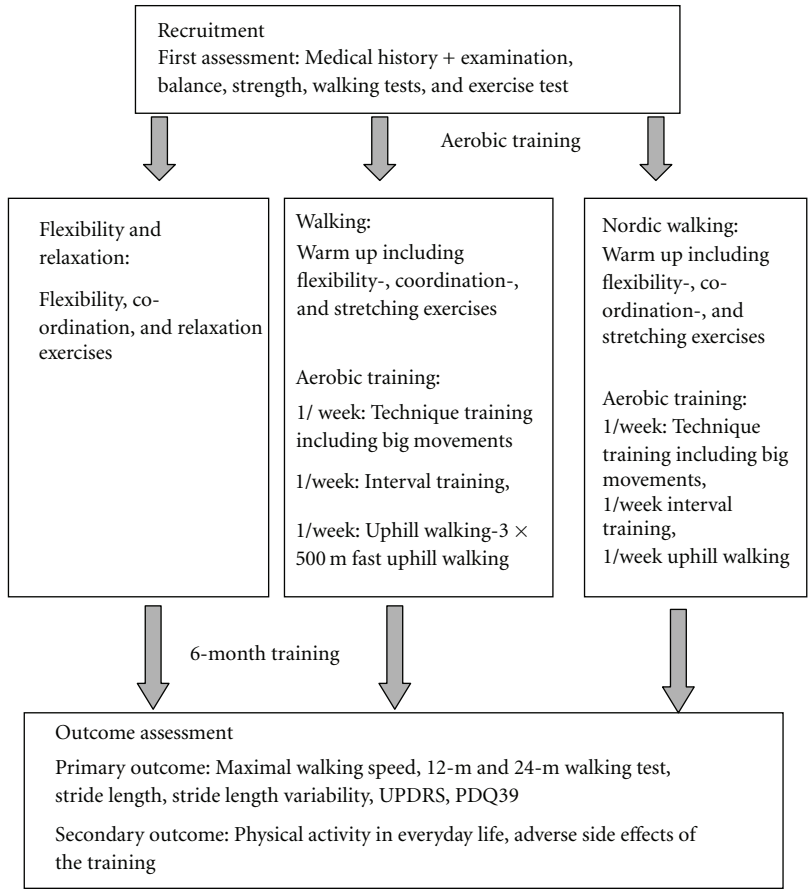

Figure 1: Study design.

(unified Parkinson's disease rating scale) [28] and HRQL (Parkinson's disease questionnaire 39; PDQ39) [29]. Outcome was assessed in all patients at baseline and after completion of the training period.

Secondary outcome measures were physical activity in everyday life and adverse effects of the training.

Adverse effects included cardiovascular side effects such as exercise-induced hypotension and injuries, caused by fall or overuse.

Outcome was assessed by two movement disorder specialists (IR, SM), who were blinded to the treatment arm.

2.3. Scales Used. The unified Parkinson's disease rating scale (UPDRS) is the most frequently used outcome measure in clinical trials in Parkinson's disease [28]. The UPDR scale has four subscales: part 1, which has 4 questions on mentation, behaviour, and mood (range 0–16 points), part 2, which has 13 questions on activities of daily living (ADL) (range 0–52 points), part 3, which has 14 questions on motor functions (range 0–108 points), and part 4, which has 11 questions on motor and other complications of advanced disease (0–23 points). The UPDRS-Sum score ranges from 0 to 199 points, with a higher score indicating greater problems.

Posture, postural stability, alternating movements and leg agility were assessed by the single items of the UPDRS motor scale (score of each item ranging between 0 and 4 points).

For assessment of health-related quality of life, patients filled in the Parkinson's disease-specific questionnaire (PDQ 39), which consists of 8 subscales: subscale 1 mobility (max 40 points); subscale 2 activities of daily living (max 24 points), subscale 3 emotional well-being (max 24 points), subscale 4 stigma (max 16 points), subscale 5 social support (max 12 points), subscale 6 cognition (max 16 points), subscale 7 communication (max 12 points), and subscale 8 bodily discomfort (max 12 points) [29]. The sum score of raw data ranges from 0 to 156 points, with high scores indicating lower health-related quality of life. For better comparison of the results, raw data were transformed and expressed in percentages of maximal possible sum score.

For exclusion of significant depression and anxiety the hospital anxiety and depression scale was applied [30]. The scale consists of two subscales, an anxiety scale and a depression scale ranging from 0 to 21 points, respectively. Patients are asked to choose one response from the four given for each question. Patients were strongly encouraged to respond promptly. Questions related to anxiety are marked

with A and to depression with D. Depression and anxiety are scored separately. On each scale 0 to 7 points indicate a normal, 8 to 10 points a borderline abnormal and 11 or more points an abnormal result.

Minimental state examination (MMSE) was used as screening tool for dementia. The test assesses orientation, registration, attention, calculation, recall, language, writing, and copying. The maximum score is 30 points; high scores indicate good performance [31]. Cut off criteria for an abnormal result are 24 points and below. Dementia is assumed for less than 20 points [32].

Pain was rated by using a visual analogue scale for several regions of the body (neck, arms, hands, back, iliosacral joint, hip, knees, feet, and toes). Pain was recorded to evaluate potential adverse events of the training, health risks, injuries and overuse injuries during the training period [33].

2.4. Balance. Balance was tested by using the Berg-Balance scale [34]. The test assesses balance in several different positions. The 14 items have a choice of 5 answers, numerically scored from 0 to 4. Maximal sum score adds up to 56 points with a higher score indicating good balance.

2.5. Walking Tests

2.5.1. 12-m and 24-m Webster-Walking Tests [35]. Patients were asked to walk as fast as possible a distance of 12 m, and after a 5-minute break a distance of 24 m with a turn after 12 m. The time was taken for the 12 m distance and the 24 m distance.

2.6. Assessment of Gait Parameters. Stride time (time from initial contact of one foot to subsequent contact of the same foot), percentage of double stance time ([time of bilateral foot contact/stride time] $\times$ 100), stride length (distance from initial contact of one foot to subsequent contact of the same foot) and the coefficient of stride length ([standard variation/mean] $\times$ 100) [36–38] were assessed at different walking speeds on a motorized medical treadmill ergometer. There is sufficient evidence that gait variability is increased in basal ganglia disorders [39]. Furthermore, increased stride-to-stride variability might reflect a failure of automatic stepping mechanisms [36]. Increased gait variability can be seen throughout the course of Parkinson's disease and has been found to be one aspect of walking, closely associated with risk of falls in the elderly [40–42].

For better comparison of the training effects patients walked at 6 different walking speeds (1.5 km/h, 1.8 km/h, 2.1 km/h, 2.4 km/h, 2.7 km/h, and 3 km/h) prior and after the training period. The treadmill was equipped with force platforms, that allowed an accurate determination of foot-ground contact. Patients were not allowed to use the handrails of the treadmill for support.

2.7. Exercise Test. Patients performed a maximal exercise test on a medical motorized treadmill ergometer (Woodway PPS Med) and were instructed to walk on the treadmill. Switching to jogging was prohibited, since walking and jogging put different demands on the cardiovascular and muscular system. The test started at a walking speed of 3.0 km/h. Every 2-minute the speed was increased by 0.5 km/h. At the end of each 2-minute stage blood pressure (BP) and heart rate (HR) were taken. BP and HR responses to maximal and submaximal exercise testing were recorded. Maximal exercise testing assesses the aerobic capacity and requires subjects to exercise to exhaustion. However, fatigue, pain, and muscle weakness might hinder patients from successfully completing the test. Therefore, we assessed as well performance at submaximal exercise intensity. Blood pressure and heart rate changes between resting conditions and maximal walking speed were recorded at baseline and final assessment. Maximal exertion was defined as reaching a heart rate of 220—age or a perceived exertion of 17 on the Borg scale [27]; this means walking with very hard effort. For assessment of exercise capacity at submaximal level after completion of the training programme, two approaches were chosen:

(a) the BP and HR responses to increasing work load between a walking speed of 3 km/h and 5 km/h were assessed,

(b) BP and HR changes between resting conditions and the walking speed which corresponded to the maximal walking speed at the first assessment were recorded and compared to the BP and HR change between resting conditions and maximal walking speed at the first assessment.

Patients were secured with a safety harness, suspended from the ceiling, without weight support. Before testing patients were given 5 min to familiarise themselves with the treadmill locomotion. Patients were not allowed to use the handrails of the treadmill for support.

To assess the attractiveness of the exercise programme for the patients, all patients were contacted by phone six months after completion of the training period and a short telephone interview was conducted. Patients were asked the following questions.

(a) Do you continue the instructed training regime practiced during the course of the study?

(b) If not, did you stop exercising or did you switch to another sports activity?

(c) How often do you exercise per week?

(d) Do you exercise on your own or together with your spouse or your friends?

3. Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics 18.0 (IBM, Somers, USA) statistical software. Formal power analysis was performed prior to the study. The results indicated that a sample size of 30 subjects per group was sufficient. The power analysis regarding the UPDRS was based on an improvement of the UPDRS motor scale by 5 points, which is clinically relevant according to the findings of Schrag et al. [43]. Demographic data on ordinal level were analysed by using a nonparametric test (Kruskall-Wallis). The Kruskall-Wallis test was also applied for the analysis

Table 1

(a) Demographic data

	Flexibility and relaxation group $N = 30$	Walking group $N = 30$	Nordic walking group $N = 30$
	Mean ± std	Mean ± std	Mean ± std
Age (years)	62.1 ± 2.5	63 ± 3.1	62 ± 3.2
BMI (kg/m^2)	27.16 ± 4.38	27.21 ± 3.91	26.37 ± 3.6
Length (cm)	171.87 ± 5.9	170.1 ± 7.1	171.84 ± 7.5
Body weight (kg)	80.4 ± 14.3	78.87 ± 13.1	78.1 ± 12.8
Duration of disease (months)	62.33 ± 38.2	71.9 ± 50.5	64.1 ± 48.7
Weekly sports activity in the past (min)	120 ± 17	135 ± 21	118 ± 19

(b) Comorbidity of PD patients

Comorbidity	Flexibility & relaxation group $N = 30$	Walking group $N = 30$	Nordic walking group $N = 30$
	Percentage (%)	Percentage (%)	Percentage (%)
Hypertension	40	30	33
Chronic obstructive pulmonary disease (COPD)	10	13.3	10
Coronary heart disease	6	6.2	8.3
Thyroid disease	16.7	16.7	20
Diabetes mellitus	8	10	10
Hypercholesterinaemia	40	40	33
Osteoarthritis	36	40	36

of improvement in posture, postural stability, alternating movements, freezing, gait pattern, and leg agility. Continuous data were analysed by using a One-way ANOVA. Results of the UPDRS, gait parameters and cardiovascular data were assessed by using the repeated measure analysis. The repeated measure analysis provides information about "between and within subjects" effects. Within subject effects give information about training effects over the assessment period. Linear trends were extracted by orthogonal polynomials and analysed for days and for trials (gait parameter). Linear trends showed if there was a systematic change of training effects over time. The interaction between groups and the linear trend of days yielded information about difference in the rate of improvement between groups. The between-subject factor compared the overall treatment effect between the groups. Post hoc analysis was done using Bonferroni tests (corrected for multiple comparisons). Parametric data were tested for normal distribution by using the Kolmogorov Smirnov test. Significance level was set at 0.05.

The study was approved by the Ethical Committee of the Justus-Liebig University Giessen, and all patients gave written informed consent.

4. Results

Demographic data of the participating patients are shown in Tables 1a and 1b. There were 4 smokers in the flexibility and relaxation group and 5 smokers in the walking and Nordic walking group, respectively. Baseline assessments did not reveal any statistical differences in demographic data, health condition, and fitness between the groups. There were no significant differences in severity of the disease 14 patients of the NW group, 15 of the Walking group, and 16 of the flexibility and relaxation group were in Hoehn & Yahr stage II. All other patients were in Hoehn & Yahr stage III. The randomisation procedure was successful. There were no drop outs during the study.

Table 2 shows the medication of the patients at the beginning of the study. Medication had to be adapted in 2 patients of the walking and the flexibility and relaxation group respectively and in 1 patient of the Nordic Walking group. Three patients reported wearingoff, 1 patient dyskinesias and 1 patient early morning dystonia. Since change of medication had been minor (increase of levodopa dosage by 50 mg in 3 patients, reduction of levodopa dose by 100 mg in one subject, and addition of entacapone in one case), the patients continued the study. All patients received one physiotherapy session per week.

All patients showed normal results in the MMSE screening test for dementia. Three patients scored in a range of mild depression at baseline on the HAD, two patients at the final assessment. None of the patients became depressed during the study.

Table 2: Medication used by the patient groups.

Medication	Relaxation and flexibility group $N = 30$		Walking group $N = 30$		Nordic walking group $N = 30$	
	Total number	(%)	Total number	(%)	Total number	(%)
Levodopa	20	66	22	73.3	20	66.7
Dopamine agonists	27	90	26	86.7	26	86.7
Mao-Inhibitor	12	40	13	43.3	12	40
COMT-Inhibitor	11	36.7	12	40	10	33
Amantadine	10	33	10	33	9	30
β-blockers	4	13.3	3	10	3	10
ACE-inhibitors	3	10	3	10	3	10
Antidepressants	7	23.3	8	26.7	8	26.7

(%) = percentage.

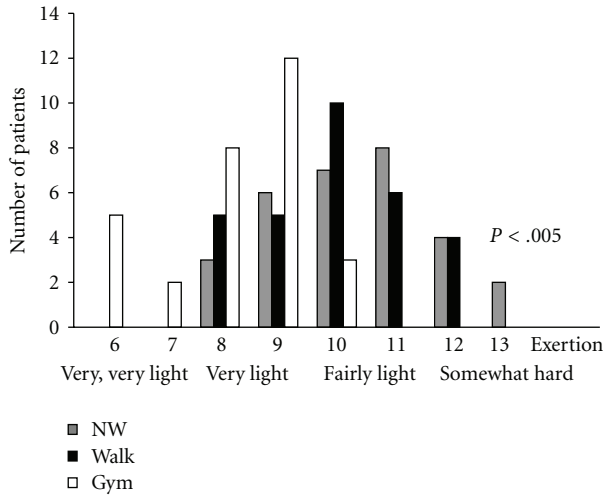

Figure 2: Borg scale: Patients of the Nordic walking group and walking group perceived more exertion than the flexibility and relaxation group suggesting that the training of both groups was more demanding.

All patients attended at least 70 of 78 training sessions offered. The attendance of training sessions was similar in all three groups. Figure 2 shows the overall rating of perceived exertion during the training sessions; participants of the flexibility and relaxation group rated the intensity of the training significantly lower ($F[2, 89] = 22.88; P < .005$).

4.1. Assessment of Technical Skills. The technique of the Nordic walking training appeared to be very challenging for the patients. Patients had difficulties in opening the hands during the push-off phase. Furthermore, patients tended to carry the pole without weight loading with the more affected hand. However, the group managed to learn the Nordic walking technique, but the level of performance differed between the patients. 17 of the patients mastered the NW technique very well, 10 patients showed a good technical performance and 3 patients performed poorly. Both the NW group and the walking group had difficulties in employing a diagonal sequence and an interlimb coordination. Patients did not notice the technical deficits and depended on the coaching of the instructors.

4.2. Adverse Side Effects of the Training. Two patients of the NW group and one patient of the walking group experienced exercise-induced hypotension after intense walking uphill in hot weather. Patients felt dizzy but did not lose consciousness and recovered after fluid intake within 10 min.

During the supervised 6-month training period, four patients of the NW group fell due to obstacles. The falls did not lead to severe injuries. Five patients twisted their ankles during cross-country walking, but only one patient complained of pain and missed three training sessions. Two patients of the NW group developed shoulder pain which required medical treatment with nonsteroidal anti-inflammatory drugs. Both patients abstained from sports activities for one week.

Four patients of the walking group had falls during the supervised 6-month training period. Two patients tripped over roots and two patients slipped on wet ground while walking downhill. There was one fall in the flexibility and relaxation group during an attempt to stand up from the floor.

Muscle soreness was reported in all groups by 15% of the patients during the first three weeks of exercising.

4.3. Pain. Apart from the initial muscle soreness and the few injuries caused by falls and overuse, physical activity had a positive effect on pain. About 70% of patients complained of pain prior to the study. Table 3 shows the percentage of patients who suffered from pain in specific localisations of the body at baseline and after completion of the training. In the Nordic walking group up to 30% of patients became free of pain after the training. Furthermore, intensity of pain also decreased in patients, who still reported pain at the second assessment. Figures 3(a)–3(c) illustrate the decrease of pain severity in different areas of the body. Pain of the neck, hip, and iliosacral joint diminished in all groups likewise. Pain of the back ($F[2, 59] = 10.25; P < .001$), hands ($F[2, 35] = 12.44, P < .001$), and legs ($F[2, 29] = 7.93; P < .002$) was more eased by walking and NW than by the flexibility and relaxation programme.

Table 3: Localisation of pain:comparison between baseline and final assessment.

Localisation of pain	Flexibility & relaxation group $N = 30$		Walking group $N = 30$		Nordic walking group $N = 30$	
	Percentage (%)					
	Baseline	Final	Baseline	Final	Baseline	Final
Neck	53.3	40.0	56.6	43.3	53.3	40.0
Arm	30.0	30.0	30.0	33.3	43.3	33.3
Hand, finger	36.6	36.6	43.3	36.7	43.3	20.0
Chest	23.3	26.6	20.0	20.0	20.0	20.0
Back	73.3	43.3	66.6	40.0	73.3	40.0
Hip	33.3	26.6	36.6	23.3	36.6	20.0
Iliosacal joint	36.6	20.0	43.3	26.6	50.0	33.0
Leg	30.0	26.6	33.0	26.6	36.6	20.0
Feet, toes	26.6	26.6	23.3	23.3	26.6	20.0

4.4. PD-Specific Disability. UPDRS score did not differ significantly at baseline assessment between the groups. The sum-score of the UPDRS decreased in the Nordic walking and walking group significantly between baseline and the final assessment ($F_{\text{lin}}[1, 87] = 5.70; P < .02$), which could be attributed to the improvement in the UPDRS subscale 3 (motor function) (Figure 4). There were clear group differences with lower scores for the walking and Nordic Walking groups at the final assessment indicating less Parkinson's disease-specific disability (UPDRS sum score: $F[2, 87] = 3,77; P < .05$; UPDRS motor score: $F[2, 87] = 7.48$; $P < .05$) (Figure 4). 83.3% of the NW group, 63.3% of the walking group, and 33% of patients of the flexibility and relaxation group improved more than 5 points on the UPDRS motor score (Chi-Quadrat = 25.82; df = $2, P < .001$). The mean improvement of the UPDRS motor score amounted to 6.4 ± 4.1 points in the NW group and 4.4 ± 5.1 points in the walking group. Patients, who performed a walking or NW training, had a better posture ($P < .01$), showed less freezing ($P < .001$), and were faster in alternating movements ($P < .003$) at the final assessment. Nordic walking improved postural stability ($P < .004$) and gait pattern ($P < .001$) more than the walking and the flexibility and relaxation training.

Table 4 shows the percentage of patients, who improved in postural stability, posture, gait pattern, freezing, leg agility and alternating movements and the range of improvement.

4.5. HRQL. The score of the PDQ 39 decreased in all groups indicating a better health-related quality of life ($F_{\text{lin}}[1, 87] = 23.2; P < .001$). Apart from subscale 6, no differences between the groups neither at baseline nor at the second assessment were revealed. Subscale 6 reflects patients' estimation of their cognitive function. Patients who performed a walking or Nordic walking training felt that they could better concentrate, memorize, and recall information ($F[2, 87] = 4.09; P < .02$).

4.6. Balance. There were no differences between groups at baseline testing on the Berg balance scale scores. Although patients performed on a high level at baseline ($\varnothing = 48 \pm 2.1$ points), they showed in particular difficulties in the functional reach test and the one leg stance. The majority of patients could reach less than 12.5 cm forward. All groups improved on the Berg-balance scale ($F_{\text{lin}}[2, 87] = 61.2; P < .001$). There was no difference between the groups ($\varnothing = 51 \pm 1.8$ points).

4.7. 12-m and 24-m Webster Walking Test. There was no difference between the groups at baseline assessment (flexibility and relaxation group: 8.6 ± 1.6 s; walking: 8.0 ± 1.1 s; Nordic walking: 8.4 ± 0.7 s). All groups improved in walking velocity after 6 months ($F_{\text{lin}}[1, 87] = 138.13; P < .001$). While the flexibility and relaxation group improved only slightly by 0.6 s, there was a clear improvement of the NW group and walking group by 2.1 ± 0.6 s and 1.8 ± 0.7 s, respectively, resulting in a clear interaction between group and days ($F[2, 87] = 13.96; P < .001$). Thus, the time needed for the 12 m distance was significantly shorter for the Nordic walking and walking group ($F[2, 87] = 5.01; P < .01$).

The improvement was even more significant in the 24-m walking test. The walking and NW walking groups improved by 4.3 s and 4.7 s, respectively, compared to 0.7 s in the flexibility and relaxation group ($F[2, 87] = 6.06; P < .01$). The post hoc test revealed no difference between the walking and Nordic walking group.

4.8. Stride Length, Stride Length Variability, Stride Time, and Double Stance. Stride length increased with increasing walking speed in all groups on both days ($F_{\text{lin}}[1, 87] = 243.2; P < .001$), but only the walking and Nordic walking group showed an increase of stride length after completion of the training compared to the baseline assessment. There was a significant interaction between groups and days ($F[2, 87] = 31.08; P < .001$) and a clear group effect ($F[2, 87] = 3.588; P < .05$).

The Nordic walking group was most effective in improving stride length. The post hoc test revealed that there was a clear difference between the Nordic walking and the flexibility and relaxation group ($P < .001$) and a small

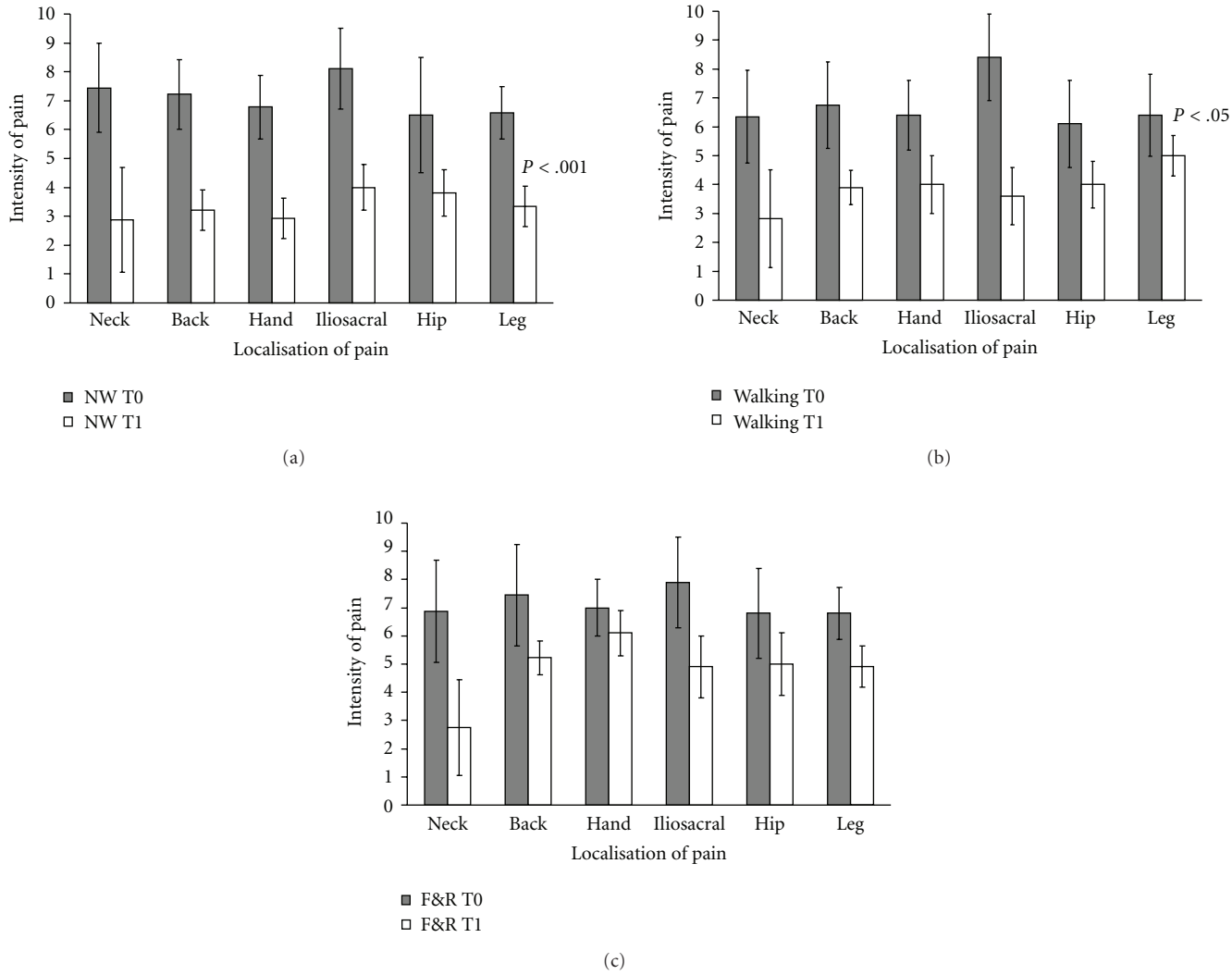

Figure 3: Intensity of pain was significantly lower at the second assessment compared to baseline assessment ($P < .001$). Pain of the back, hands, and legs was more eased by the Nordic walking and walking group. (a) Nordic walking group T0 = first assessment, T1 = second assessment, error bars indicate standard deviations. (b) Intensity of pain in the walking group T0 = first assessment, T1 = second assessment, error bars indicate the standard deviation. (c) Intensity of pain in the flexibility and relaxation group (F&R) T0 = first assessment, T1 = second assessment, error bars indicate standard deviations.

but significant difference between the Nordic walking and walking group ($P < .05$) (Figure 5(a)).

4.9. Stride Length Variability. Stride length variability was higher during slow walking indicating more instability. With increasing walking speed, stride length variability decreased in all groups. On the first day, the three groups did not differ in stride length variability, after completion of the training programmes stride length variability decreased in all groups ($F_{\text{lin}}[1, 87] = 205.4; P < .001$). However, the improvement in stride length variability was only significant in the walking and NW group indicated by an interaction between group and days ($F[2, 87] = 25.9; P < .001$). The improvement of stride length variability of the walking and NW group resulted in a significant group difference ($F[2, 87] = 29,51; P < .001$). The post hoc test revealed that the NW group was superior to the flexibility and relaxation group ($P < .001$) and the walking group ($P < .01$) (Figure 5(b)).

The groups differed as well in the improvement of stride length variability with increasing walking speed on the second day. While the Nordic walking group improved further in stride length variability at a walking speed of 2.7 km/h and 3.0 km/h, the walking and flexibility and relaxation group did rather deteriorate at the higher walking velocities (Day × trial × group $F[2, 87] = 3,24; P < .05$). A decrease of stride length variability might be important to reduce the risk of falling (Figure 5(b)).

4.10. Stride Time. Stride time decreased with increasing walking speed, there was no significant difference between the groups on the first assessment. After the training period

Table 4: Comparison of improvement in leg agility, alternating hand movements, posture, postural stability, freezing, and gait pattern between the training groups.

Parameters	Flexibility and relaxation group $N = 30$			Walking group $N = 30$			Nordic walking group $N = 30$		
	no	yes 1 pt	yes 2 pts	no	yes 1 pt	yes 2 pts	no	yes 1 pt	yes 2 pts
	Percentage (%)								
Leg agility left	60	30	10	23.3	36.7	40	20	30	50
		40			**76.7**			**80**(%)	
Leg agility right	56	40	3	23.3	40	36.7	16.7	40	43.3
		43			**76.7**			**83.3**(%)	
Alternating movements right hand	53.3	33	13	30	43.3	26.7	23.3	30	46.7
		46			**70**			**76.7**(%)	
Alternating movements left hand	60	20	20	30	40	30	26.7	33	40
		40			**70**			**73**(%)	
Posture	43.3	23.3	33	36.7	36.7	26.7	20	40	40
		56.3			**63.7**			**80**(%)	
Freezing	53.3	36.7	10	23.3	40	36.7	20	40	40
		46.7			**76.7**			**80**(%)	
Postural stability	46.7	43.3	10	36.7	26.7	36.7	16.7	40	43.3
		53.3			**63.7**			**83.7**(%)	
Gait pattern	50	43.3	6.7	40	23.3	36.7	13.3	33	53.3
		50			**60**			**86.3**	

The first column indicates the percentage of patients who did not improve, the next column the percentage of patients who improved by 1 point, and the second column indicates the percentage of patients who improved by 2 points. The Bold value presents the percentage of all patients of a group who improved regardless of the amount of improvement.

stride time decreased further, shown in a linear trend of days ($F_{\text{lin}}[1, 87] = 120.6; P < .001$). Since the Nordic walking and walking group improved more, an interaction between groups and days was found (day × group $F_{\text{lin}}[1, 87] = 18.132; P < .001$).

The Nordic walking group was superior to the walking group and the flexibility and relaxation group, shown in a clear between-subject effect ($F[2, 87] = 3,263, P < .05$).

4.11. Double Stance. The double stance phase decreased with increasing walking speed in all groups on both assessments. Compared to the baseline test, the double stance phase was shorter on the second assessment in all groups ($F_{\text{lin}}[1, 87] = 1857.24; P < .001$), but the reduction of the double stance phase was only significant in the walking group and NW group, resulting in a significant interaction between groups and days ($F[2, 87] = 83.08; P < .001$) and a significant difference between the groups ($F[2, 87] = 64.29; P < .001$) (Figure 5(c)).

4.12. Exercise Test. All groups showed already a good performance level at baseline assessment with a mean maximal walking speed of 6.0 ± 1.1 km/h; the maximal walking speed did not differ significantly between the groups.

While the flexibility and relaxation group reached with 6.0 ± 0.4 km/h the same walking speed on the second assessment as on the first assessment, the walking and NW group improved further. The NW group managed on average 7.6 ± 0.6 km/h at the second assessment, the walking group 6.8 ± 0.4 km/h. The NW group was significantly faster than the flexibility and relaxation group, shown in the interaction between group and days ($F[2, 87] = 21.11, P < .001$) and a clear group effect ($F[2, 86] = 8, 165; P < .001$). The walking group did not differ significantly from the flexibility and relaxation group and the Nordic walking group.

4.13. Cardiovascular Effects. Blood pressure and heart rate at resting conditions were similar on the first and second assessment. Blood pressure and heart rate changes between resting conditions and the respective maximal walking speed on the first and the second assessment did not significantly differ between the groups.

On both days 30% of each training group reached maximal exertion according to the formula maximal heart

Table 5: Time spent sitting per day and doing heavy work per week.

Time spent	Flexibility & relaxation group $N = 30$	Walking group $N = 30$	NW group $N = 30$	Significance (group effect)
Sitting per day baseline (h)	9.11 ± 2.34	7.9 ± 1.86	8.11 ± 1.61	$F(2, 87) = 14.218; P < .001$
Sitting per day final (h)	8.9 ± 2.12	5.7 ± 2.4	5.60 ± 1.80	
Doing heavy work per week baseline (h)	4.7 ± 3.1	5.87 ± 3.3	5.2 ± 3.12	$F[2, 87] = 11.254; P < .001$
Doing heavy work per week final (h)	3.8 ± 3.41	6.33 ± 3.12	9.4 ± 3.12	

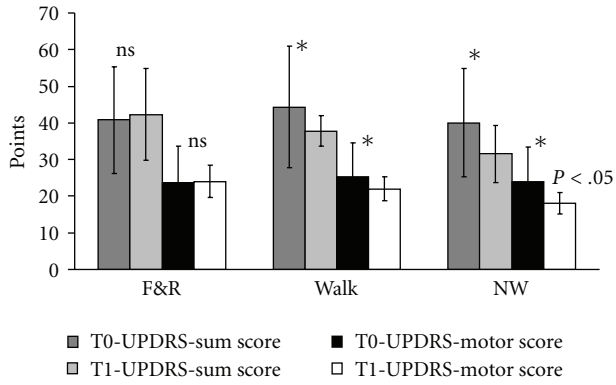

Figure 4: The UPDRS sum score and UPDRS motor score (subscale 3) did not decrease in the flexibility and relaxation group but decreased significantly in the Nordic walking and walking group resulting in a group effect. T0 = first assessment, T1= second assessment, F&R = Flexibility and Relaxation*$P < .05$, error bars indicate standard deviation.

rate = 220-age. When patients were asked to rate their perceived exertion on the Borg scale, 50% of the patients classified their effort as very hard, 10% as very, very hard and the remaining patients as hard. There was no difference between the groups. According to the Borg scale, 60% of the patients reached maximal exertion.

To evaluate whether the training led to a better adaptation to exercise the course of the BP and HR response to exercise between 3 km/h and 5 km/h was assessed. This approach includes the BP and HR responses to exercise at a submaximal level. Patients who managed 5 km/h on both days were included in the analysis. However, only 72 of the patients (25 of the flexibility and relaxation group, 23 of the walking group, and 24 of the NW group) were included in this calculation, since 18 patients did not reach 5.0 km/h at the first or second assessment.

Comparison of systolic and diastolic blood pressure between 3 km/h and 5 km/h showed a better efficiency of the cardiovascular system to adapt to exercise in the Nordic walking and walking group. The submaximal walking speeds were less demanding for the patients after the training period. This is shown in a significant linear trend for days (systolic BP: $F_{\text{lin}}[1, 69] = 16.99; P < .001$; diastolic BP $F_{\text{lin}}[1, 69] = 6.75; P < .01$). The systolic blood pressure of the walking and Nordic walking group dropped significantly more than the systolic blood pressure of the flexibility and relaxation group, indicated by the interaction between groups and days ($F[2, 69] = 4.43; P < .001$) (Figures 6(a)–6(c)). However, there was neither a significant group effect for the systolic nor for the diastolic blood pressure.

The heart rate was lower in all groups on the second assessment shown in a significant linear trend for days ($F_{\text{lin}}[1, 70] = 4.38; P < .01$). However, the Nordic walking (Figure 7(a)) and walking (Figure 7(b)) showed a significant lower heart rate at all walking speeds of the exercise test, while the flexibility and relaxation group showed a lower heart rate at low walking speeds only (Figure 7(c)). Consecutively, there was a clear interaction between groups and days ($F[2, 69] = 3.82; P < .05$) and a clear group effect ($F[2, 69] = 8.91; P < .001$). Post hoc test (Bonferroni) revealed that the heart rate of the Nordic walking group was lower than the heart rate of the walking ($P < .05$) and flexibility and relaxation group ($P < .001$).

In order to get information on the adaptation to exercise of all patients a second analysis was performed. A different approach was chosen for this calculation. The blood pressure changes between resting conditions and the blood pressure at the walking speed, which corresponds to the maximal walking speed of the first day, were analysed on the second assessment and compared with the blood pressure changes between resting conditions and maximal walking speed on the first assessment. The mean systolic blood pressure change was significantly lower on the second assessment ($F_{\text{lin}}[1, 87] = 65.24; P < .001$) in all groups. The blood pressure change of the Nordic walking and walking group was significantly lower than the blood pressure of the flexibility and relaxation group on the second assessment. Hence, there was an interaction between days and groups ($F[2, 87] = 21, 11; P < .001$), and a clear group effect ($F[2, 86] = 8.17; P < .001$) was found. The diastolic blood pressure changes were significantly lower on the second assessment in all groups, shown in a significant linear trend ($F_{\text{lin}}[1, 87] = 28.26; P < .001$).

The heart rate change between resting conditions and the walking speed corresponding to the maximal walking speed of the baseline assessment was lower at the second assessment, indicating an adaptation to exercise. The Nordic walking group and the walking group improved more than the flexibility and relaxation group, which is shown by an interaction of groups and days ($F[2, 87] = 3.64; P < .03$) and a clear group effect ($F[2, 87] = 6.75; P < .002$).

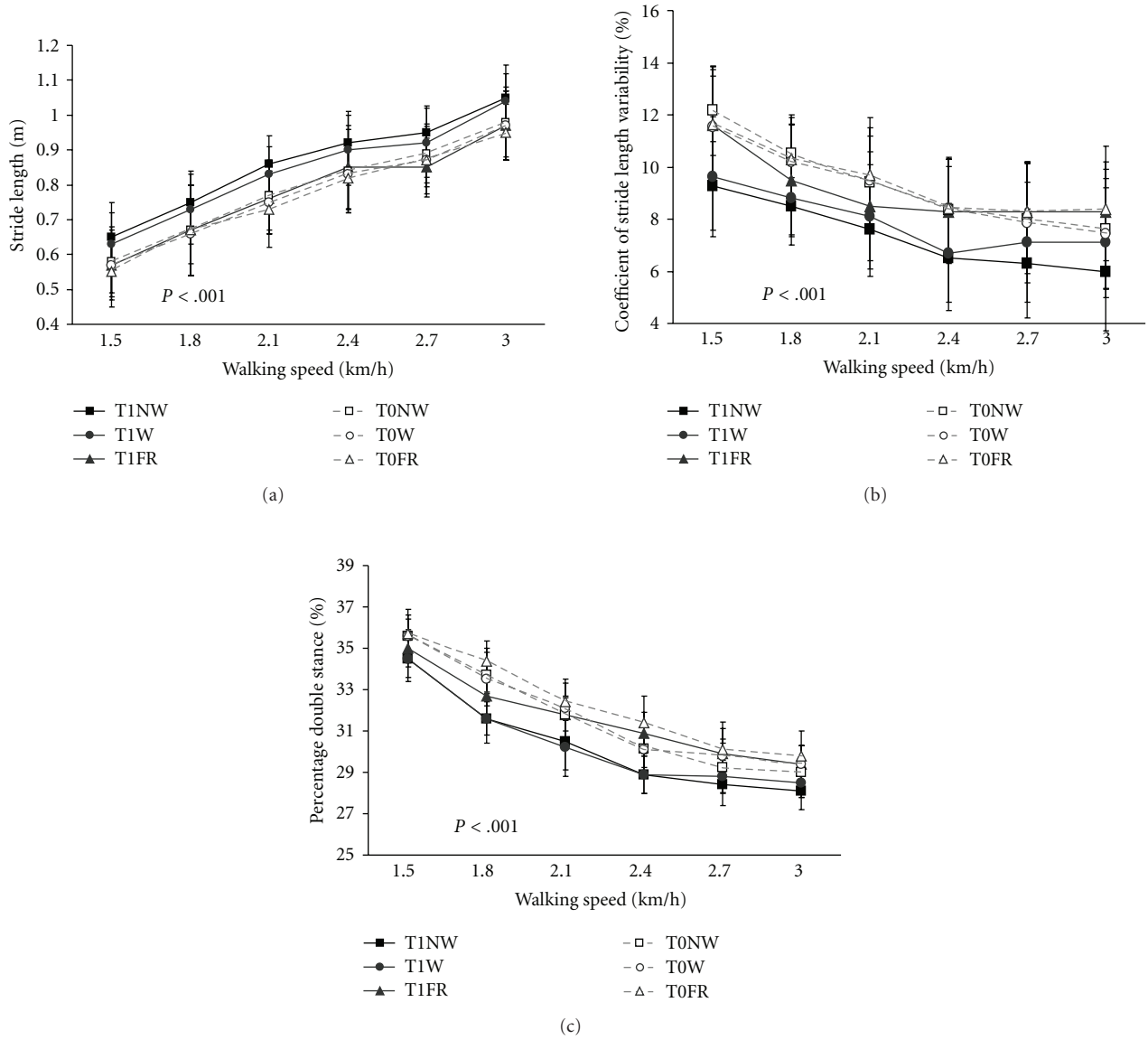

Figure 5: (a) Stride length increased significantly with increasing walking speed, and improved further on the second assessment ($P < .001$). Stride length improved significantly more in the Nordic walking and walking groups than in the flexibility and relaxation group ($P < .001$). T0 = first assessment; T1 = second assessment, error bars indicate the standard deviation. (b) Stride length variability improved most in the Nordic walking group. Nordic walking training was superior to walking ($P < .01$) and the flexibility and relaxation programme (F&R) ($P < .001$). T0 = first assessment; T1 = second assessment, error bars indicate the standard deviation. (c) The duration of the double stance phase decreased with increasing walking speed in all groups but significantly more in the Nordic walking and walking group ($P < .001$); T0 = first assessment, T1 = second assessment, error bars indicate the standard deviation.

Patients were asked to keep an activity log for one week prior to the training period and during the last week of the study. While there was no difference in general physical activity of the groups prior to the training, patients of the walking and Nordic walking groups spent more time doing heavy work, such as gardening, and spent less time sitting than the flexibility and relaxation group after six months training (Table 5).

The patients were on average slightly overweight at the beginning of the training (Table 1). The BMI in all groups was >25. Despite the mild increase of daily activity, patients did not lose weight during the training.

Six months after completion of the study, patients were asked whether they were still exercising. All patients of the NW group continued and had formed training groups. They walked with an instructor once a week. 60% of the participants of the walking group continued walking 2-3 times per week, 10% gave up exercising and 30% started practising NW. The flexibility and relaxation programme seemed to be less attractive. It was difficult to find a gym,

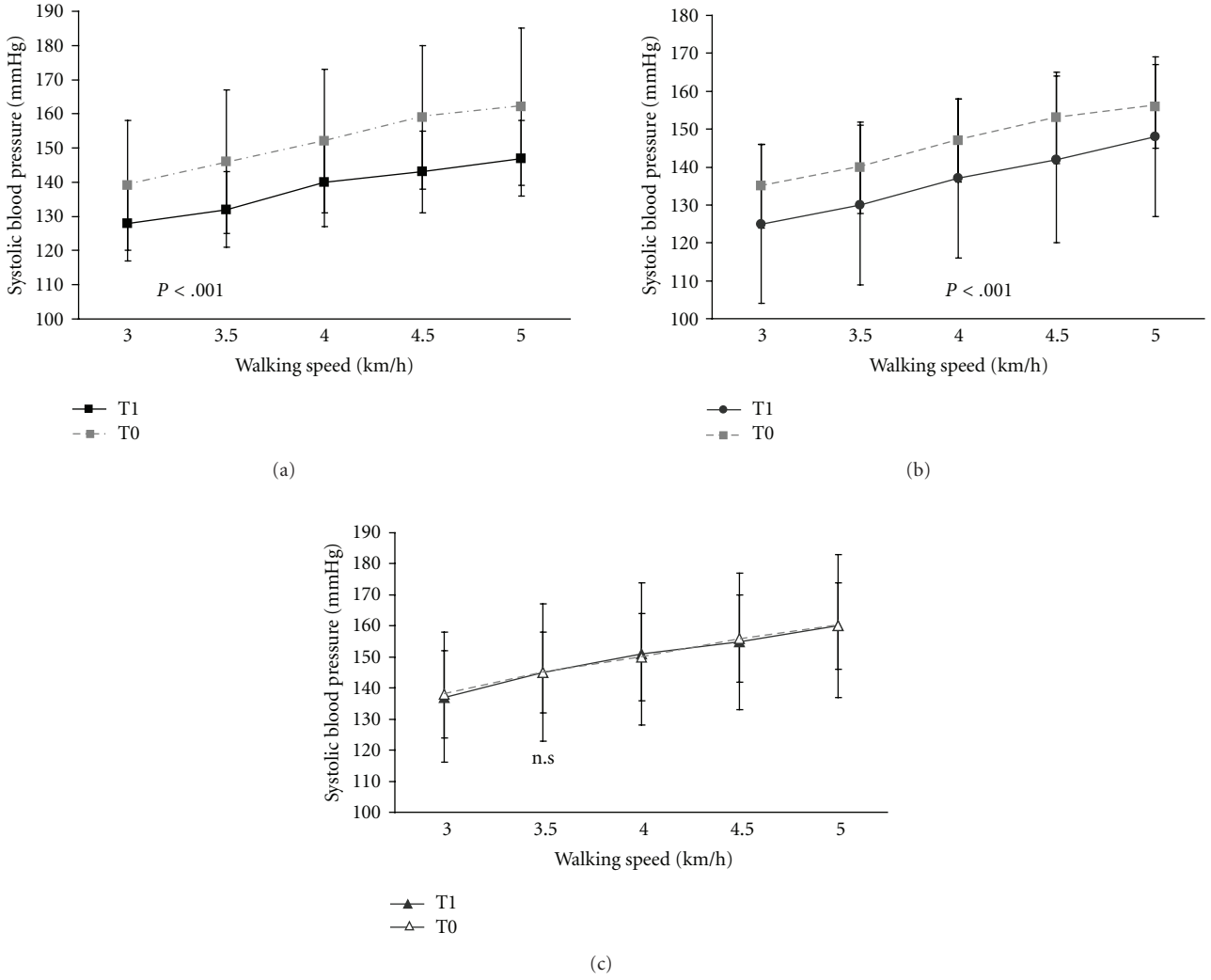

Figure 6: (a) The increase of the systolic blood pressure with increasing walking speed was significantly lower after completion of the training programme in the Nordic walking ((a)) and the walking group ((b)) but not in the flexibility and relaxation group; ((c)) T0 = first assessment, T1= second assessment, error bars indicate the standard deviation. (b) Walking group. T0 = first assessment, T1 = second assessment, error bars indicate the standard deviation. (c) Flexibility and relaxation group, there was no difference between the first and second assessment; T0 = first assessment, T1 = second assessment, error bars indicate the standard deviation.

and patients were more dependent on a physiotherapist to run the sessions. Only 50% of the patients continued the flexibility and relaxation programme.

5. Discussion

In summary, the main results of the study were that all training programmes provided some benefit for the patients. Pain of the neck, hips, and iliosacral joint, health-related quality of life, and balance improved in all groups. In contrast maximal walking speed, stride length, double stance, exercise capacity at submaximal level, subscale 6 (cognition) of the PDQ 39 and the UPDRS Sum score and UPDRS-motor score improved only in the walking and NW group significantly. Patients, who completed a walking or Nordic walking training, had a better posture and postural stability, showed less freezing, and were faster in alternating movements. NW was superior to walking and the flexibility and relaxation programme in improving postural instability, gait pattern, stride length and stride length variability. The exercise programmes were not associated with an increased risk of falls or injuries.

Based on the results of the study, the first hypothesis that all training programmes improve walking speed, gait parameters, balance, cardiovascular parameters, Parkinson specific symptoms, pain, and HRQL can be partly corroborated only. The flexibility and relaxation programme did not improve significantly maximal walking speed on the treadmill, cardiovascular capacity, stride length and Parkinson's specific disability.

Gait and/or mobility were the outcome measures in most studies. Neurological symptoms served rarely as outcome measures for exercise programmes, and only a few studies found significant benefit in direction of exercise

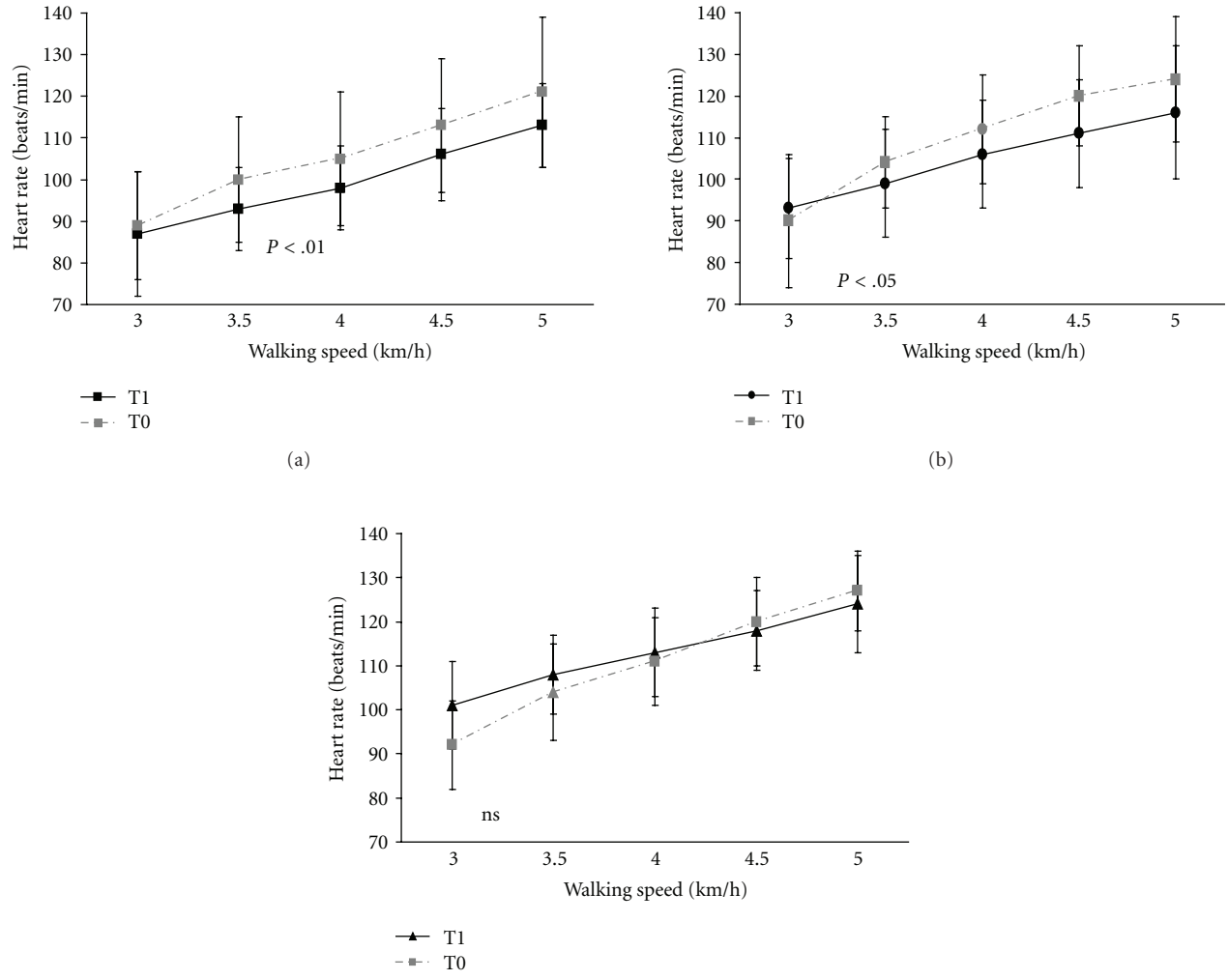

Figure 7: (a) Heart rate increase at submaximal walking speeds was lower in the Nordic walking ((a)) and walking group ((b)) than in the flexibility and relaxation group ((c)) at the second assessment resulting in a significant group effect ($P < .001$). T0 = first assessment, T1 = second assessment, error bars indicate the standard deviation. (b) Walking group: The heart rate response to exercise was significantly lower on the second assessment. T0 = first assessment, T1= second assessment, error bars indicate the standard deviation. (c) The heart rate of the flexibility and relaxation group (F&R) was only significantly lower at low but not at higher walking speeds. Therefore, the course of heart rate response to exercise was not significantly lower on the second assessment in the F&R group; T0 = first assessment, T1 = second assessment, error bars indicate the standard deviation.

intervention [44]. In the present study, we found a clinical relevant improvement on the UPDRS score. Analysis of the results shows that the improvement can be referred to the improvement of the motor scale, especially freezing, posture, alternating movements, walking pattern, and postural instability. Schrag et al. [43] have shown that a reduction of the UPDRS motor scale by 5 points is clinically relevant. The Nordic walking training resulted in a mean improvement of 6.4 ± 4.1 points of the UPDRS motor scale, while the walking group failed to reach a 5-point improvement despite the significant reduction of motor disability compared to baseline. 83.3% of the NW group, 63.3% of the walking group, and 33% of patients of the flexibility and relaxation group improved by more than 5 points on the UPDRS motor score as stated above. Neurological signs such as rigidity and tremor were not improved by exercise treatment, but it is to note that walking and Nordic walking had positive effects on some key symptoms of PD such as posture, alternating movements, freezing, and postural stability. These symptoms have major impact on mobility and the risk of falling. However, the UPDRS might not be sensitive enough to detect the differences generated by the exercise training.

Schenkman and Butler [45] proposed that a restricted range of motion of axial structures might contribute to loss of postural control, gait impairment and decline in overall function. Several studies have shown that trunk flexibility is associated with balance control [46]. Exercises, designed to improve axial range of motion, were shown to improve functional reach distance [46] and timed gait tasks. This might explain that improvement of balance was observed

in all groups even in the flexibility and relaxation group. Posture and postural instability were most improved by NW. Supported by the poles patients walked cross-country during the training, and it has been shown that a training, which challenges the balance control, can improve the postural stability and gait control [47]. The cross country training has possibly improved balance so far that subjects of the NW group are also more stable without poles. Furthermore, the poles represented external triggers [15], and patients remembered to use the more affected arm to handle the pole. The increased involvement of the more affected hand in motion sequences might have led to an improvement of the agility of the more affected hand.

In contrast to the findings of Schenkman et al. [46], the flexibility and relaxation programme did not improve the walking speed in the Webster walking test in the present study. It is well accepted in competitive sport that training has to be specific [48]. This is known as the SAID principle (Specific adaptation to imposed demands). Therefore, walking and NW training resulted in more specific adaptations with regard to the outcome measures. The importance of the specificity of training is shown in the results of the 12-m and 24-m walking tests and the exercise test on the treadmill. Walking and Nordic walking improved walking speed and gait parameters most. Thus, the specific walking training was superior to the flexibility and relaxation programme regarding walking speed, stride length and gait variability.

In agreement with other studies [5, 49, 50], the majority of patients reported a better health-related quality of life at the end of the study independent of the training programme. Since patients enjoyed the social aspects of the training, emotional aspects might contribute to this improvement. Interestingly, the patient group with the greatest perceived exertion improved most on the subscale 6 (cognition) of the PDQ39 and reported better concentration and memory. There is a large body of studies reporting beneficial effects of endurance exercises on cognitive functions especially executive functions [51]. However, we did not perform a formal cognitive test battery after completion of the 6-month training period. At baseline assessment, all patients scored in a normal range on the MMSE although this test does not assess executive functions in particular.

The second hypothesis that Nordic walking is generally superior to the flexibility and relaxation programme and walking could not be confirmed. In most of the tests, Nordic walking was only superior to the flexibility and relaxation programme but not superior to the walking group, especially in the exercise test. It was expected that Nordic walking is most effective in increasing cardiorespiratory capacity. However, there was no superiority of the NW group. Earlier studies purported an enhancement of cardiovascular metabolism and an increase in walking speed by NW. However, recent studies have shown that the physiological effects of NW depend largely on the technical skills of the individuals. Without being competent in using the correct NW technique patients cannot exercise with high intensity. The participants of the NW group had difficulties to employ the correct technique in the beginning of the training period, and it took a long time until they involved the upper body. Although, at the end of the training period nearly all patients showed at least good technical skills, at the assessment after 3-month training, only 50% of the patients showed good technical skills. Probably due to these technical difficulties, most of the patients of the NW group did not walk significantly faster with poles for most of the training period. Therefore, the metabolic and cardiovascular demands on the body might not have been much higher than in the walking group. Consequently, the effects of walking and NW walking might have been quite similar.

However, PD patients were able to learn the technique of NW. There is growing evidence that the capacity to learn remains in early stages of PD [52, 53]. In a previous study (unpublished data so far), we had shown that PD patients learnt a throwing task comparably to healthy age-matched subjects, but their performance level dropped significantly more than that of healthy subjects between the training sessions. A similar learning pattern was observed in the present study, patients who managed the push-off phase at the end of a training session had again difficulties in the next training session. Therefore, the 6-month study period might have been still too short to detect different effects of walking and NW training.

Cardio-respiratory capacity increases by adaptations of muscle fibres, better muscle recruitment, and improvement of cardio-respiratory parameters. PD patients have deficits in muscle recruitment and development of dynamic muscle strength. During the first weeks of training, the body learns to recruit the correct muscles in a proper sequence while inhibiting unnecessary muscle recruitment. These adaptations take several months to occur and depend on a specific training. Since walking was not practised in the flexibility and relaxation group, gait parameters and walking speed did not improve significantly. In addition, fitness training involves systematic progressions that apply the overload principle to purposeful short- and long-term goals [48]. The overload principle states that, for adaptations to occur, a threshold level must be exceeded. Cardio-respiratory capacity improves when an adequate stimulus is set. The demands of the walking and NW training on the body were greater than the demands of the flexibility and relaxation programme. Accordingly patients of the walking and NW group perceived a higher degree of exertion during the training than the flexibility and relaxation group. The ability of the patients of the walking and NW group to realise a higher walking speed with lower blood pressure levels and a lower heart rate showed the successful adaptation to exercise. Although studies on cardiovascular parameters are inconsistent, there is some evidence that PD patients can improve oxygen consumption by aerobic conditioning programmes [46, 54]. Since oxygen consumption was not measured in the present study, we cannot claim that cardiovascular fitness of the patients had improved. At least lower increases of blood pressure and heart rate during the exercise test in patients having completed a walking or Nordic walking training programme can likely be attributed to a better efficiency of the cardiovascular system.

We did not specifically assess the effect of the exercise programme on concomitant diseases. However, the capacity

of the patients to respond to demands on the cardiovascular system with a lower blood pressure increase after completion of the training has to be regarded as a positive effect of the training.

It is always desired to have a carry-over effect of the exercise training into daily life. However, the carry-over effect in PD is often small. PD patients often use cognitive strategies during exercises. As long as the patients are cognitively intact and do not have marked postural instability, they are immediately able to walk faster and with long steps. During the training sessions, patients are focused on walking and their attention is directed to the desired movement patterns. Patients might compensate for the neurotransmitter imbalance through bypassing the defective basal ganglia and instead using the frontal cortex to regulate movement size and timing [55, 56]. Therefore, patients are often not able to keep the gait pattern, when they are distracted. We did not assess whether there was an improvement of gait pattern in every day life. However, the walking and Nordic walking training had an impact on the activities of daily life. Patients became more active and spent less time sitting during the day and instead more time doing heavy work during the week. This is in agreement with findings from a previous study [49].

Another positive effect was the reduction of pain, especially of musculoskeletal pain. Pain is one of the most common nonmotor symptoms in PD and leads to reduction of physical activity, since patients fear an increase of pain by movements. Pain in PD is thought to have several origins; either neuropathic pain that is central in nature, increasing during off-phases, or musculoskeletal pain. The latter responds well to physical therapy and exercises. This was confirmed in the present study. About 36% of the subjects participating in the study suffered from osteoarthritis. Osteoarthritis is often associated with pain and leads to a decreased range of joint motion and to a reduction of physical activity which is especially detrimental to PD patients. The neurodegenerative disease already induces rigidity, a reduction of joint movement leads to slow movements. Pain can start a vicious circle and leads to a significant loss of muscle strength and mobility. There is now sufficient evidence that muscle weakness, immobility, and neurodegenerative diseases are risk factors for osteoarthritis [57, 58]. Current treatment regimes include exercise programmes to recover muscle mass and increase strength [59]. Furthermore, exercises, especially weight-bearing exercises, decrease pain scores, increase muscle strength, and might improve position sense [60]. All exercise programmes had a positive effect on pain. Walking and Nordic walking involves many large core and upper body muscles. Therefore, the impact of walking and NW on back and leg pain might have been stronger. There was also a tendency that hand pain was most improved by NW, which might be due to the required rhythmic hand opening and closing.

Nordic walking was only in some aspects superior to walking but improved postural stability, stride length, stride length variability, and percentage of double stance phase more than the other training programmes. These gait parameters seem to be important for a steady gait, and have major effects on mobility. Reduced stride length variability and a shorter double stance phase are associated with a lower risk of falling [39–41], while a reduction of stride length is associated with fear of falling [41]. Nordic walking was also most effective in improving walking speed on the motorized treadmill. Beauchet et al. [61] found a close relationship between slow walking speed and increased gait variability. Gait might be more unstable when subjects walk slower. Although we did not assess the most comfortable walking speed of the patients, the patients with lower gait variability felt more comfortable during walking compared to those with higher gait variability.

NW was most attractive for the patients, and all patients continued the training, which might be a prerequisite to maintain an active life style.

Supportive was that 70% of the spouses took up NW and accompanied the patients after completion of the study. Since social aspects were very important for the PD patients, the participation of the spouses in NW might support further physical activity.

Physiotherapists should be encouraged to teach PD patients NW and to provide practise sessions with high intensity. Presumably the combination between motor learning, some flexibility exercises, and endurance training produces the best training effects. Three training lessons per week are necessary to learn the right technique and to improve cardiovascular fitness. A lower frequency of trainings sessions and lower intensity of the training in a previous study had been less effective. Exercise training should already be offered to patients in early stages of the disease to prevent a loss of muscle strength and a rapid decline of mobility. Nordic walking might also be suitable in advanced stages of PD, since the support of the poles reduces the risk of falls. However, in advanced stages, fluctuations of motor symptoms and autonomic disturbances, such as exercise-induced hypotension, have to be considered. In addition, at least some of the training sessions should be supervised, since patients do not notice their technical deficits.

The risk of injuries due to accidents during the training was low, but attention has to be drawn to a small risk of overuse injuries, especially of the shoulder, in NW. Therefore, an accompanying physiotherapy treatment is recommended, training should be supervised, and training frequency and intensity has to be gradually increased.

5.1. Limitations of the Study. We included patients in mild-to-moderate stages of the disease and without a history of falls in the past. In another study (personal communication), we assessed the risk of falls in NW training in PD patients with frequent falls. Patients had been able to perform the training and did not sustain severe injuries. Patients participating in the current study did not suffer from severe concomitant diseases, which might have resulted in a positive selection of patients. Many patients of this age have significant concomitant diseases and might be less suitable for an aerobic exercise programme. Cognitive functions have not been formally assessed after completion of the training. Thus, the perception of the NW group, that they can better memorize and recall information, might be confounded by

improved emotional well-being. Due to the lack of technical facilities, the exercise test did not include the measurement of $V0_2$ consumption. Hence, we cannot comment on an improvement of fitness by the training.

5.2. Probable Mechanisms Contributing to Beneficial Effects of Exercise. Peripheral and central parameters might contribute to effects of exercise training. Better muscle coordination and recruitment, improvement of strength flexibility and increase of range of movements and balance reflect the peripheral mechanisms of adaptation to exercise. Cardiovascular effects and reduction of risk factors might contribute as well. In recent years, there is growing evidence from animal and human studies, that physical exercise enhances brain plasticity [62–65]. Physical activity modifies the release of dopamine and dopamine turnover and enhances the release of BDNF (brain-derived neurotrophic factor). These mechanisms might play an important role in central effects of physical activity [66, 67]. Furthermore, BDNF improves neural plasticity and promotes axon outgrowth and development of synapses [67]. Thus, NW, when performed with higher intensity, might provoke a greater release of BDNF. Since walking with poles requires more coordination, interconnectedness might be promoted as well. Further studies are needed to approve these hypotheses.

In conclusion, the study has shown that all forms of exercises had some positive effects on symptoms and deficits caused by PD, but walking and Nordic walking, which involve aerobic endurance training, were superior to the flexibility and relaxation programme. Walking and Nordic walking reduced Parkinson-specific disability and pain, improved health-related quality of life, gait and led to a more active life style. However, PD patients needed more time to practise NW in order to obtain the necessary technical skills. Therefore, it might take longer for training effects to appear, since improvement of motor function is a prerequisite to participate in training sessions with higher intensity. Furthermore, patients showed adaptation to exercise. Participation in sports activities including aerobic training sessions has positive effects on daily activity, gait and PD-specific disability. Exercise therapy does not replace medication but is an important adjunct treatment. Prospective randomised long-term studies are needed to decide whether exercise therapy might also slow down the progression of Parkinson's disease.

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Review Article

Aging, Resistance Training, and Diabetes Prevention

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With the aging of the baby-boom generation and increases in life expectancy, the American population is growing older. Aging is associated with adverse changes in glucose tolerance and increased risk of diabetes; the increasing prevalence of diabetes among older adults suggests a clear need for effective diabetes prevention approaches for this population. The purpose of paper is to review what is known about changes in glucose tolerance with advancing age and the potential utility of resistance training (RT) as an intervention to prevent diabetes among middle-aged and older adults. Age-related factors contributing to glucose intolerance, which may be improved with RT, include improvements in insulin signaling defects, reductions in tumor necrosis factor-α, increases in adiponectin and insulin-like growth factor-1 concentrations, and reductions in total and abdominal visceral fat. Current RT recommendations and future areas for investigation are presented.

1. Introduction

With the aging of the baby boom population and an increased life expectancy, individuals aged 65 years or older are the fastest growing segment of our population [1]. Increases in the number of individuals aged 65+ years will increase demands on health care and health care costs, which could lead to inadequate public resources and less care for the aged [1]. Chronic conditions such as diabetes exert a profound economic impact on our nation; this disease and its associated comorbidities are a major cause of disability and death [2]. In 2007, the total estimated cost of diabetes was $174 billion, which included $116 billion in medical costs and $58 billion in reduced productivity [3].

Total diabetes prevalence (undiagnosed and diagnosed) is currently estimated to be 14% of the U.S adult population [4] and is highest in those aged ≥65 years [2]. Prediabetes, that is, impaired fasting glucose (IFG; 100 mg/dl (5.6 mmol/l)–125 mg/dl (6.9 mmol/l)), or impaired glucose tolerance (IGT; 2-h plasma glucose 140 mg/dl (7.8 mmol/l)–199 mg/dl (11.0 mmol/l)) [5] is also becoming more prevalent in the United States [6]. Individuals with prediabetes are at increased risk for developing diabetes, with the progression of diabetes within 6 years of those with IFG and IGT being 65%, as compared to a 5% progression rate for those with normal blood glucose levels [7]. Recent estimates indicate that by the year 2050, diabetes prevalence could be as high as 33% [4]. The increased prevalence of diabetes among older adults, coupled with the aging of our population, suggests a clear need for effective diabetes prevention strategies. The purpose of the present paper is to review what is currently known about changes in glucose tolerance with advancing age, and the potential utility of resistance training (RT) as an intervention to prevent diabetes among middle-aged and older adults. Current RT recommendations and areas for future investigation are also presented.

2. Aging: Changes in Body Composition and Glucose Tolerance

2.1. Aging and Sarcopenia. Aging brings about a decline in skeletal muscle mass termed sarcopenia [8–10]. Muscle mass declines at a rate of 3–8% each decade after the age of 30 [11]. This loss of muscle mass increases the risk of developing

glucose intolerance and diabetes due to the fact that muscle tissue is the primary site of glucose disposal [12–14]. There are many potential causes of sarcopenia including a reduction in muscle cell number through apoptosis, loss of motorneurons, and a reduction in calcium pumping activity. In addition, a decrease in the muscle twitch time and force is experienced, which can be considered a cause or an effect of sarcopenia [9, 15–17]. Increases in inflammatory cytokines and oxidative stress may also contribute to sarcopenia [18]. Other consequences of this decline in muscle mass include reduced muscle strength, reduced resting metabolic rate, reduced lipid oxidative capacity, and increased adiposity (reviewed in [8]). Many clinical studies have shown that increasing lean body mass (primarily muscle mass) parallels the improvements in glucose tolerance seen with resistance training among older adults [19–31]. However, others have suggested that the prevalence of glucose intolerance in older individuals is not a direct reflection of one's lean body mass, but a result of age-associated increases in abdominal fat [32–34]. Although lean mass may not be the most robust predictor of glucose tolerance, the results of numerous clinical trials suggest that increases in lean body mass with RT are associated with improvements in glucose tolerance [19–31]. Therefore, increasing lean mass regardless of baseline levels should improve glucose tolerance and insulin-resistance, which may be an important strategy to combat the age-related increases in insulin-resistance and glucose intolerance.

2.2. Aging and Body Fat Distribution. Along with reductions in lean mass, older individuals often experience increases in adipose tissue [35–37]. Aging is strongly associated with increases in body weight and body fatness [38, 39]. Based on the 2007-2008 National Health and Nutrition Examination Survey (NHANES), 78.4% of men and 68.6% of woman ≥60 years were considered overweight or obese (BMI ≥ 25 kg/m^2). This represents the highest prevalence of overweight or obesity across all age groups [40]. This could partially be due to reductions in physical activity; for example, older adults average 37% fewer steps per day when compared to younger adults, and perform significantly less moderate to vigorous physical activity [41]. Older adults often do not achieve the recommended amount of physical activity (i.e., ≥30 minutes of moderate physical activity on five or more days/week) proposed by organizations including the World Health Organization, Center for Disease Control and Prevention, Health Canada, and the Department of Health and Ageing [41].

Body fat accumulation is associated with an increased risk of premature mortality and morbidity [39], as well as hyperinsulinemia and glucose intolerance [38, 42]. Older individuals also demonstrate changes in body fat distribution, with increasing levels of upper body fat [35–37]. This increase in upper body fat (specifically abdominal visceral fat) has been linked to glucose intolerance and diabetes [43–45], and abdominal visceral fat is an independent predictor of glucose intolerance [34, 45]. This adipose tissue depot is sensitive to lipolytic stimuli, and in obese states may lead to increased circulating free fatty acid (FFA) concentrations [46, 47]. Visceral fat lipolysis may be responsible for 5–10% of circulating FFAs in lean individuals, while this value may increase to 20–25% in obese individuals [47, 48]. However, upper body, nonvisceral fat is the primary contributor to FFA concentrations [48]. Increased FFA concentrations have been implicated in the development of insulin-resistance and metabolic inflexibility [47–50].

3. Aging and Glucose Intolerance: Potential Contributing Factors

Although factors such as a reduction in lean body mass, physical inactivity, obesity, and changes in fat distribution may contribute to glucose intolerance, age appears to be an independent determinant of impaired glucose tolerance [42, 51, 52].

3.1. Insulin Signaling within Skeletal Muscle. Insulin's effects on peripheral tissues (i.e., skeletal muscle, adipose tissue) involve a complex framework of signaling pathways that result in the translocation of GLUT4 transporters to the cell surface, which are responsible for the transport of glucose across the plasma membrane into the target cell [53]. An alteration in any of the related pathways reduces insulin's effectiveness and leads to the insulin-resistance and glucose intolerance associated with advancing age. The insulin signaling process is complex and not fully understood (reviewed in [53, 54]). Both diabetes and age-associated declines in glucose tolerance are hallmarked by a decreased uptake of glucose by peripheral tissues, primarily skeletal muscle. The age-associated reduction in glucose uptake is not due to impaired insulin binding, but instead to a defect in the postreceptor intracellular insulin signaling pathway [53, 55–57]. This defect has not been fully elucidated; however, a reduction in the number of insulin-stimulated glucose transport units occurs with aging [56]. Thus, fewer GLUT-4 transporters and/or postreceptor defects in the insulin signaling cascade results in insulin-resistance. Exercise-induced, contraction-mediated GLUT4 translocation to the muscle membrane is independent of insulin and occurs via an alternative mechanism (reviewed in [58]). Importantly, older adults with diminished glucose tolerance do not demonstrate a decline in exercise-induced contractile-mediated GLUT4 translocation [59].

3.2. Aging and Pancreatic Beta Cell Function. Insulin secretion decreases at a rate of 0.7% per year with advancing age, and is accelerated twofold in individuals with glucose intolerance [60]; yet it is uncertain the extent to which reduced insulin secretion is due to β-cell dysfunction or reduced β-cell mass [60]. Individuals with glucose intolerance demonstrate a 50% reduction in β-cell mass [61], which may be attributed to increased β-cell apoptosis. The aging of β-cells appears to decrease proliferation and increase sensitivity to hyperglycemia-induced apoptosis [62].

Diminished β-cell function has been reported among individuals with glucose intolerance, which decreases as fasting plasma glucose concentrations increase [63]. Therefore, a combination of β-cell dysfunction and β-cell apoptosis may contribute to age-related declines in glucose tolerance.

3.3. Aging and Mitochondrial Function. A reduction in mitochondrial function may also contribute to age-related declines in glucose uptake [64–67], possibly arising from increases in mitochondrial DNA deletions and mutations [67, 68]. This may lead to a 40% decrease in mitochondrial oxidative metabolism in older adults compared to younger individuals [66]. Specifically, cytochrome c oxidase gene expression and enzyme activity are reduced in aged skeletal muscle [67]. This mitochondrial dysfunction contributes to the decline in physical fitness and oxidative capacity older adults may experience [67, 69]. Insulin resistance is related to increased plasma FFA concentrations and enhanced FFA influx into skeletal muscle [66, 70–72]; decreased mitochondrial oxidative capacity may cause intramyocellular accumulation of fatty acid metabolites such as fatty acyl coenzyme-A, diacylglycerol, and ceramide to accumulate and produce insulin-resistance through serine kinase activation [65, 66, 72]. Serine kinases impede insulin signaling by reducing IRS phosphorylation [64, 65, 72] which leads to a decline in insulin-stimulated GLUT4 translocation and impaired skeletal muscle glucose uptake [64, 65].

3.4. Aging: Adiponectin, Tumor Necrosis Factor Alpha, and Insulin-Like Growth Factor-1. Two strong correlates of aging and insulin-resistance include adiponectin and tumor necrosis factor alpha (TNF-α), with low concentrations of adiponectin and high concentrations of TNF-α being linked to insulin-resistance [43, 73–75]. Both may also play a role in body fat distribution [37, 43, 44, 76, 77] and sarcopenia [18]. Adiponectin is secreted by adipose tissue (i.e., an adipokine) and is a key modulator of insulin sensitivity [43, 75, 78]). Low plasma adiponectin concentrations are associated with insulin-resistance, diabetes, obesity, body fat percentage, body fat distribution, and BMI [37, 43, 76, 79–82]. Adiponectin is believed to activate 5′-AMP-activated protein kinase (AMPK), which activates insulin-independent glucose uptake by the muscle, downregulates gluconeogenic enzymes and increases muscle fatty acid oxidation [83].

Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine secreted by adipose tissue, macrophages, and other cells, which appears to influence insulin-resistance. Elevated TNF-α concentrations are linked to obesity and insulin-resistance, while obese mice lacking TNF-α are protected from insulin-resistance [84]. Inflammatory pathways that impair insulin signaling at the level of IRS proteins are activated in the presence of TNF-α [73, 84]. TNF-α is correlated with body fat distribution [77] and sarcopenia [18] which may also lead to insulin-resistance among individuals with elevated TNF-α concentrations.

Unlike adiponectin and TNF-α, insulin-like growth factor-I (ILGF-I) is not secreted by adipose tissue, but instead a peptide hormone which possesses insulin-like properties such as the promotion of glucose uptake by peripheral tissues [85, 86]. Insulin-like growth factor-I concentrations decline with age, and is associated with the age-related changes in body composition by both increasing fat mass and decreasing muscle mass [87–89], thus potentially being a modulator of insulin-resistance. Administration of recombinant ILGF-I improves glucose uptake in those with insulin-resistance and type 2 diabetes. Other factors may be involved in the role of ILGF-I and glucose metabolism including binding proteins, hybrid receptors, and growth hormone secretion [90].

4. Resistance Training: Influence on Insulin Resistance

The diabetes prevention program (DPP) demonstrated that lifestyle modification reduces the development of diabetes by focusing on weight loss, increased physical activity, and dietary modification. Lifestyle modification decreased the incidence of type 2 diabetes by 58%, as compared to the 31% among individuals taking metformin [91]. The physical activity component of the DPP recommended that individuals accumulate 150 minutes/week of moderate physical activity. The DPP stressed brisk walking as the physical activity of choice, but also lists aerobic dance, skating, bicycle riding, and swimming as options [91]. In support of the DPP's recommendations for aerobic training (AT), regular AT improves glucose control and insulin sensitivity [92, 93]. The American Diabetes Association (ADA) recommends that individuals with diabetes perform at least 150 minutes of moderate-intensity AT per week [94]. However, factors such as obesity, arthritis, low back pain, and physical disabilities affecting many older adults may preclude this population from regularly performing AT [95–97]. Environmental factors such as unsafe neighborhoods or streets also may discourage engagement in many types of aerobic activity [97]. Therefore, alternative approaches for increasing physical activity among older adults should be considered.

Resistance training is one such alternative that can be safe and effective for older adults, including the elderly [95, 98–102]. The ADA encourages individuals with type 2 diabetes to perform resistance exercise three times a week targeting all major muscle groups, progressing to three sets of 8–10 repetitions at high intensity [103]. By using machines that provide external resistance with controlled movements, even those confined to a wheel chair or a walker can perform some types of RT. Though older adults demonstrate reduced overall muscle protein synthesis (MPS) relative to younger adults after a bout of resistance training [104], clinical trials investigating RT interventions among older adults have shown improvements in insulin-resistance and sarcopenia, by increasing lean body mass [19–31].

To identify published research relevant to the focus of this paper, a literature search was conducted using the PubMed search engine, developed by the US National Library of Medicine of the National Institutes of Health, without restrictions on publication date. Additional inclusion criteria

were as follows: randomized controlled trial study design, studies conducted in middle-aged and older adults, study duration greater than one month. Intervention studies which met inclusion criteria are described in Table 1. Of the RT intervention studies reviewed, most reported improvements in glucose uptake, and reduced diabetes risk (i.e., 4 of 5 interventions report beneficial effects of RT on diabetes-related outcomes). Intensity appears to influence the magnitude of improvement in these outcomes; high intensity RT (defined as training loads above 75% one-repetition maximum (RM) [105]) produces greater improvements than RT performed at a moderate or low intensity (training loads between 50%–74% of one RM and below 50% one RM, respectively [105]) [102, 106]. Although AT has been an accepted (see DPP [91]) and recommended (ADA [94, 103]) exercise intervention to improve glucose metabolism, some investigations of the combined effects of RT and AT conclude that RT + AT exercise programs enhance diabetes related outcomes [23, 30], while others have suggested that RT-alone programs have benefits comparable to that of AT-alone programs [22, 107–109]. Evidence to support one mode of training (RT versus AT) over the other is limited and should be further investigated before conclusions can be made as to the superiority of one form of exercise over the other.

Two RT modes were used in the five investigations included in Table 1. Four interventions utilized weight-training machines [27, 31, 79, 109] while one used therabands [110]. Interestingly, all four studies using a weight-training machine protocol reported improvements in diabetes-related measures, whereas the RT intervention utilizing therabands did not lead to differences between exercise and control groups. The number of studies in this area is limited, yet these findings suggest that RT mode may be an important issue with regard to improvements in glucose metabolism.

Although Table 1 only includes studies investigating chronic RT effects, others have investigated glucose metabolism with acute bouts of RT, and reported conflicting results. Black et al. found that a single RT session performed at either low or high intensity, using either a multiple set or single set protocol, improved 24-hour postexercise insulin sensitivity measured via fasting plasma glucose [106]. Conversely, Jimenez et al. assessed insulin sensitivity using the euglycemic-hyperinsulinemic-clamp technique preexercise, and 12 and 36 hours postexercise, and reported no differences between control and exercise groups [111]. Methodological difference may have contributed to the conflicting findings (i.e., RT protocol, outcome measures, study population). Thus it remains uncertain the extent to which improvements in glucose/insulin metabolism with RT could be attributed to an acute exercise bout versus a result of chronic training.

4.1. Resistance Training: Changes in Insulin Signaling, Adiponectin, TNF-α, and ILGF-1. Resistance-trained muscle has shown increased rates of insulin-stimulated glucose uptake and transport [112, 113]. This has been attributed to the fact that RT increases aspects of the insulin signaling cascade that result in the upregulation of this pathway. Increases in the protein content of the insulin receptor and kinase activity (PIP-3, Akt/PKB, aPKC) are evident in resistance-trained muscle, even without increases in lean mass, and may enhance glucose uptake [96, 112–114]. Akt/PKB, insulin receptor protein, and glycogen synthase activity are increased with RT, all of which are downstream targets in the insulin signaling cascade that may be important in the translocation of GLUT-4 receptors and skeletal muscle glucose uptake [96]. These changes in the insulin signaling cascade are observed even without increases in lean mass [96]. In addition to (or possibly as a result of) the increased activity of the insulin signaling cascade, an increase in GLUT-4 protein concentration has also been observed with RT in humans [96] and rodents [112–114]. Thus, the two possible insulin signaling defects that result in insulin-resistance (decreased number of GLUT-4 transporters and/or post receptor default in the insulin signaling cascade resulting in less GLUT-4 translocation) appear to be improved with RT. Increased insulin signaling activity, along with increases in GLUT-4 protein expression, may lead to increased GLUT-4 translocation thereby increasing glucose transport and reducing insulin-resistance.

Improvements in adiponectin concentrations have been reported with weight loss [115–117], aerobic exercise [78, 80–82, 118] and RT [119, 120]. Since low adiponectin concentrations are associated with obesity, interventions often include weight loss to promote increases in adiponectin. However, some exercise interventions report increases in serum adiponectin concentrations without changes in body weight [20], although others do not [121]. There is also conflicting data on the influence of RT on adiponectin concentrations; some have reported no change [79, 116, 122] while others have reported increases [119, 120]. Methodological differences (i.e., RT intensity, measurement of total versus low/high molecular weight adiponectin) may explain conflicting findings. With regard to TNF-α, high intensity RT appears to reduce TNF-α concentrations and improve insulin sensitivity [20, 123, 124], even when fat mass is unchanged [20].

There is conflicting data on the influence of RT on ILGF-I concentrations. Borst et al. reported that 25 weeks of 1 or 3-set resistance training increased ILGF-I in healthy adults aged 25 to 50 [125]; however, this was not observed in a subsequent study by the same group using adults aged 60–85 years and high and low-intensity resistance training [126]. Conversely, others have reported significant increases in ILGF-I with resistance training in the elderly [99, 127]. These studies concluded that despite atrophy and ultrastructural damage, elders respond to RT with significant increases in musculoskeletal remodeling, cross-sectional area and elevated IGF-I levels [99, 127]. Increases in ILGF-I concentration are also associated with increases in lean mass, indicating that ILGF-I may be important in addressing age-related sarcopenia and insulin-resistance. Although more research is needed in this area, it appears that ILGF-I concentrations can be increased in older adults to augment glucose uptake and improve insulin-resistance.

Table 1: Randomized controlled trials >1 month in duration investigating the effect of resistance training on diabetes-related outcomes among nondiabetic middle-aged and older adults[†].

Source	Study design	Study duration	RT protocol	Study population	Primary findings
Traditional Weight Training only[*]					
Iglay et al. [27]	RCT ($n = 36$): RT + 0.9/g/kg/d protein intake, $n = 16$ RT + 1.2 g/kg/d, $n = 16$	3 months	3x week, 8 machine exercises, 2 sets 8 reps + one set to voluntary fatigue at high intensity	Healthy individuals, aged 60–62 yrs.	↓ glucose OGTT AUC 25–28% with RT, no differences between diet groups.
Onambélé-Pearson et al. [110]	RCT ($n = 30$): LI (~40% 1RM), $n = 18$ HI (~80% 1RM), $n = 12$	3 months	3x week, 6 exercises using therabands, progressing from 8–11 reps and 2–4 sets, different intensity groups: HI versus LI	Sedentary individuals, aged 55–80 yrs.	↑ fasting plasma glucose (4.8 ± 0.19 to 5.51 ± 0.08 mmol/L) in HI group, no change in plasma glucose for LI, no change in plasma insulin for either group.
Zachwieja et al. [31]	RCT ($n = 15$): RT + GH injections, $n = 6$ RT only, $n = 9$	4 months	4x week, 9 machine exercises, 4 sets, 4–10 reps at high intensity.	Healthy men, aged 64–75 yrs.	↑ in glucose disappearance rate (3.0 ± 0.3 to 4.0 ± 0.4 mg/100 mL/min minimal model of glucose kinetics, IVGTT) with RT only
RT + AT (either alone or combined)					
Ahmadizad et al. [79]	RCT ($n = 24$): AT, $n = 8$ RT, $n = 8$ Control, $n = 8$	3 months	3x week, circuit weight training, 11 machine exercises, 4 sets, 12 reps, at moderate intensity with 30 sec. rest between exercises.	Healthy men, aged 35–48 yrs.	↓ HOMA-IR 35.7 and 38.5% after AT and RT respectfully; no differences between groups.
Smutok et al. [109]	RCT ($n = 37$): RT, $n = 14$ AT, $n = 13$ Control, $n = 10$	4.5 months	3x week, 11 machine exercises, 2 sets, 12–15 reps at moderate intensity.	Men at risk for CHD with either abnormal glucose tolerance, dyslipidemia, or hypertension, aged 41–59 yrs.	↓ plasma glucose at 60, 90, and 120 minutes after glucose ingestion with RT; ↓ plasma glucose at 90 and 120 min after glucose ingestion with AT. ↓ fasting glucose with RT, no changes with AT. Insulin OGTT AUC ↓ 24% for AT and 21% for RT, no changes in control.

[*] Traditional Weight Training= any muscle strengthening exercises using resistance training machines/equipment, free weights (e.g., dumbbell, barbell) or therabands.

[†] Abbreviations used: AT: Aerobic training, AUC: Area under curve, GH: Growth Hormone, HI: High intensity, HOMA: Homeostasis model assessment, IVGTT: Intravenous glucose tolerance test, IR: Insulin Resistance, LI: Low intensity, OGTT: Oral glucose tolerance test, Reps: Repetitions, RCT: Randomized controlled trial, RT: Resistance training.

4.2. Resistance Training and Body Fat Distribution. Body fat distribution may play a major role in the development of insulin-resistance, particularly abdominal fat [33, 42]. Resistance training reduces abdominal fat, including visceral fat, among individuals with diabetes [116, 128, 129]. Both low intensity RT three times per week [128], and high intensity RT twice per week [116] improve insulin-resistance and reduce body fat mass. Strength training-induced changes in abdominal visceral fat were also reported without significant weight loss [129]. Thus, RT alone may reduce abdominal and visceral fat, which is known to increase with advancing age and influence insulin-resistance.

An overview of how RT may influence age-related physiological changes impacting diabetes risk is presented graphically in Figure 1.

5. Current Recommendations: Aging, Resistance Training, and Diabetes Prevention

Major health organizations such as the American College of Sports Medicine (ACSM), American Heart Association (AHA), and the American Geriatrics Society (AGS) have issued recommendations regarding RT for older or diabetic individuals. As stated previously, the ADA encourages individuals with type 2 diabetes to perform resistance exercise three times per week targeting all major muscle groups, and progressing to three sets of 8–10 repetitions at high intensity [103]. According to the ACSM, older adults should engage in RT at least twice per week. These sessions should include 8–10 exercises of 8–12 repetitions, involving the major muscle groups, done at a moderate

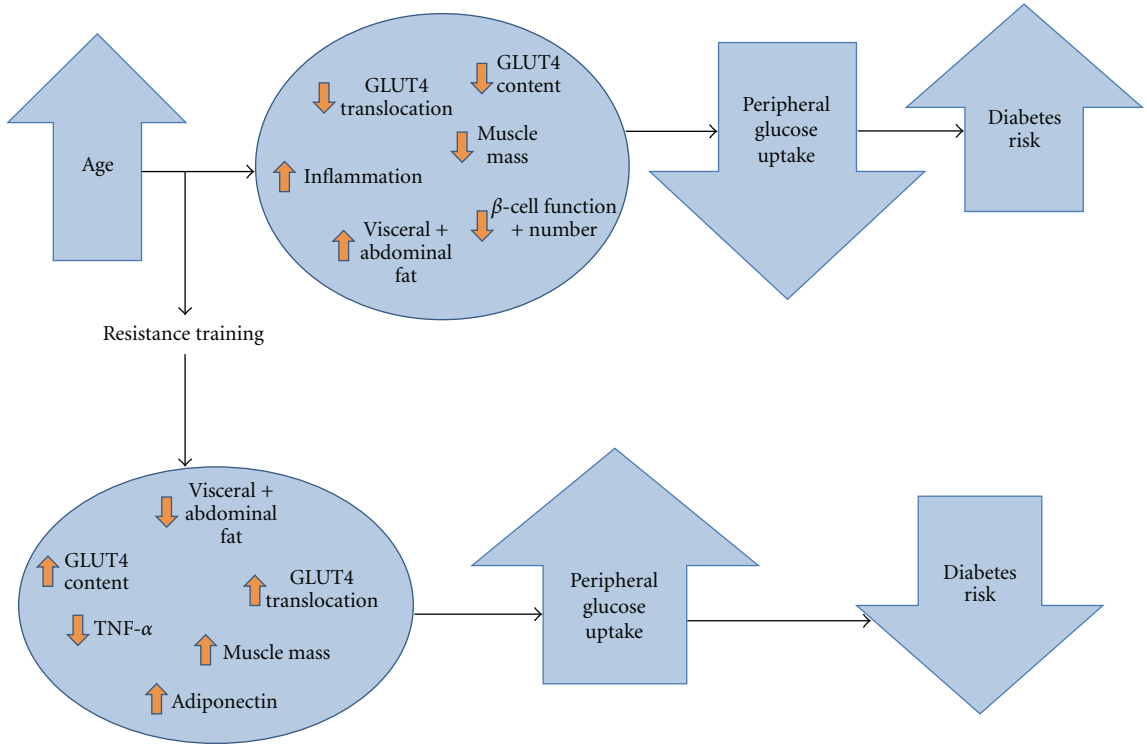

Figure 1: Age-related physiological changes and diabetes risk: Potential influence of RT.

to vigorous intensity [130]. Similarly, ACSM's position stand on exercise prescription for diabetes care recommends that individuals engage in RT at least twice per week, with 8–10 exercise involving the major muscle groups to be performed with at least one set of 10–15 repetitions. This position stand recognizes that increased intensity of exercise or adding additional sets may produce greater benefits, but may not be appropriate for some individuals [131]. Both ACSM position stands advocate progressive RT, with increases in resistance as the individual progresses through the program [130, 131]. The AGS recommends 2-3 days per week of RT with 10–15 repetitions at low intensity, 8–10 at moderate intensity, or 6–8 at high intensity [132]. The AHA recommends that older adults engage in resistance training 2-3 nonconsecutive days per week doing one set of 10–15 repetitions at low intensity, and also recognizes that multiple set regimens performed at higher intensities and frequencies (>2 days a week) may provide greater benefits [133]. These recommendations are similar to protocols used in many clinical trials investigating the effect of RT on diabetes-related outcomes among older adults (see Table 1). Two of the four trials included in Table 1 used a high intensity protocol, while 2 used moderate intensities and one had high intensity and low intensity groups. All of the studies used multiple set protocols. Frequency of training was most commonly three days per week ($n = 4$), while one study used a 4 day per week protocol.

Some studies have addressed the issue of RT intensity and volume on insulin sensitivity. High-intensity protocols show significant increases in insulin sensitivity as compared with moderate intensity protocols [106], and single set protocols may be less effective than multiple set protocols in lowering fasting blood glucose concentrations [106]. A meta analysis concluded that high intensity protocols were more effective than low intensity protocols at increasing strength in older adults [102]. Higher volume interventions are also associated with greater increases in lean body mass in older individuals [134] as well as young men [135]. This suggests the possibility of a dose-response relationship, such that improvements in strength and insulin-resistance are increased as RT intensity and volume increase. Additionally, others have reported that twice weekly RT at low intensity but high volume (three sets of ten repetitions) improved insulin-resistance [136]. Recently, RT interventions stressing volitional fatigue (i.e., the point at which the exercise could not be completed with proper technique) have been conducted [137, 138]; more work is needed to determine if this RT approach is beneficial with respect to blood glucose control and insulin-resistance.

Taken together, existing recommendations and these research studies suggest that high volume and high intensity RT may produce greater improvements in muscle mass gains, insulin-resistance and glucose tolerance; however, it would be prudent for sedentary older diabetic or prediabetic individuals to begin an RT program at low intensity (rate of perceived exertion of ~5-6) and low volume (1 set per exercise, 10–12 reps) twice weekly, and if time and fitness are sufficient, progressively increasing intensity, volume, and frequency [130, 131, 133].

5.1. Future Directions. Research suggests that RT may play a role in improving the age-related increases in insulin-resistance, and prevent the onset of diabetes. Major health organizations have recognized the benefits of RT. However, according to the CDC, only 13% of men and less than 10% of woman aged ≥65 yrs reported engaging in strength training at least two days per week [139]. Possible reasons for low rates of adoption and minimal adherence may include barriers such as the perceived complexity and knowledge needed to perform RT, misinformation of expected RT outcomes (e.g., excessive or undesirable hypertrophy), and the emphasis many public health programs and clinicians place on AT rather than RT. Once effective RT interventions are identified, the translational capabilities of intervention approaches should be investigated. Adherence, simplicity, and cost effectiveness are important for RT interventions to be successful in real-world settings.

Differences in traditional RT versus circuit weight training have not been addressed, as well as differences in protocols using free weights and those using machine weights. It is possible that certain RT approaches lead to greater rates of adoption, adherence and greater cost effectiveness among older, insulin resistant individuals.

Dietary and weight loss interventions in conjunction with RT should be investigated to determine the optimal approach for diabetes prevention with advancing age. For example, the role dietary protein intake may play in reversing insulin-resistance and improving glucose control should be studied more in depth, as high protein diets improve glucose control in individuals with type 2 diabetes when compared to those on a low protein diet [140, 141]. Additionally, a positive relationship between protein intake and change in whole body fat-free mass has been observed after pooling RT studies investigating protein intake in adults aged 50–80 [142]. Based upon these findings, it has been suggested that the RDA for protein intake (0.8 g/kg) is inadequate for older adults who engage in RT [142]. With the possibility that high protein diets can be beneficial to those with impairments in glucose metabolism as well as older adults engaging in RT, the synergistic effect of RT and high protein diets on glucose tolerance warrants further investigation.

Finally, additional work should be done to address mechanisms for RT-induced improvements in insulin-resistance and glucose tolerance. The specific effects of RT on insulin signaling are uncertain, and the effect of RT on pancreatic β-cell function/mass and mitochondrial dysfunction are unknown. It is also possible that other inflammatory markers not yet identified may influence sarcopenia and the response to RT among older adults. Although some work has been done addressing the effect of RT on visceral adipose tissue [76, 77], direct effects on FFA concentrations and gluconeogenesis are uncertain. By continuing to identify the mechanisms by which RT improves insulin-resistance, and by determining optimal combinations of RT with other lifestyle factors to prevent diabetes, interventions can be developed which optimize reduction in diabetes risk with advancing age.

In conclusion, it appears RT may be an effective intervention approach for middle-aged and older adults to counteract age-associated declines in insulin sensitivity and to prevent the onset of type 2 diabetes. Older adults who engage in RT may see benefits with respect to improvements in body composition, body fat distribution, inflammatory markers, and blood glucose homeostasis. Future research investigating mechanisms, optimal RT protocol, and intervention approaches with high translation potential are needed to enhance knowledge in this area, and to increase public awareness and adoption of RT.

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Research Article

Eicosanoid Production following One Bout of Exercise in Middle-Aged African American Pre- and Stage 1 Hypertensives

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Endothelial dysfunction and a sedentary lifestyle may be involved in the development of hypertension which is proliferative among middle-aged African Americans (AA). Signaling molecules derived from the oxidation of 20-carbon fatty acid molecules known as eicosanoids influence vascular tone. The relationship between aerobic fitness and eicosanoid formation following exercise in middle-aged African American hypertensives is unknown. *Purpose*. To determine the relationship between aerobic capacity and eicosanoid formation after a bout of moderate-intensity exercise in middle-aged AA hypertensives. *Methods*. Ten sedentary hypertensive AA underwent 50 min of aerobic exercise at 65% VO_2max. Urine was collected for 24 hr on two occasions, prior to testing and immediately following the bout of exercise. Urinary metabolites of prostacyclin (6-keto $PGF_{1\alpha}$) and thromboxane (11-$dTXB_2$) were measured during the day and night periods by high-performance liquid chromatography (HPLC). *Results*. 6-keto $PGF_{1\alpha}$ levels significantly increased ($P = .04$) following the bout of exercise compared to the control day. There was a significant relationship ($r = .49$, $P < .05$) between 6-keto $PGF_{1\alpha}$ levels and VO_2max during the exercise day. *Conclusion*. Based on this preliminary study, there appears to be a relationship between aerobic capacity and exercise-induced 6-keto $PGF_{1\alpha}$ production in middle-aged hypertensive AAs. AAs with lower VO_2max had lower 6-keto $PGF_{1\alpha}$ formation.

1. Introduction

Hypertension is a multifactorial disease that has high prevalence in African Americans [1, 2]. National surveys show that the majority of middle-aged, urban African Americans engage in little or no leisure-time physical activity [3]. This high prevalence of physical inactivity contributes to the disproportionate burden of obesity, hypertension, diabetes, and coronary heart disease in African Americans [3–5].

A number of important causal factors for hypertension have been identified. Research has implicated endothelial dysfunction as a factor involved in the pathogenesis of hypertension and is evident in the early stages of the development of coronary atherosclerosis [1, 6–9]. Hypertension is also more prevalent with advancing age. The prevalence of endothelial-impaired function disorders such as hypertension is disproportionately higher in the African American population in contrast to Caucasians [1, 2, 10].

Eicosanoids are 20-carbon molecules derived from arachidonic acid, a polyunsaturated fatty acid. Cyclooxygenase 1 or 2 (COX-1 or COX-2) and cell-specific synthases convert free arachidonic acid to a biologically active compound. The biologically active eicosanoid binds to receptors on the target cell plasma membrane to cause a wide range of biologic effects including platelet aggregation, lymphocyte aggregation and proliferation, bronchoconstriction, and vasodilation or vasoconstriction. Stable metabolites of the eicosanoids can be measured in urine, plasma, or tissue and are thought to represent whole-body synthesis of eicosanoids [11, 12].

Table 1: Study timeline.

Screening	Baseline						Testing					
Casual BP Screening blood draw Bruce maximal TM test Modified GXT with gas analysis	Diet log	Diet log	Diet log	Diet log	Diet log	24 hr urine Diet log	Diet logs returned Diet	Diet	Diet	Diet	Exercise Diet	24 hr urine Diet
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6

Thromboxane (TXA_2), a vasoconstrictor and platelet aggregator, and prostacyclin (PGI_2), a vasodilator and antiplatelet aggregator, are the most well-characterized eicosanoids influencing vascular tone. TXA_2, a very unstable compound produced by platelets, has thrombogenic properties and is cytotoxic. The stable metabolite of TXA_2 is 11-dehydro-thromboxane B_2 (11-dTXB$_2$). The stable metabolite of PGI_2 is 6-keto $PGF_{1\alpha}$.

Acute exercise enhances the generation of reactive oxygen species (ROS) which can lead to the oxidation of lipids, proteins, and nucleic acids altering cellular function. The increase in ROS after acute exercise promotes an acute phase of local inflammation that characteristically induces the release of inflammatory cytokines. These cytokines stimulate the release of arachidonic acid and ultimately an increase in PGI_2 production. Thus, the exercise-induced increase in PGI_2 is a normal consequence following exercise [13, 14]. A recent study by Zoladz reported an attenuated PGI_2 release following exercise in coronary artery disease and hypertensive patients when compared to healthy controls [15]. There is contrasting evidence reported on exercise-induced TXA_2 production. Some research indicates an increase in TXA_2 following exercise when others have reported no change [15–19].

There is little, if anything, known about the acute exercise-induced responses of PGI_2 and TXA_2 in middle-aged African Americans. The purpose of the study was to assess the changes, if any, in PGI_2 and TXA_2 production following a single bout of aerobic exercise in middle-aged hypertensive African Americans.

2. Protocol

2.1. Participants. Participants were recruited from the Baltimore, MD and Washington, DC area. Ten volunteers (5 male, 5 female; 58 ± 2.3 yrs) completed the study. The participants were sedentary (regular aerobic exercise ≤2 sessions/wk and <20 min/session, sedentary occupation) African Americans who were categorized as having prehypertension (pre-HTN) or stage 1 hypertension (systolic and diastolic blood pressure (BP) 143 ± 7/87 ± 7 mmHg).

2.2. Screening. Subjects had a physical examination, routine fasting blood chemistries, and BP measured under standardized conditions. Inclusion criteria required participants to be pre- or stage 1 hypertensive according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines [2] having an average systolic BP of 120–139 mmHg (pre-HTN), 140–159 mmHg (stage 1), and a diastolic BP of 80–89 mmHg (pre-HTN), or 90–99 mmHg (stage 1). No participants were taking antihypertensive medications. BP level was determined by the average of three casual BP readings from three separate days according to the standards established by the JNC 7 guidelines. Blood samples were drawn in the morning following a 12-hour fast and sent to Quest Diagnostics for routine chemistries. In addition, blood lipids, serum creatinine, and glucose were also measured. Blood lipids were assessed to rule out hyperlipidemia; serum creatinine was measured to rule out renal dysfunction; fasting glucose was measured to rule out diabetes. Individuals with abnormal blood chemistries were excluded from further participation in the study. Each participant then underwent a physical examination by the study physician. Exclusion criteria included smoking, a body mass index (BMI) >35, alcohol intake of more than 3 drinks per day, diabetes (fasting glucose level >126 mg/dL), total cholesterol >240 mg/dL, and evidence of renal or cardiovascular disease.

The screening GXT was a maximal test to screen for signs and symptoms of coronary artery disease. During the test, the participants walked on a treadmill while their blood pressure, heart rate, and ECG response were monitored. The speed and/or degree of incline of the treadmill increased every 3 minutes until the participants could no longer continue or showed signs or symptoms of cardiovascular events. Participants having a negative screening graded exercise stress test (GXT) were excluded from further participation in the study. The study protocol was approved by the Institutional Review Board of the University of Maryland, College Park. Informed consent was obtained from each participant. A timeline of the protocol is provided in Table 1.

2.3. 24-Hour Urine Collection. Urine was collected for a 24-hour period one week prior to the exercise session (Baseline). Samples were collected in five time periods (00:00–08:00, 08:00–12:00, 12:00–16:00, 16:00–20:00, and 20:00–0:00). Urine for each time period was collected in a separate container. All urine collection containers were kept on ice in a cooler for the entire 24-hour period. Subjects began urine collection after their first void in the morning and ended after their first void the following morning. Total urine volume was measured to the nearest .5 mL and an aliquot of the pooled 24 hour urine was sent to Quest Diagnostics for determination of creatinine concentration. Creatinine is a breakdown product of creatine phosphate in muscle. In

the absence of kidney dysfunction, creatinine clearance is relatively constant and can be used as a means to compare other excreted metabolites. Aliquots from each time period were frozen at −80°C until analysis. A second 24-hour urine collection was repeated immediately following the exercise session.

2.4. Diet. Three days prior to beginning baseline testing, subjects were instructed to maintain their usual diets and complete a 6-day dietary log. Each subject was given their dietary information recorded during the baseline period and instructed to repeat the 6-day diet leading to the exercise day.

2.5. Graded Exercise Test to Measure Aerobic Capacity. A second GXT was completed a week prior to the exercise session. All subjects completed a maximal treadmill exercise test to derive a valid prescription for the acute exercise session. When oxygen consumption (VO_2) is added to a GXT, it is possible to measure VO_2max, an index of cardiovascular fitness. Participants began at 70% of the peak heart rate achieved on the subject's screening exercise test and the treadmill grade was increased 2% every 2 minutes. Blood pressure, heart rate, and ECG were monitored during the test which was terminated when the subject could no longer continue. VO_2 was measured continuously throughout this test using a mass spectrometer (Marquette), mixing chamber (Rayfield), turbine volume meter system (model VMM, Interface Associates), and customized validated metabolic software. Standard criteria were used to determine if VO_2max had been achieved. Subjective criteria included the subject's rating of their perceived exertion and their physical inability to continue exercise. The objective criteria that were monitored were a plateau in rise in heart rate and a respiratory exchange ratio of greater than 1.15. The respiratory exchange ratio is determined by dividing the volume of CO_2 expired per minute by the volume of O_2 inspired per minute.

2.6. Acute Exercise Session. The goal of the exercise session was to accumulate 50 minutes of exercise. The exercise session began with a 10-minute warm-up consisting of walking and stretching exercises. The participants then walked on a treadmill for 30 minutes, followed by 5 minutes of rest, and then 20 additional minutes of treadmill walking or cycle ergometry for a total of 50 minutes of submaximal exercise. A heart rate monitor (Polar CIC, Inc.) was used to ensure that each subject's exercise heart rate corresponded to 65% of their aerobic capacity that was measured during the VO_2max GXT. After completing the acute exercise session, participants began a 24-hour urine collection period in the same manner as during the baseline collection.

2.7. Measurement of 6-Keto $PGF_{1\alpha}$ and 11-$dTXB_2$

2.7.1. Chemicals and Materials. The prostaglandins (6-keto $PGF_{1\alpha}$ and 11-$dTXB_2$) were purchased from Biomol (Plymouth meeting, PA, USA). Creatinine was purchased from Sigma-Aldrich (St. Louis, MO, USA). Ortho Phosphoric acid, HPLC water, and acetonitrile were purchased from Fisher Scientific (Waltman, MA, USA).

2.7.2. Instrumentation. The Jasco HPLC system consisted of a Jasco pumps (PU-980), a Jasco UV-VIS detector (UV-975; Jasco Incorporated Easton, MD, USA), and a Rheodyne manual injector (Rheodyne LLC, Rohnert Park, CA, USA). Jasco-Borwin software (version 3.3.5) was used for data collection. The analysis was done on a Symmetry C_{18} 4.6 × 250 mm column with 5 μm particle size (Waters Corporation, Milford, MA, USA).

2.7.3. HPLC Method. Acetonitrile was used as the organic phase. Phosphoric acid solution (pH = 4) was used as the aqueous phase as it gave much better chromatographic results than acetic acid solution. An acidic solution (pH of 4) was necessary to maintain the eicosanoids in the neutral state. Creatinine, at pH = 4 which is below its pKa value (4.83) will be in the protonated form. Creatinine in this form will be retained for a very short period of time on a nonpolar stationary phase compared to the neutral form of 8-iso PGF_2, a long-chain (C20) polyunsaturated fatty acid. The flow rate and ratio of the aqueous and organic phase were selected to obtain a method with a practical run time and which resulted in good separation of all the compounds. All the chromatograms showed a negative drop at around 3.0 min. This is due to the change in the wavelength from 254 nm to 196 nm. The HPLC method employed an isocratic elution of 17 mM phosphoric acid (solvent A) and acetonitrile (solvent B) in the ratio of 65 : 35. The analytes were separated at ambient temperature with an injection volume of 100 μL and using a flow rate of 1.3 mL/min. The run time for the method was 16.5 min.

Urinary metabolites 6-keto $PGF_{1\alpha}$ and 11-$dTXB_2$ were dissolved in 1 mL methanol such that the stock mass concentration for all was 1 mg/mL. 1000 mg of creatinine was dissolved in 100 mL HPLC water to obtain a stock having concentration of 10 mg/mL. Working standards for the analytes were prepared by serial dilution using 17 mM phosphoric acid and acetonitrile in the ratio of 1 : 1 as the solvent. The solutions were stored at −80°C when not in use. 75 μL of the filtered urine samples was diluted to 500 μL with a 1 : 1 mixture of 17 mM phosphoric acid and acetonitrile before injecting into the HPLC system.

2.7.4. Linearity, Accuracy, and Precision and Recovery. The HPLC method was validated as per the FDA guidance for the industry: bioanalytical method validation [20]. The linear range for 6-keto $PGF_{1\alpha}$ and 11-$dTXB_2$, the metabolites of arachidonic acid, was established by injecting in triplicate standard solutions at mass concentrations ranging from their respective LOQ to 1000 ng. Both the compounds showed a good linear response with $R^2 > 0.999$ in the range. Accuracy was determined by analyzing the compounds at three different mass concentration levels. Percent accuracy for the prostanoids was between 90.3–101.5%. Interassay and intra-assay precision were determined by injecting in triplicate. Intra-assay and interassay precision as indicated

Table 2: Baseline demographic and clinical characteristics.

Male/female	5/5
Age (years)	58 ± 2.3
BMI (kg/m^2)	30.5 ± 1.1
VO_2 (mL/kg/min)	22.6 ± 1.2
TC (mg/dL)	214.8 ± 9.2
LDL-C (mg/dL)	131.8 ± 10.1
VLDL-C (mg/dL)	27.9 ± 4.0
HDL-C (mg/dL)	55.1 ± 3.4
Casual Avg SBP (mmHg)	143 ± 7
Casual Avg DBP (mmHg)	87 ± 7

Values shown as mean ± SEM.
BMI indicates body mass index; VO_2, aerobic capacity; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

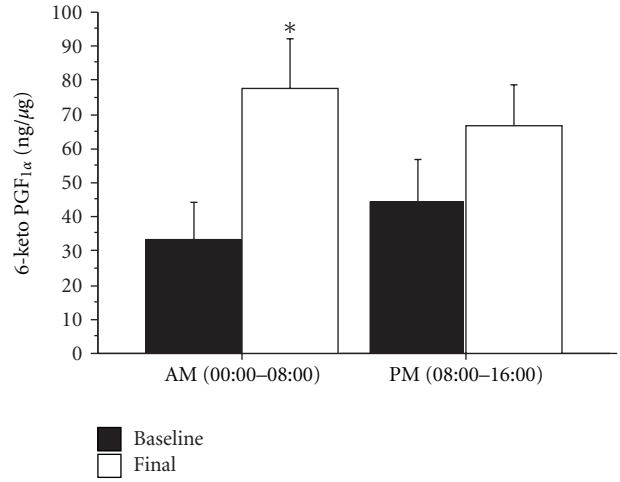

Figure 1: Urinary 6-keto $PGF_{1\alpha}$ levels increased from 33.5 ± 11 ng/ug to 77.8 ± 14.1 ng/ug during the AM period after the bout of exercise when compared to baseline. Levels returned to near baseline during the PM collection following the exercise bout, $^*P < .05$.

by the percent relative standard deviation (RSD) were <10%. The percent recovery for the prostanoids at the three concentration levels was within 95–108%.

Instrument precision was determined by injecting a single mixture containing all the compounds six times and calculating the RSD values. RSD values were found to be less than 5% for all the analytes. The RSD values for all injections were <10% for intra-assay precision, and all urine metabolites were normalized to ug of creatinine.

3. Statistics

For statistical analyses, we redefined the time periods to AM (08:00–16:00) and PM (16:00–00:00) because of insufficient data collected between 00:00–08:00. Descriptive statistics were performed for subject characteristics and are presented as mean ± SEM in Table 2. For each urinary metabolite (6-keto $PGF_{1\alpha}$ and 11-$dTXB_2$), a repeated measures ANOVA comparing groups at the two time periods; before and after acute exercise bout. Repeated measures ANCOVA was used to covary for age, BMI, and aerobic fitness. Separate simple linear regression analyses were performed with VO_2max as the independent variable and each of the urinary metabolites as the dependent variables. Values are presented as mean ± SEM. A value of $P \leq .05$ was considered statistically significant. Statistical analysis was performed using STATVIEW (SAS Institute, Cary, NC).

4. Results

Subject characteristics are shown in Table 2. Ten African American men and women (5 male, 5 female), age 58 ± 2.3 years, participated in the study. VO_2max determined from the GXT ranged from 17.4–29.3 mL/kg/min (mean 22.6 ± 1.2 mL/kg/min), which would classify all participants as sedentary. The average LDL-C for the participants was 131.8 ± 10.1, which is borderline high according to the American Heart Association guidelines.

The urinary metabolites were examined at two time periods: 08:00–16:00 (AM) and 16:00–00:00 (PM) by ANOVA. Baseline levels of 6-keto $PGF_{1\alpha}$ and 11-$dTXB_2$ were 33.5 ± 10.9 ng/ug and 50.8 ± 20.4 ng/ug in the AM, respectively. 6-keto $PGF_{1\alpha}$ levels increased by more that twofold from 33.5 ± 10.9 ng/ug at baseline to 77.8 ± 14.1 ng/ug ($P < .05$; Figure 1) during the AM collection period after the acute exercise session. ANCOVA using VO_2max as the only covariate, followed by Fisher's PLSD, improved the effect of the acute exercise bout ($P = .03$). Based on regression analysis, there was a significant relationship ($P = .04$) between 6-keto $PGF_{1\alpha}$ levels and VO_2max during the AM collection period following exercise (Figure 2). Regression analysis also identified VO_2max as a significant predictor of 6-keto $PGF_{1\alpha}$ following the exercise bout.

Correlational analysis conducted using the baseline values revealed a significant positive relationship ($r = .97$, $P = .04$ AM collection; $r = .99$, $P = .01$ PM collection) between LDL-C and 11-$dTXB_2$. This relationship was not observed between LDL-C and 6-keto $PGF_{1\alpha}$. Analysis also revealed a significant negative correlation between 6-keto $PGF_{1\alpha}$ levels and age ($r = -.92$, $P = .003$).

The urinary 11-$dTXB_2$ concentrations were decreased at both collection times; 51% AM and 35% PM relative to baseline levels; however, this trend, though reproducible and consistent throughout the study, did not meet the test of significance as defined by $P \leq .05$ following the acute exercise session.

5. Discussion

Increases in vascular shear stress and mobilization and activation of cytokines and immune cells occur as a result of exercise. This leads to arachidonic acid liberation from the plasma membrane. COX-1 or COX-2 and cell-specific

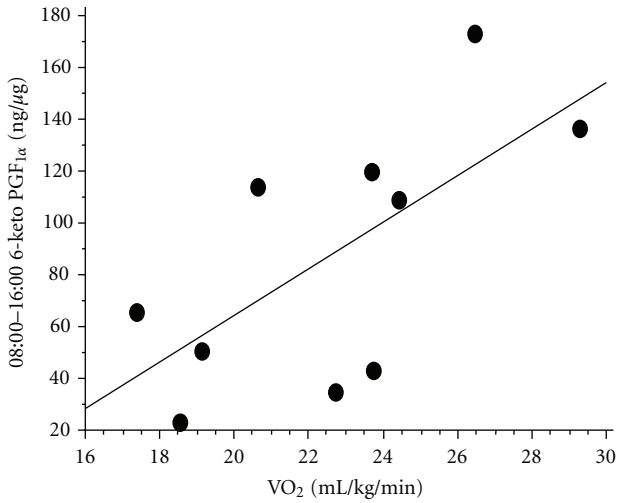

FIGURE 2: 6-keto $PGF_{1\alpha}$ measured in urine collected in the AM following a moderate intensity exercise bout was found to significantly correlate with VO_2max in sedentary African American pre- and stage 1 hypertensives ($r = .67$, $P < .05$).

synthases convert the free arachidonic acid to a biologically active compound with cytoprotective properties.

Platelet activation increases during exercise. It has been suggested that metabolic activity in the arachidonic acid cascade may be increased equally at various exercise intensity levels, but that the synthesis of PGI_2 and TXA_2 may be more heavily influenced by the exercise intensity level [16]. Alternatively, the conversion of arachidonic acid to eicosanoids other than PGI_2 and TXA_2 may be affected by exercise, which may be responsible for the observed decrease in 11-$dTXB_2$ following the acute exercise bout. The increase in PGI_2 generation could be compensating for the prothrombotic environment induced by exercise. Prostacyclin production is initiated by an influx of calcium into the cytoplasm resulting from the emptying of intracellular stores, which occurs only in the initial minutes of cellular activation [21]. This could explain why the increase in the excretion of 6-keto $PGF_{1\alpha}$ occurred in the morning following the exercise bout and not later in the day.

Rodrigo et al. reported that blood antioxidant activity was lower in hypertensives when compared to normotensive controls [22]. Acute exercise enhances the generation of ROS, which can lead to the oxidation of lipids, proteins and, nucleic acids leading to altered cellular function. ROS increases the expression of antioxidant enzymes, but this is attenuated in hypertensives [23, 24]. It has been documented that, in a hypertensive population, plasma levels of 6-keto $PGF_{1\alpha}$ were significantly lower than those of healthy controls [21]. In the current study, individuals who were more aerobically fit (assessed by VO_2max) produced higher concentrations of urinary 6-keto $PGF_{1\alpha}$ following an acute bout of exercise. This may suggest that there is greater antioxidant activity in those individuals who are more aerobically fit than those who are less aerobically fit.

Laustiola et al. and Carter et al. observed that plasma levels of 6-keto $PGF_{1\alpha}$ increased following a low-intensity (30–50% VO_2max) bout of exercise, which suggests that exercise at lower intensities may stimulate a greater production of 6-keto $PGF_{1\alpha}$ [16]. This trend was seen in the present study population with a 1.5-fold to 2-fold increase in 6-keto $PGF_{1\alpha}$. Todd et al. showed that 6-keto $PGF_{1\alpha}$ levels decreased incrementally as exercise intensity increased to near maximal levels [16]. In the present study, moderate intensity aerobic exercise increased urinary levels of 6-keto $PGF_{1\alpha}$ following exercise in the AM urine sample. This is consistent with findings by Okahara et al. that have documented an increase in 6-keto $PGF_{1\alpha}$ production as a result of increased vascular shear stress and cytokine release [25]. The 6-keto $PGF_{1\alpha}$ levels during the PM sample were not different than the baseline day.

Tokunga et al. demonstrated an age-related decline in PGI_2 synthesis which is consistent with our findings. Reduced PGI_2 production, as a result of aging or selective COX-2 inhibition, has been proposed as a mechanism involved in the atherogenic process, myocardial infarctions, and stroke [26, 27]. Nicholson et al. reported that forearm vasodilation responses to PGI_2 were significantly impaired in an older group when compared to a younger group matched for BMI and sex. They further suggested age-related differences in PGI_2-mediated vasodilation are likely attributed to a reduced contribution of the endothelium-derived relaxing factor, nitric oxide (NO) [27]. In a race comparison study, healthy African Americans demonstrated blunted NO-mediated vasodilation when compared to a group of healthy Caucasians supporting evidence of race-related defects in endothelial function [10].

The highly reactive oxygen radical, superoxide anion (O_2^-) has a high affinity for NO, which increases the likelihood of the inactivation of NO and the formation of peroxynitrite ($ONOO^-$), a potent oxidant [28, 29]. Kalinowksi et al. reported racial differences in the steady-state $NO/O_2^-/ONOO^-$ balance in endothelial cells from African Americans. Basal levels are reportedly closer to the redox states characteristic for endothelium-impaired function disorders [1]. In the current study, LDL-C was highly correlated with the urinary metabolite 11-$dTXB_2$ at baseline. LDL-C has been reported to increase the generation of O_2^-, along with NO. Weisser et al. showed that LDL-C increases thromboxane synthesis in a dose-dependent manner [30]. Kuklinska et al. reported a significant negative correlation between LDL-C and PGI_2 but we did not observe such a finding [6].

Decreases of 11-$dTXB_2$ following the exercise session could be due to arachidonic acid being used as a precursor for prostacyclin to compensate for the prothrombotic state. TXA_2 synthase may be at the same expression level, but competing PGI synthase may be in higher concentrations. Todd et al. suggested that exercise intensities below 70% of VO_2max may not be sufficient to stimulate significant alterations in TXA_2 activity [16]. There has been some conflicting evidence in regards to how exercise influences TXA_2 concentrations following exercise. Aerobically trained individuals seem to have an enhanced antioxidant system

[29, 31], which could explain the lack of significant alterations in TXA_2 activity at the low exercise intensity.

Increased risk and incidence of disease are associated with low aerobic capacity [5]. In the present study, there was a relationship between aerobic capacity as assessed by VO_2max and exercise-induced PGI_2 production in pre- and stage 1 middle-aged hypertensive African Americans. African American subjects with lower VO_2max had lower PGI_2 formation. Impaired PGI_2 production in response to exercise may be suggestive of endothelial dysfunction. When racial comparisons are made, the endothelium of African Americans is closer to the state characteristic for endothelium-impaired functional disorders than Caucasians [1]. This may explain, in part, the predisposition of African Americans to complications associated with cardiovascular disease.

The middle-aged participants were carefully screened to provide us with a homogenous population of healthy participants. The strict inclusion criteria lead to the small sample size which is a limiting factor of this study. The lack of significance found for the urinary metabolite 11-$dTXB_2$ following the acute exercise bout could be due to the small sample size and/or the intensity level of the exercise session.

6. Conclusion

William Aird suggests that to develop an understanding of the endothelium in health and disease, one would have to look back at the early ancestral environment where the endothelium evolved to a state of maximal fitness [32]. He further comments that the endothelium is not adapted to withstand the rigors of high fat diet, epidemics associated with high-density populations, sedentary lifestyle, or old age.

The present study examined the most well-characterized eicosanoids affecting endothelial function in a population of sedentary, middle-aged pre- and stage 1 hypertensive African Americans who reside in an urban area. Our preliminary study showed that those with a lower aerobic capacity had a diminished capacity to produce PGI_2, the cardioprotective eicosanoid produced by the vascular endothelium, after exercise. Future studies should examine the effects of long-term aerobic exercise training and diet change (in order to mimic ancestral eating habits) on endothelial function in African American hypertensives.

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Review Article

Intervening on the Side Effects of Hormone-Dependent Cancer Treatment: The Role of Strength Training

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While prostate and breast cancers are both highly prevalent and treatable using hormone suppression therapy, a constellation of side effects ensue, which mimic typical aging effects but at an accelerated pace. Because strength training is considered to be an intervention of choice for addressing the musculoskeletal and metabolic consequences of normal aging in older adults, it may be an effective intervention to attenuate or reverse the side effects of hormone-dependent cancer treatment. This paper provides an overview of the independent effects of strength training on common musculoskeletal and metabolic side effects of hormone-dependent therapy used for prostate and breast cancers. Strength training appears to be an effective complementary therapy for some of the adverse effects of prostate and breast treatment. Future research needs to address potential mechanisms to explain recent findings and to explore the role of strength training in addressing specific risk factors resulting from cancer treatment.

1. Introduction

Cancer is the leading cause of death worldwide, accounting for 7.4 million deaths (~13% of all fatalities) in 2004 and is projected to rise to more than 12 million deaths by the year 2030 [1]. Prostate cancer (PCa) in men (28% of all cancer sites) and breast cancer (BCa) in women (28%) are the most prevalent types of cancer in the US [2]. They are the second leading causes of cancer-related deaths for men and women in the US, respectively [2], while BCa is the leading cause of cancer death in women across the globe [1].

The prevalence of all cancers increases with age [2], with those ≥65 years of age accounting for >60% of all cancers [3]. Because this age group is also more likely to have other comorbid conditions, such as osteoporosis, arthritis, and cardiovascular disease than younger age groups [3], treatment options become more complicated. Moreover, these patients tend to avoid physical activity, leading to some of the same adverse consequences as those previously experienced by cardiac patients who failed to engage in physical activity [4]. As is the case for cardiac patients, this course of action can result in losses of functional capacity and quality of life (QoL) measures for cancer patients. In contrast, regular exercise can reduce cancer-related fatigue and other adverse symptoms of the disease, as well as substantially improve the QoL in cancer patients [4, 5]. Because five-year survival rates in localized PCa and BCa remain high [2], QoL related issues are of great concern. Although regular exercise has long been recommended for cancer patients, investigators have only recently focused on some of the specific musculoskeletal and metabolic adverse consequences (side effects) of cancer treatment, particularly those of hormone ablation medications.

There appears to be an interesting parallel between the many side effects of both PCa and BCa treatment and the changes that occur with typical aging [6–9], but at an accelerated pace. Given the role of strength training (ST) as a countermeasure for the age-related changes in body composition and physical function [10], this review will focus on the effects of ST on the side effects elicited from medications used in the two most common hormone-dependent cancers, that is, PCa and BCa. It will not include combined exercise training programs (e.g., those using both aerobic and resistance exercise) unless combined training

programs are the only source of information available on the side effect being discussed.

2. Treatments for PCa and BCa

There is a wide variety of treatment options for both PCa and BCa, depending on a patient's medical history, diagnosis, age, and current state of health. Although primary treatment for PCa may include radical prostatectomy, radiation, and other therapies, a common adjuvant treatment is the suppression of endogenous testosterone through the use of hormonal agents [11]. Likewise, while surgery is the primary therapy for BCa treatment, hormone suppression therapy serves as an important adjuvant therapy [12]. Chemotherapy is also used as a systemic treatment for BCa, either before surgery (neoadjuvant) or after (adjuvant) as needed. However, a common consequence of chemotherapy is ovarian failure [13, 14] and the onset of premature menopause.

Because most PCas are androgen dependent, androgen deprivation therapy (ADT) is a commonly used treatment for PCa [11] and results in what is sometimes referred to as a chemical castration. Although this treatment slows the growth of existing tumors, thereby potentially saving lives, the associated suppression of testosterone also leads to numerous adverse side effects, including an increase in the number of comorbidities, which ultimately have a negative impact on QoL.

Analogous to the treatment of PCa, hormonal therapy for the treatment of BCa is to inhibit the effects of estrogen. This can be accomplished using selective estrogen-receptor modulators, such as tamoxifen [15], or aromatase inhibitors, another example of an antiestrogen treatment [12]. Both treatments reduce growth in estrogen-responsive tumors. Historically, tamoxifen has been a mainstay in BCa treatment and can be administered to both premenopausal and postmenopausal women [15] while aromatase inhibitors are typically reserved for postmenopausal women [12].

3. Side Effects of PCa and BCa Therapy and Strength Training

3.1. Does Hormone Therapy Mimic Aging Effects?

Sex hormone levels decline gradually with age in men and, abruptly, with menopause in women. Previously, the cessation of endogenous production of androgens and estrogens during PCa and BCa treatment has been equated with increases in hormone-dependent age-related changes [6, 9]. While it is evident that treatment of hormone-dependent cancers via ablation or modulation of the sex hormones is effective in shrinking tumor masses and extending long-term survival rates, such treatments also bring about declines in muscle mass [16–20], strength [21, 22], and bone mineral density (BMD) [17, 22–27] and increases in fat mass [16, 17, 19–21, 28, 29], insulin resistance [30–33], and fatigue [17, 34–36]. Collectively, these effects negatively influence physical function [18, 22, 37–39] and QoL [21, 34, 36, 40, 41].

ST has been advocated as the intervention of choice for addressing many age-related declines [7, 8]. In this regard, many researchers have demonstrated that ST can reverse age-associated losses in muscle mass [42, 43], strength [44], muscle power [42, 45], bone loss [46], insulin sensitivity [47, 48], and increases in regional fat deposition [49], as well as the deterioration of muscle functional abilities, leading to declines in activities of daily living [50, 51]. Losses in muscle mass are also associated with declines in resting metabolic rate, which can lead to obesity. In this context, our group has shown increases in resting metabolic rate with ST [52, 53]. These results from healthy individuals support the hypothesis that ST can reverse or delay the musculoskeletal and metabolic consequences of hormone-dependent cancer treatment. Below is an overview of the evidence from studies that have tested this hypothesis.

3.2. Muscle Mass and Strength. Significant loss of muscle mass is observed within the first year of ADT in PCa patients [16, 17, 19, 20], and the longer the treatment period, the greater the loss in muscle mass [18]. When compared with healthy controls and PCa patients not undergoing ADT, ADT treatment revealed substantial reductions in muscle mass as well as strength [21, 22]. Ultimately, the loss of muscle mass and strength may be adversely linked to survival because higher levels of muscular strength are associated with lower cancer mortality risk in men, independent of other risk factors [54]. Declines in strength and mass may also occur in BCa patients during treatment, but the cause of this effect is unclear. In one study involving BCa patients undergoing localized treatment alone versus localized treatment and chemotherapy, there was a slight decline (<0.5 kg) in fat-free mass over 12 months in the dual treatment group while the localized treatment only group increased fat-free mass [28]. However, this difference was no longer present when results were adjusted for other factors that may have influenced fat-free mass, such as age, race, radiation therapy, baseline body mass index, and baseline fat-free mass. In another study, the effects of chemotherapy and tamoxifen on fat-free mass depended on what method was used to assess fat-free mass [55]. Other investigators have also observed no treatment effect on fat-free mass [56, 57] or strength [58] in BCa patients. Thus, declines in muscle mass and strength appear to be a concern primarily for PCa patients on ADT, given the anabolic role of androgens on muscle mass [59].

In two separate randomized trials, Segal et al. [60, 61] observed strength gains with ST in patients with PCa undergoing ADT. Another study showed that ST improved strength but without changes in whole body fat-free mass in PCa patients on ADT, though a significant increase in quadriceps thickness was reported [62]. Hansen et al. [63] examined the muscle hypertrophic response in PCa patients with and without ADT. Using eccentric resistance exercise, the men not on ADT experienced significant regional hypertrophy whereas the men on ADT did not. No significant differences between groups were observed, but the low statistical power from the small sample size may have contributed to this result. In contrast, we recently detected significant increases

in thigh muscle volume, directly assessed by computed tomography and whole body fat-free mass with ST in African Americans with PCa on long-term ADT (Hanson et al., unpublished data). BCa patients undergoing treatment are also able to increase their strength levels with ST [41, 57, 58, 64]. However, many of the existing exercise and cancer studies use a mixture of aerobic and ST protocols, which precludes the independent effects of ST. Nevertheless, it is likely that the strength increases reported in these studies are due to ST, given that aerobic exercise training does not typically result in significant strength increases.

3.3. Muscle Power. Muscle power is the product of the force and speed of muscular contractions. It is a strong predictor of the ability to perform the activities of daily living necessary for maintaining a high QoL in older adults [65], to an even greater extent than muscle strength [66, 67]. For this reason, power has the potential to be an important QoL indicator for patients with cancer. While muscle power declines with advancing age [68], the effects of cancer therapy on muscle power have not yet been reported in PCa or BCa patients.

The authors [42] and others [45, 69] have reported significant improvements in peak muscle power with ST in older healthy adults. Since movement speed is unlikely to improve with hormone therapy or decline with ST, it is likely that ST would improve power in cancer patients on hormone therapy, as it does for healthy people, given the reported ST-induced strength increases in these patients. To the best of our knowledge, this has not been studied. However, similar to our unpublished muscle volume data, we observed significant improvements in muscle power at various relative loads with ST (Hanson et al., unpublished data).

3.4. Bone Mineral Density. The hormone therapies used for PCa [17, 22, 27] and BCa [15, 58, 70, 71] are both associated with a loss in BMD. However, the specific type of BCa treatment affects BMD differently, as patients on aromatase inhibitors led to declines in BMD while those on tamoxifen experienced significant increases [23–25]. Moreover, bone loss associated with aromatase inhibitor treatment in women with BCa is twofold higher than that of healthy, age-matched postmenopausal women [26]. Chemotherapy treatment for BCa also reduces BMD, probably as a result of ovarian failure, and occurs in ~71% of patients [13, 14, 58]. Patients who retained ovarian function did not show any loss in BMD [14]. With the possible exception of fatigue, BMD loss and fracture risk appear to be the single largest consequence of BCa treatment.

We could find only one study each for PCa and BCa reporting the effects of ST on bone mass [58, 62]. ST for 20 weeks did not result in any changes in BMD in PCa patients [62]. In a randomized clinical trial of BCa patients, six months of home-based aerobic training versus resistance training versus usual care, demonstrated BMD declines of −0.76%, −4.92%, and −6.23%, respectively, with only a significant difference between the aerobic training and usual care groups [58]. However, the ST program was performed using Thera-Bands and light resistance. Recently, Newton et al. [72] proposed a study that could potentially be the best controlled and most thorough physiological investigation on ST effects in patients on ADT. In particular, they propose to address the impact of ST on bone density as an indicator of fracture risk. They will also determine the effects of impact-loading exercise on bone mass. The rationale for this latter aspect of their study is that high and frequent impact forces on long bones are thought to stimulate bone formation.

Despite the lack of direct evidence of significant improvements in BMD in cancer patients, ST can increase BMD in healthy older adults [46, 73–75]. Although not all studies report improvements, those that have compared ST results to controls support the hypothesis that ST is effective for preventing or delaying the loss of BMD over time in older adults. Therefore, it is logical that a similar effect could be present in cancer patients if sufficient intensities are used, despite limited evidence to the contrary [58]. While increases in BMD directly reduce fracture risk, it has been argued that the ST-induced gains (<5%) are not sufficient to overcome the estimated 20% gain in BMD that may be necessary to actually prevent a fracture during falls [76]. Instead, ST may indirectly reduce fracture risk by improving walking mechanics, balance, and strength, some of which have been observed in PCa patients during treatment [62], leading to a reduced risk of falling.

3.5. Fat Mass. Unlike fat-free mass, treatment of both PCa [16–20, 61, 77] and BCa [28, 29, 55] is consistently associated with a significant increase in fat deposition. The increase in fat mass can lead to obesity, diabetes, and metabolic syndrome. Although not directly assessed in previous cancer studies, it is quite likely that PCa and BCa therapies increase fat infiltration in muscle, leading to the accumulation of intermuscular fat [78]. This too has important health implications because elevated levels of intermuscular fat have been linked to insulin resistance and to the development of type 2 diabetes [79]. In addition, fat infiltration is associated with reduced strength [80], poorer leg function [81], and greater incidence of mobility limitations in older adults [82]. While weight gain is widely reported with BCa treatment, it is not well established if the gain is specifically due to tamoxifen. In a cohort of women who experienced weight gain of 1.7 kg and increased body fat 2.1%, there were no differences in weight and percent body fat increases between those being treated with tamoxifen and those who were not [29].

Segal et al. [61] found that ST may play a preventative role against the increase in body fat associated with PCa treatment. The patients who performed ST had no change in fat mass while those in the control group experienced significant increases in fat mass. Along these same lines, Galvão et al. [62] reported no change in body fat with ST and ADT, but had no control group for comparison. Similar findings of no significant reductions in body fat have been reported in BCa [57]. Mixed training protocols (ST and aerobic exercise training) can result in a significant loss of fat mass in some [56] but not all [83] studies in BCa patients during treatment.

3.6. Insulin Resistance. Insulin resistance refers to a reduction in the effectiveness of glucose uptake. This defect is linked to a whole spectrum of disorders, including obesity, cardiovascular disease, and the metabolic syndrome. Basaria et al. [30] observed a substantially higher prevalence of insulin resistance in PCa patients on ADT than in two other control groups, one in normal healthy controls and the other in a group having a similar disease state, but not on ADT. These results were independent of age and obesity. Similar declines in insulin sensitivity were found after a 12-week prospective study at the onset of ADT [32]. In addition, two independent reviews have corroborated this conclusion showing a strong link between ADT administration and insulin resistance [77, 84] and that this association becomes evident within the first few months of treatment. The authors emphasize the need for men receiving ADT to develop healthy lifestyle practices, such as regular exercise, particularly ST [84]. Furthermore, Basaria [77] found that ADT use for 12 months revealed a higher prevalence of diabetes, metabolic syndrome, and death from cardiovascular disease compared to controls. Similar to PCa patients, BCa patients on hormone therapy also have elevated insulin, glucose, and HbA1c levels [33]. Moreover, low doses of hormone therapy result in a loss of insulin sensitivity in women at a high risk for BCa [31]. Women being treated for BCa also had higher C-reactive protein levels and incidence rates of metabolic syndrome [33, 85].

To the best of our knowledge, however, the independent effect of ST has not been studied in cancer patients undergoing treatment for hormone-dependent cancers. The best evidence available is that BCa patients who underwent supervised ST and home-based aerobic exercise had significant decreases in fasting insulin levels with no change in the control group [83]. There was only a trend for between-group differences and no change in fasting glucose levels were found. Patients on ADT undergoing a mixed training protocol had no adjusted group differences after 12 weeks of training for insulin or glucose [86]. In healthy individuals, ST reduces insulin resistance and is as effective as aerobic training in both healthy older adults [48] and diabetics [47]. ST improves the insulin responses during oral glucose tolerance testing and hyperinsulinemic-euglycemic clamps in older men [87, 88] and postmenopausal women [89]. The similarity of findings between ST effects in healthy older adults and those undergoing cancer treatments for other risk factors supports the hypothesis that ST would also produce improvements in insulin resistance in cancer survivors. The data available do not entirely support this, but the independent effects of ST have yet to be evaluated.

3.7. Fatigue and Physical Activity Levels. Fatigue may be the most prevalent and distressing side effect during and after cancer treatment [4, 5], as high numbers of patients report suffering from chronic fatigue during this time [17, 34–36, 55, 90]. It is likely that both aging and hormone therapy contribute to fatigue by eliciting physiological events (such as anemia, declines in strength and fat-free mass, and increased fat mass) that promote loss in fatigue resistance and the ability or willingness to engage in physical activity. Both PCa and BCa patients have reduced physical activity levels after the onset of treatment [17, 91]. Lower levels of physical activity, in part, result in overall reductions in fitness levels, leading to declines in physical function and ultimately to loss in QoL.

Compliance to regular exercise may break the vicious cycle of fatigue followed by avoidance of physical activity [4, 5]. Segal et al. [60, 61] found that fatigue negatively impacts on activities of daily living and QoL measures but both were improved as a result of ST in men with PCa. They also observed improvements in muscle endurance with the ST group compared to a control group [60]. This finding has been corroborated by others [62], supporting the hypothesis that ST improves fatigue resistance in patients undergoing ADT. Reductions in fatigue with ST have also been observed in patients being treated for BCa [57], but these reductions were not significantly different from those of a control group. As described for other factors previously, the independent effects of ST are not entirely clear because many studies used both aerobic and ST [36, 92, 93]. There is little doubt, however, that regular exercise reduces fatigue in BCa patients undergoing therapy.

3.8. Physical Function. The loss of physical function during ADT treatment is a common side effect [18, 22, 37] and is likely the result of decreased muscle mass and physical activity levels coupled with increases in fat mass and fatigue. Investigators who study functional abilities in men with PCa often administer a standardized battery of tests that simulate activities of daily living. This form of testing is seldom reported in women with BCa, rather the declines in function often focus on shoulder dysfunction and lymphedema following surgery rather than hormone treatments [39] or assess function via questionnaire. Reduced shoulder function in BCa is associated with poorer physical condition, minimal physical activity, increased body mass index, and poorer physical QoL [38], similar to the loss of function and QoL associated with PCa.

ST in men on ADT led to reported improvements of 7 to 27% in simulated activities of daily living [62]. Others have also reported improved activities of daily living in men with PCa but have used either combined exercise programs or resistance in which only the lengthening phase of the exercise is loaded (eccentric) [63, 86]. Studies on the effects of ST on upper body function are limited in BCa patients, possibly because ST was previously contraindicated due to concerns of lymphedema. However, recent studies have specifically addressed this concern. While no data are available on physical function, adverse events and worsening of lymphedema symptoms did not occur with ST [57, 64, 94]. The fact that women with BCa can safely participate in this type of exercise without adverse consequences provides a rationale for future studies to examine the role of ST on upper body function given the connection between limited function and QoL [38].

3.9. Quality of Life. Quality of life is arguably the most egregious side effect resulting from cancer treatment and is intertwined with strength, body composition, fatigue, and physical function. The changes observed with cancer treatment to the above traits are likely to influence QoL. Thus, it is not surprising that men and women undergoing hormone therapy for PCa and BCa report reduced QoL indicators [21, 34, 36, 40, 41]. The questionnaires used to assess QoL varied between studies, although several trends appear to be evident. For example, lower QoL scores were observed for the physical function but not the mental health in both PCa and BCa patients [21, 40, 41]. Other studies that used QoL questionnaires specific to each cancer type demonstrated reduced overall scores with treatment [34, 36]. Improved QoL scores with ST are observed in some studies in PCa and BCa patient populations [41, 60, 61], though not in others [57, 63]. Moreover, Ohira et al. [41] reported that several musculoskeletal improvements with ST were correlated with higher QoL indicators.

4. Conclusions and Future Directions

Some of the effects of hormone-related treatments for persons with PCa and BCa are similar to the typical effects of normal aging but occur at an accelerated pace. These include a long list of musculoskeletal, metabolic, body composition, and functional outcomes. ST appears to have a positive influence on many, but not all of these characteristics. In particular, ST is effective in reversing the loss of strength and function and may be able to slow fat gains and bone losses common to both types of cancer treatments. Due to the widespread use of mixed training protocols, there are some side effects that are reduced from training, but the independent effects of ST cannot be distinguished from effects of other training modalities, such as aerobic exercise. With five-year survival rates for BCa and PCa approaching 100% [2], maintaining high QoL in cancer patients is of paramount importance. In this regard, ST may contribute toward achieving this goal by serving as an effective adjunct therapy and countermeasure to the adverse effects of PCa and BCa treatment.

Over the past decade, the role of exercise has expanded from a means of improving QoL in cancer patients toward addressing specific risk factors resulting from cancer treatment, as well other lifestyle choices that limit function and influence QoL. Future research should address the issue of whether ST can (1) reverse ADT-induced muscle atrophy through direct assessments of muscle area in PCa patients, (2) enhance direct measures of whole body physical function in BCa patients, (3) improve muscle power and bone mineral densities in both populations, and (4) establish a relationship between favorable functional outcomes (activities of daily living, fatigue, QoL) and specific ST-induced adaptations (strength, power, body composition). This additional information will help guide clinicians in exercise prescription designed specifically to reduce comorbidities and particular side effects to enhance QoL in men and women undergoing hormone treatment for PCa and BCa, respectively.

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Research Article

The Melanocortin 3 Receptor: A Novel Mediator of Exercise-Induced Inflammation Reduction in Postmenopausal Women?

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The purpose of this study was to determine whether resistance exercise training-induced reductions in inflammation are mediated via melanocortin 3 receptor expression in obese (BMI 32.7 ± 3.7) women (65.6 ± 2.8 yrs) randomized to either a control ($N = 11$) or resistance training group ($N = 12$). The resistance trained group performed resistance training 3 days/week for 12 weeks. Resting blood samples were collected before and after the training intervention in both resistance trained and control groups. Resistance training upregulated melanocortin 3 receptor mRNA by 16-fold ($P = .035$) and decreased monocyte count, without changing leukocyte number, body composition, or body weight. Resistance trained individuals exhibited increased sensitivity to inflammatory stimuli, whereas control individuals exhibited no change. While there was no change in whole blood tumor necrosis factor alpha mRNA between the groups, whole blood interleukin 10 mRNA was higher in the resistance trained group following the intervention period. In summary, it appears that resistance training may modulate melanocortin 3 receptor expression, providing a possible mechanism for the anti-inflammatory effects of exercise training.

1. Introduction

Postmenopausal women exhibit higher concentrations of inflammatory markers and are also at increased risk for many of the age- and inactivity-related diseases that are prevalent in our society today, including cardiovascular disease and type 2 diabetes mellitus [1]. Chronic exercise has been shown to create favorable changes in the inflammatory profile and is a viable means for preventing the onset and slowing the progression of these diseases [2]. While this reduction in inflammation has been linked to a decrease in cardiovascular disease risk [3], understanding the molecular underpinnings associated with this response may provide further support for the use of resistance exercise as an adjunct or primary treatment for postmenopausal women with inflammatory risk factors.

Acute alterations in inflammation immediately after exercise are evidenced by elevated concentrations of inflammatory cytokines, such as interleukin 6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α), and increased activity of macrophages [4–7]. In conjunction with increased macrophage activation, acute alterations in inflammation after an exercise bout cause downstream increases in circulating levels of macrophages, natural killer

cells, monocytes, lymphocytes, granulocytes, T-helper, and T-cytotoxic cells [6, 8]. Conversely, a previous work has shown that chronic, combined resistance, and aerobic exercise leads to a reduction in inflammation within 10–12 weeks [9], and a recent report suggests that resistance training alone may have a significant role in reducing inflammatory markers [10]. Specifically, consistent exercise is associated with a reduction in inflammatory cytokines and an increase in anti-inflammatory cytokines in circulation in conjunction with altered sensitivity of macrophages to inflammatory stimuli [7, 10, 11].

One area of cellular signaling that has been seemingly overlooked in the exploration of the effects of exercise on inflammation is the melanocortin system. Melanocortin receptors are well characterized G-protein-coupled transmembrane receptors (GPCRs) that act to increase cyclic adenosine monophosphate (cAMP) [12–14]. There are five known melanocortin receptor subtypes: melanocortin 1 receptor (MC1R) through melanocortin 5 receptor (MC5R). One of the most well-studied systems with respect to the MC3R is the leptin signaling pathway. Briefly, leptin is an endocrine hormone secreted in proportion to the amount of adipose tissue present. Leptin binds to leptin receptors located on pro-opiomelanocortin (POMC) neurons within the hypothalamus, specifically the arcuate nucleus and paraventricular nucleus [14, 15]. POMC is upregulated in response to leptin binding and is proteolitically cleaved into several active peptides, including alpha melanocyte stimulating hormone (α-MSH) and adrenocorticotrophic hormone (ACTH) [12, 14]. These peptides act as agonists within the CNS for MC3Rs. Activation of CNS MC3Rs leads to increases in lipolysis and energy expenditure [14, 16]. MCRs are also expressed in the periphery where they may play a role in immunomodulation. The melanocortin receptor subtypes, MC1R, MC3R, and MC5R are found on the plasma membranes of monocytes, macrophages, CD4+ T helper cells, granulocytes, and natural killer cells, where, separately, they are activated in response to stress [12, 17–19]. We hypothesize that a redundant signaling mechanism involving POMC and its peptide variants may activate and modulate expression of MCR on systemic monocytes. Interestingly, activation of the MC3R by α-MSH and ACTH in the periphery causes secretion of an anti-inflammatory cytokine, interleukin 10 (IL-10) [15, 20, 21]. The MC3R-induced secretion of IL-10 underscores the potential importance of MC3R as an anti-inflammatory modulator due to the ability of IL-10 to inhibit inflammatory cytokines, including IL-6, TNF-α, and IL-1β secretion from leukocytes [22]. Because of its anti-inflammatory properties as well as its role in energy metabolism, the melanocortin system has become an area of robust research as a potential therapeutic target to pharmacologically treat inflammatory-related conditions [12].

It is possible that MC3R may play a novel role in exercise-mediated changes in inflammation. Using chronic resistance training in overweight, postmenopausal women, we hypothesized that RT may increase MC3R expression, reduce inflammation, and change the sensitivity of leukocytes to inflammatory stimuli.

2. Materials and Methods

2.1. Subjects. Obese (BMI 32.7 ± 3.7) women aged 65.6 ± 2.8 years, not having participated in consistent exercise for the previous 6 months, signed an informed consent, completed a medical history form, and obtained written approval from their personal physician. Potential subjects underwent a medical screening (physical exam and dementia screening) by our study physician and completed a submaximal treadmill test while blood pressure and ECG were monitored. Any subject meeting the exclusion criteria of the American College of Sports Medicine for exercise testing was excluded. NSAID users were asked to refrain from taking their medication until after the experimental trials on test days. Other exclusion criteria were severe arthritis, central or peripheral nervous system disorders, previous stroke, acute or chronic infection, major affective disorder, HIV infection or autoimmune disorders, metabolic disorders (type 1 or type 2 diabetes mellitus), smokers or smokeless tobacco users, regular aerobic or resistive exercise within the previous six months, oral steroid use, and alcohol intake greater than "moderate" (1 drink/day). Subjects were asked to maintain their "normal" diet regimen throughout the intervention period and to consume no alcohol the days prior to any blood sampling. Subjects recorded all food consumed during the 24 hours prior to the pretraining blood sample which was to represent a "normal" day's diet. After the 12-week intervention, they were given a copy of that food log and asked to record and consume the same meals during the 24 hours prior to the posttraining blood sample. Several subjects were taking general multivitamins, but no one was taking supplemental fish oil or omega-3. Subjects were randomized to either a control (CON: $N = 11$) or exercise group (EX: $N = 12$). This project was approved by Institutional Review Boards at Texas Christian University and John Peter Smith Hospital.

2.2. Anthropometrics. To assess the effects of resistance training (RT) on body mass and composition, body mass and percent fat were measured in all participants prior to the first and following the last exercise or control session. Body mass was measured to the nearest 0.1 kg with a calibrated digital scale, and height was measured to the nearest 1 mm with a stadiometer. Body mass index (BMI) was then calculated by dividing body weight (kg) by height squared (m^2). In addition, body composition was estimated using a seven-site skinfold procedure [23, 24] by a trained technician. Body composition was obtained in the morning after an overnight fast. Percent body fat was estimated from body density using the Siri equation [25].

2.3. Intervention Protocol. EX underwent progressive RT 3 days per week on nonconsecutive days for 12 weeks while CON attended health education and craft classes twice per week to control for social interaction. All exercise sessions were directly supervised by trained technicians. EX performed 3 sets of the following exercises at their 8-repetition maximum (8RM): chest press, "lat" pull-down,

shoulder press, seated row, leg abduction, leg adduction, leg extension, leg flexion, chest flys, and leg press. Subjects performed 8 repetitions in the first two sets and exercised to exhaustion/failure in the third set. When the subject was able to complete 12 repetitions in one set, a technician increased the resistance for the exercise to match her new 8RM on the following training day.

2.4. Blood Collection/Analyses. Resting blood samples were collected from CON and EX groups before (PRE) and after (PO) the intervention period. Subjects reported to the exercise physiology lab at Texas Christian University after an overnight fast (10 hr) and assumed a supine position for 20 minutes prior to blood collection. Blood samples were collected into Na+ heparin and K+ EDTA tubes. Whole blood from heparinized tubes was diluted 1 : 10 into culture medium (RPMI cell culture medium (100 mL; Sigma Diagnostics, St. Louis, MO) supplemented with 2 ml penicillin ($100\,\mathrm{U}\cdot\mathrm{ml}^{-1}$), 2 ml streptomycin ($100\,\mu\mathrm{g}\cdot\mathrm{ml}^{-1}$), and 1 ml glutamine (2 mM)). Cultured cells were stimulated with lipopolysaccharide (LPS from *s. enteriditis*, final concentration $25\,\mu\mathrm{g}\cdot\mathrm{mL}^{-1}$, Sigma Diagnostics, St. Louis). After 24 h incubation (37°C, 5%CO_2), culture supernatants were harvested and analyzed by ELISA for TNF-α production, following the manufacturer's protocol (Invitrogen, Carlsbad, CA). Total leukocyte number and 5-part differentials were assessed using the AcTDiff 5 hematology analyzer (Beckman-Coulter, Brea, CA) using K+ EDTA-treated blood. LPS-stimulated cytokine production was expressed as per monocyte ($\mathrm{fg}\cdot\mathrm{monocyte}^{-1}$).

2.5. Real-Time PCR. Total RNA was isolated from whole blood samples using Trizol LS per the manufacturer's protocol followed by column purification (RNeasy mini kit, Qiagen). cDNA was synthesized using M-MLV reverse transcriptase (Promega). Real-time PCR was completed on each sample in duplicate using commercially available MC3R and cyclophilin B primers and probes (Applied Biosystems) and IL-10, TNF-α, and cyclophilin B primers designed to span exon-exon boundaries (IDT) with Taqman or SyBR Green based detection (Applied Biosystems) on the ABI 7900 HT platform. IL-10, TNF-α, and MC3R Ct values were normalized to cyclophilin Ct values, and mRNA differences were determined using the delta-delta Ct method.

2.6. Statistical Analysis. Mean and standard deviations were calculated for descriptive data, including age, height, body weight, body fat percentage, and estimated BMI. Dependent variables are expressed as mean ± standard error. Age, height, BMI, body composition, LPS-stimulated production of TNF-α, whole blood monocyte and leukocyte number, and IL-10, TNF-α, and MC3R mRNA were analyzed using a 2×2 ANOVA with a Tukey post hoc. Pearson stepwise correlation analysis was used to determine relationships between all measurements. Significance was set at $P < .05$.

Table 1: Descriptive data for the subjects before (PRE) and after (PO) the 12-week resistance training or educational period (values are means ± SD). (CON: educational control group; EX: resistance training group). There were no significant differences between the groups.

Variable	Time	CON ($n = 11$)	EX ($n = 12$)
Age		66.1 ± 3.0	65.2 ± 2.6
Height (cm)		159.5 ± 8.2	161.6 ± 5.3
Body weight (kg)	PRE	83.9 ± 13.1	84.8 ± 9.1
	PO	84.4 ± 13.5	84.2 ± 8.8
BMI (kg/m^2)	PRE	32.9 ± 4.3	32.5 ± 3.3
	PO	33.1± 3.9	32.2 ± 3.4
% Body fat	PRE	35.7 ± 3.1	35.5 ± 3.1
	PO	35.2 ± 2.8	35.3 ± 2.8

3. Results

This was a supervised exercise intervention, and data presented here represent a subset of subjects from a larger study. Adherence to the exercise protocol was excellent as all EX subjects completed the prescribed 36 resistance exercise sessions. CON participants attended an average of 91% (22 of 24) of their control sessions. There was no difference in body weight, BMI, or percent body fat between groups prior to the intervention period. No differences were observed after the intervention period for the descriptive variables above in resistance trained or untrained control postmenopausal women. (Table 1). Percent change in strength for each exercise was significantly greater for EX compared to CON ($P < .01$). Strength improvements ranged from 21 to 69% for the various exercises in EX with no significant changes in CON.

At baseline, there were no differences between CON and EX with respect to MC3R, TNF-α, or IL-10 mRNA. MC3R mRNA from whole blood samples was significantly upregulated (16 fold increase; $P = .035$) in response to RT. In comparison, control individuals showed no change in MC3R mRNA expression following the intervention period. (Figure 1). Additionally, when the EX group was stratified into groups of low responders (LR: fold change < 2; $n = 4$) versus high responders (HR: fold change ≥ 2; $n = 5$), HR EX showed a 34.9-fold increase ($P = .002$) in MC3R mRNA in response to RT, whereas LR EX showed no change in MC3R mRNA in response to RT when compared to CON ($P > .05$) (Figure 2). We observed a twofold increase in whole blood IL-10 gene expression in the EX group, although this change was not statistically significant ($P = .249$, Figure 3). IL-10 mRNA expression did not change in CON, and there was no change in whole blood TNF-α gene expression in either CON or EX groups.

TNF-α concentrations from LPS-stimulated whole blood cultures increased after training (Figure 4) in EX individuals. There was no significant difference in LPS-stimulated TNF-α production in control individuals after the intervention period (Figure 4). There were no significant differences between HR and LR EX MC3R groups with respect to TNF-α or IL-10 mRNA or LPS-stimulated TNF-α production. There

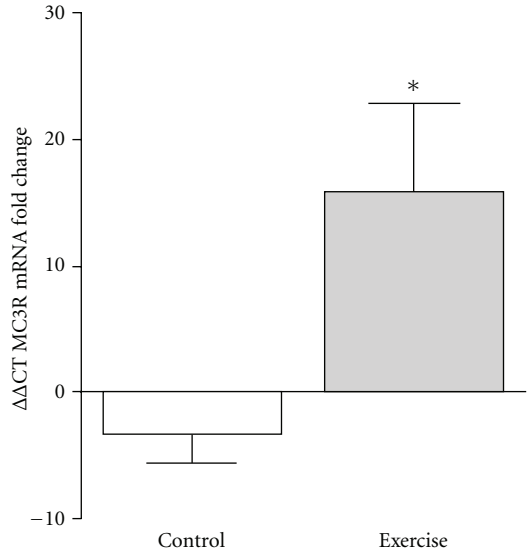

Figure 1: MC3R gene expression as assessed by real-time PCR in whole blood samples in CON ($N = 10$) and EX ($N = 9$). Values are expressed using the delta-delta Ct method to derive relative fold change. *MC3R mRNA was significantly upregulated 15.9-fold in the EX in comparison to CON ($P = .035$).

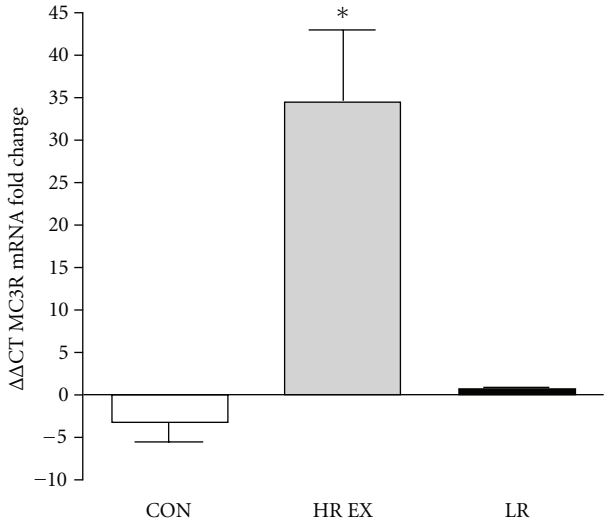

Figure 2: MC3R gene expression stratified into high responders (HR EX: fold change ≥ 2) and low responders (LR EX: fold change < 2) as assessed by real-time PCR in whole blood samples in CON ($N = 10$) and HR EX ($N = 4$) and LR EX ($N = 5$). Values are expressed using the delta-delta Ct method to derive relative fold change. *HR EX was significantly upregulated 34.9-fold in comparison to CON ($P = .002$).

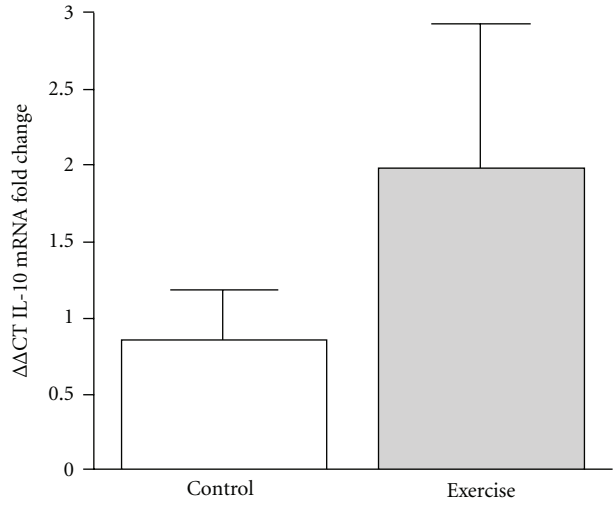

Figure 3: IL-10 mRNA fold change, expressed as fold change using the delta-delta Ct method in CON ($N = 9$) and EX ($N = 8$) groups. There were no significant differences between the groups.

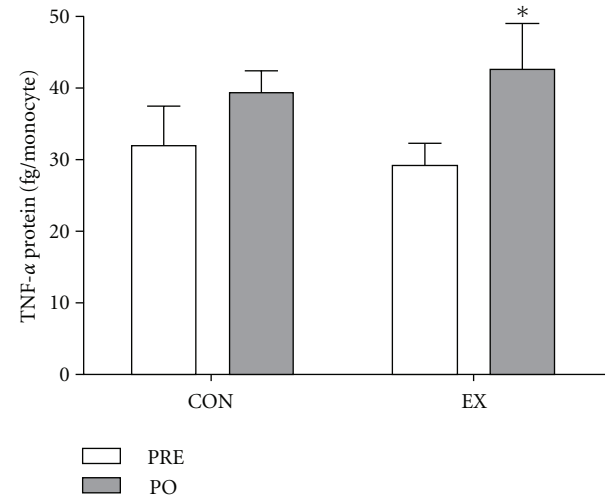

Figure 4: LPS-stimulated TNF-α expressed in fg/monocyte for control (CON: $N = 6$) and resistance trained (EX: $N = 8$), before (PRE) and after (PO) the intervention period. *denotes significance ($P < .05$).

was no significant change in leukocyte number from PRE to PO training in either group EX PRE 6.3 ± 0.410^3/ul, EX PO 5.9 ±1.810^3/ul, CON PRE 6.2 ± 0.410^3/ul, CON PO 6.1 ± 0.4 10^3/ul; ($P > .05$); however, significant training-induced differences in whole blood monocyte number were observed. Specifically, RT decreased monocyte number, but there was no difference in monocyte number in the CON group after the intervention period (Figure 5). There were no significant correlations between MC3R mRNA and IL-10 or TNF-α mRNA, LPS-stimulated TNF-α production, or monocyte number.

4. Discussion

Traditionally, exercise has been used to help prevent or slow the progression of several inflammatory diseases including type 2 diabetes and coronary heart disease [26]. More recently, RT has been found to positively alter inflammatory profiles [9, 10, 27]. Here, we show evidence that MC3R may play a novel role in explaining these improvements. Specifically, our results are the first to suggest that chronic

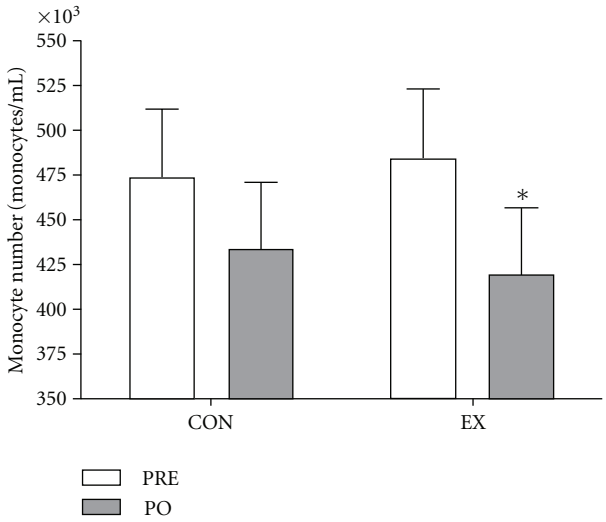

Figure 5: Whole blood monocyte number before (PRE) and after (PO) the intervention in CON ($N = 6$) and EX ($N = 8$) participants. *denotes significance ($P < .05$).

resistance training may be involved in increasing MC3R gene expression in human whole blood. These results are provocative given that there was a slight increase in IL-10 mRNA coupled with a significant increase in MC3R gene expression without a concomitant change in leukocyte number and a reduction in monocyte number. Given the lack of change in leukocyte counts and the reduction in monocyte number that has been shown in other studies [28], these findings point to changes in gene expression and cell function that are not merely reflective of changes in cell population number.

Previous data have suggested that other cell populations or tissues may be involved in controlling inflammation [29, 30]. Adiposity is directly related to inflammatory status, where inflammation is an indication of dysfunction in cellular metabolism and increased adiposity [31]. For example, MC3R KO mice exhibit increased adiposity and nutrient partitioning in addition to impaired immune function, evidenced by decreased macrophage infiltration and decreased monocyte chemoattractant protein 1 (MCP-1) and chemokine of differentiation 68 (CD68) mRNA expression into adipose tissue in comparison to wild-type mice [16, 32]. Conversely, Trevaskis et al. have shown an increase in macrophage infiltration and increases in and CD68 and MCP-1 mRNA expression within the adipose tissue in MC3R KO mice compared to control [33]. Comparisons of the two studies are difficult to make, as the mice in the study by Ellacott et al. were weaned directly onto 40% HF diet for 4 weeks and sacrificed thereafter, whereas the mice in the study by Trevaskis et al. were weaned onto a standard 10% chow diet then switched to an HF 60% diet at 12 to 14 weeks of age until 24 to 26 weeks of age at which time they were sacrificed [32, 33]. Differences in outcome variables may be due to the age of the mice as well as the fat content of the diet, with a dose response occurring due to each. Further support for an anti-inflammatory role of the MC3R occurs in models of vascular inflammation [34] and arthritis [35]. Within the mesenteric artery, it has been shown that stimulation of MC3R by αMSH decreases cell adhesion, emigration, and cytokine expression in response to ischemia and reperfusion injury of the vasculature [34]. Agonist stimulation of MC3R also decreases arthritis incidence and severity, evidenced by decreased nuclear factor kappa B (NFκB) DNA-binding activity in response to receptor activator of NF-kappaB ligand (RANKL) stimulation and decreased chemokine (C-C motif) ligand 2 (CCL2) expression. Additionally, MC3R expression is crucial in mediating the anti-inflammatory effects induced by vascular tissue injury, as MC3R KO mice exhibit increased cell emigration and adhesion and increased monocyte chemotactic protein-1(MCP-1) and keratinocyte-derived chemokine mRNA expression in response to mesenteric artery tissue injury [34]. MC3R KO mice also express increased IL-1β, IL-6, chemokine receptors, and chemokine ligands within isolated osteoclasts from arthritic joints, indicating increased inflammation in response to inflammatory stress, further supporting a role of MC3R in mediating the inflammatory response [35]. While it is well established that adiposity and MC3R expression play a significant role in inflammation [36], it is possible to achieve alterations in inflammation without changes in body composition. For example, exercise training studies have shown that inflammation can be altered, even with short intervention periods without a change in body composition [9, 37]. Thus, it is important to note that while the EX subjects in the current study tended to experience an increase in IL-10 mRNA expression and had increased expression of the MC3R, they did not experience significant alterations in body weight or composition. RT causes changes in gene expression independent of changes in adiposity and despite decreases in monocyte number.

The results presented here provide a glimpse into how circulating cell function may be altered with exercise. Specifically, maximal capacity to produce inflammatory cytokines, as evidenced by the LPS-stimulated TNF-a production, was increased in EX compared to CON groups. These data differ from a previous work which has shown a decrease in LPS-stimulated TNF-α after exercise training in postmenopausal women [28, 37]. It is possible that alterations in MC3R expression lead to sensitization of circulating immune cells to inflammatory stimuli. Thus, future studies that involve stimulating whole blood cultures with agonists and antagonists to MC3R and measuring inflammatory markers may provide more information on the activity of these receptors in response to RT. Exercise-induced changes in MC3R may be mediated by ACTH and αMSH [19, 38]. It is known that an increase of ACTH is observed during an acute bout of exercise [39]. Possible mechanisms responsible for these increases in ACTH may be related to the induction of IL-6 or IL-1β observed acutely after exercise [4, 6, 40]. Postexercise increases in IL-6 may be due to changes in macrophages/monocytes or myocyte IL-6 production, whereas IL-1β secretion is more tightly linked to leukocytes [5, 6]. These cytokines may be associated with increased exercise-induced concentrations of ACTH and our observed monocyte/macrophage (whole blood)

sensitization and MC3R upregulation. It is also possible that sensitization of the MC3R and expression, indirectly regulated by proinflammatory cytokine production acutely during and following an exercise bout, may be linked to the reductions in circulating inflammatory markers observed in other exercise studies [2].

There were several limitations in this study. This was an exploratory investigation designed to examine the relationship between exercise and inflammation, but it was not specifically focused on the melanocortin receptor. As a result, we acknowledge that our subject pool was somewhat small. Regardless of sample size, however, we observed a statistically significant upregulation (16-fold) of the MC3R in our participants with a statistical power of 0.5811 with the current number of subjects. Yet, when we divided our EX group into LR and HR, we observed a significant upregulation (34.9 fold) of MC3R with a statistical power of 0.902. A larger study will be necessary to explore the reasons for the variation (HR versus LR) in response to the RT program. Furthermore, although MC3R is expressed in a number of immune cell populations, its actions have been most explored in the monocyte population because they are some of the most responsive and largest producers of inflammation in the body [41]. Thus, measuring exercise-induced changes in MC3R cell-surface expression in specific immune cell populations, including monocytes, may be an important direction for future work. Finally, stimulation assays in untrained and trained individuals with known agonists and antagonists to MC3R will help further understand the role of exercise in modulating the sensitivity of this receptor.

In summary, it appears that 12 weeks of moderate-intense resistance training led to a 16-fold upregulation of MC3R gene expression in whole blood from obese postmenopausal women. We are the first to examine the influence of exercise on aspects of the melanocortin system in humans. These findings may help to explain previously observed reductions in inflammation consequent to consistent exercise training.

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Research Article

Effects of Tai Chi Training on Antioxidant Capacity in Pre- and Postmenopausal Women

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The risk of oxidative stress-related metabolic diseases increases with menopause and physical inactivity. We hypothesized that an 8-week Tai Chi (TC) training program (2 sessions in class; 2 sessions at home; 1-1:15/session) would improve antioxidant capacity and reduce cardiovascular risks in both pre- ($n = 8$) and postmenopausal ($n = 7$) sedentary women. Selected measures of physical fitness and blood parameters were analyzed before and after the program. Besides the well-known effects of TC on balance, flexibility, and maximum leg extensor strength, TC (1) increased erythrocyte glutathione peroxidase activity—an aerobic training-responsive antioxidant enzyme—and plasma total antioxidant status and (2) decreased plasma total homocysteine, a cardiovascular risk marker. In addition to being a low-velocity, low-impact, and relatively safe, TC is a suitable physical activity design for pre- and postmenopausal women to increase antioxidant defenses. Investigating breathing effects during TC movements would be an interesting area for further research in diseases prevention.

1. Introduction

The risk of oxidative stress-related metabolic diseases increases with menopause and physical inactivity [1, 2]. The decline in exercise capability with aging contributes to physiological limitations, such as declines in muscle strength, flexibility, balance, and cardiovascular function [3]. Regular strength training can counteract, at least partly, this aging effect, improving functional ability and reducing the risk of fall [4]. However, it has little effect on cardiovascular risk [5] and antioxidant defense markers, which are elicited mostly by metabolic changes, induced by aerobic physical activity [6, 7]. Some clinical markers, such as oxidative stress markers, are associated with lung capacity that is inversely related to the increasing risk of metabolic diseases during menopause [8]. With aging exercise tasks are performed at a higher percentage of maximal aerobic capacity ($\dot{V}O_{2\,max}$), shifting substrate use from lipid-derived energy to carbohydrate. During menopause, the decreasing levels of estrogens reinforce the deterioration of both lipid metabolism and antioxidant status that is observed when the level of physical activity is chronically low [9, 10]. Although physical activity has many benefits on health, some exercises are not suitable and not recommended for older women. The combination of inappropriate training loads (high intensity, high impact, low recovery time, etc.) and aging can lead to a failure of endogenous antioxidants to adapt to acute or chronic oxidative stress exposure [11, 12].

Interestingly, Tai Chi, an ancient Chinese mind-body exercise, is a martial art form combining breathing with rotational and multisegmental postures that flow smoothly from one side to the other side, through slow and gentle movements [13]. It is a weight-bearing exercise that strengthens muscle and which corresponds to an aerobic exercise of moderate intensity [14]. Tai Chi training has been shown to increase muscular strength, functional mobility, flexibility

and balance, to improve sleep quality and duration and psychological well-being and to enhance microcirculatory function [13, 15, 16]. However, its possible effects on the adaptive antioxidant system have been largely ignored. Yogic "*pranayama*" breathing, an Indian mind-body exercise, has been shown to improve endogenous antioxidant capacity and to lower oxidative stress markers [17]. Breathing synchronization with cardiovascular rhythms may enhance cardiorespiratory performances as previously suggested [18]. Recently, we have shown in a cross-sectional study that pre- and postmenopausal women, who were regularly practicing Tai Chi, had a higher erythrocyte glutathione peroxidase (GPx) activity compared to their sedentary counterparts [19]. To confirm a potential antioxidant effect of Tai Chi training in women, we have conducted an interventional study. Eight weeks of Tai Chi training—combining classical Tai Chi postures with slow and deep breathing (6 breaths per minute)—were expected to induce not only functional, but also antioxidant effects. It was hypothesized that menopausal women would benefit from these adaptations. Particularly, we hypothesized that Tai Chi training would improve antioxidant capacity and reduce plasma lipid peroxidation as well as cardiovascular risk markers concentrations in pre- and postmenopausal women.

2. Methods

2.1. Subjects and Design. Eight healthy premenopausal (pre-M; 39 ± 6 yrs old) and 7 postmenopausal (post-M; 54 ± 3 yrs old) women volunteered to participate in an 8-week Tai Chi (TC) training program (characteristics in Table 1). All participants were community-dwelling sedentary women who worked for the same organization in Bangkok. All participants completed inclusion and lifestyle questionnaires. Excluded subjects from this study were smokers, regular alcohol consumers, antioxidant supplement users, women treated with hormone replacement therapy, and women with renal, cardiovascular or hepatic disease, diabetes, asthma, or cancer. One participant did not attend the TC class regularly, and her data were excluded from statistical analysis. Given the condition of inclusion, sample sizes were smaller than expected, but groups were homogeneous according to their lifestyle. Participants were informed of the nature of the experiment before giving their formal consent. The protocol was approved by the Ethics Review Committee for Research Involving Human Subjects, Health Science Group of Faculties, Colleges and Institutes, Chulalongkorn University, Thailand (Approval no. 087/2008), constituted in accordance with the International Conference on Harmonization—Good Clinical Practice (ICH-GCP).

2.2. Experimental Design. The 8-week TC training protocol consisted of two training sessions per week with 75 min per session. In addition, all participants were given a video CD demonstrating Tai Chi postures and were asked to practice twice a week at home, with 60 min per session. Eligible participants were required to attend classes for at least 80% of the training program.

The class protocol included 5 min of check-in, 10 min of warm-up exercise (stretching), and 60 min of Tai Chi (comprising 45 min of 18-posture Tai Chi and 15 min of Tai Chi Fan style). Classical Tai Chi postures are characterized by slow rotational movements performed in semisquat postures with varying degrees of arm movement. Not only lower-body balance by leg and knee extension, but also upper-body flexibility by arm contractions, was exercised. The TC training program was a modified 18-movement Yang style with three versions. Each motion was performed slowly coupling breathing to music, and usually took 1–1.5 min per motion or 18–25 min per completed set. The TC practitioners imitated the movements of the experienced TC instructor at the same speed. The major requirement of this modified 18-posture was that the TC practitioners had to concentrate and carefully control the slow and deep breathing with a frequency of 6 breaths per minute (or 10 seconds per breath). To ensure the breathing rhythm and control the time course, the movements were performed to traditional Chinese music that has sound signals for inhalation. Five to ten movements were taught each week, so a complete 18-postured set was practiced for 2 weeks, and three versions of the 18-postured set were completed in 6 weeks. After performing conventional TC in each session, all participants were also taught TC fan style, which combined TC training and a fan dance with traditional Chinese music. During the class, the instructor monitored and corrected the posture of each subject. To ensure that the participants were practicing at home, participants had to complete a training log in which they had to report details about their home practice.

Anthropometric data, dietary intakes, blood draws, physical activity, and selected measures of physical fitness blood were assessed at the beginning and after 8 weeks of TC training. All participants were asked to maintain their usual dietary behavior and activity habits.

2.3. Anthropometric Data. Body weight was measured with a calibrated electrical balance (Tanita, Inner Scan BC533 model, Japan). Resting blood pressure and pulse were measured with a portable blood pressure monitor (Omron Hypertension HEM 780, Japan). The percentage of body fat was assessed using the standard Lange skinfold method (3 positions: triceps, suprailiac and thigh). Skinfolds readings were taken from triceps, suprailiac and thigh sites for each subject. A Lange skinfold caliper was used throughout and a single well-trained technician made all readings. Lange skinfolds were measured three times and the average of the three was recorded. Percentages of body fat were calculated by Jackson's formula [20].

2.4. Diet and Activity Records

2.4.1. Dietary Intakes. Before each venipuncture, each subject completed, at home, a 4-day food diary (including a weekend day). A standardized information session was organised to give each subject instructions on how to record their daily food intake and activities. Food quantities were

Table 1: Characteristics of pre- and post-menopausal women before and after the Tai Chi training period.

	Pre-M women		Post-M women	
	Pre-training	Post-training	Pre-training	Post-training
Age (yrs)	39 ± 6	39 ± 6	54 ± 3#	54 ± 3#
Height (cm)	160 ± 4	160 ± 4	155 ± 5	155 ± 5
Body weight (kg)	56 ± 10	56 ± 10	63 ± 9	62 ± 9
BMI ($kg \cdot m^{-2}$)	21.9 ± 4.0	21.9 ± 4	26.2 ± 3.2#	25.8 ± 3.0#
Body fat (%)	31.2 ± 6.4	30.2 ± 6.5*	38.2 ± 4.2	33.8 ± 5.1*
SBP (mmHg)	113 ± 13	114 ± 15	142 ± 18#	136 ± 22#
DBP (mmHg)	72 ± 9	79 ± 18	92 ± 14	79 ± 9
Resting HR ($beats \cdot min^{-1}$)	84 ± 17	88 ± 15	78 ± 10	78 ± 13
Balance (sec)	19.3 ± 2.1	15.6 ± 1.3*	22.2 ± 1.8#	17.9 ± 2.5*#
Flexibility (cm)	10.4 ± 6.0	12.6 ± 5.4*	8.4 ± 4.8	11.4 ± 5.3*
1-RM load leg curl (kg)	27.9 ± 3.9	32.9 ± 3.9	26.4 ± 4.8	31.4 ± 4.8
1-RM load leg extension (kg)	42.9 ± 4.9	48.6 ± 8.0*	45.0 ± 5.8	52.1 ± 7.0*
1-RM load biceps curl (kg)	7.1 ± 3.7	9.3 ± 4.5	5.7 ± 4.0	7.1 ± 3.4
1-RM load biceps extension (kg)	12.9 ± 0.9	13.6 ± 1.3	12.1 ± 2.2	13.6 ± 2.0
$VO_{2\,max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	25.9 ± 3.4	25.7 ± 4.4	22.1 ± 2.2#	21.1 ± 2.3#

Values are expressed as mean ± standard deviation; *$P < .005$: different from Pre-training in Pre-M and Post-M; #$P < .005$: different from Pre-M in Pre-training and Post-training; Pre-M: premenopausal women group; Post-M: postmenopausal women group; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate.

estimated using standard measures for a cup, tablespoon, and teaspoon (validated by the Institute of Nutrition, Mahidol University) and specifying the number of units/code corresponding to the size of the food portion by comparison with photos from an adapted portion book. Nutrient intakes were calculated using INMUCAL nutrient software, version 2007, which uses the Thai dietary database of the Institute of Nutrition, Mahidol University, and the Nutrition Division, Department of Health, Ministry of Public Health of Thailand (version 2003).

2.4.2. Physical Activity Record. In parallel to dietary records, subjects completed a 4-day activity records diary. The 4-day physical activities diary was divided according to categories of physical activity [21] ((1) sleep position; (2) sitting position activities; (3) standing position including small movements; (4) walking, gardening, etc.; (5) Tai Chi training). The compendium of physical activities [22] was used to estimate the energy cost of physical activity expressed as metabolic equivalents (METs). The appropriate MET values, based on the subject's report of the type and intensity of activity, were assigned. Daily energy expenditure (EE) was calculated by multiplying the amount of time spent in each activity and the corresponding MET, using a computer program specifically designed for this task. Activities not found in the database were carefully evaluated to determine the best-suited corresponding activity. MET values for TC training was set at 3 MET as previously measured by Chao et al. [23] and confirmed [24].

2.5. Physical Fitness Assessments. For all subjects and conditions, on the morning, a balance test was performed first and a muscle strength test second. In the afternoon, a maximal aerobic capacity test ($\dot{V}O_{2\,max}$) was performed. The next day, on the morning, subjects came back in the lab to perform a flexibility test. Except for $\dot{V}O_{2\,max}$ determination, tests were done in triplicate (every 30 minutes) and began with a warm up of 3–5 minutes. The best score was recorded.

2.5.1. Balance Test. Balance was tested by a timed up and go test. The participant sat on a chair and waited for the start signal. At the signal, the participant had to rapidly stand up, to walk quickly across two cones on the way, and to return to a seated position in the same chair. When the participant came back to the starting point, the total time was recorded. The participant was instructed to perform the test as quickly as possible [25].

2.5.2. Flexibility Test. Flexibility was measured with the sit and reach test [26]. Subjects sat on the floor with legs extended, reached forward with their hands, one placed on top of the other, and held the terminal position for at least 2 seconds. The score is recorded to the nearest centimeter as the distance reached by the hand.

2.5.3. Muscle Strength Tests. Muscle strength was measured by dynamic testing [27] on standard weight machines (Marathon, Thailand). The one-repetition maximum (1-RM) strength was evaluated in four different exercises: the biceps curl, triceps extension, leg extension (quadriceps), and leg curl (hamstring).

2.5.4. Maximal Aerobic Capacity. Subjects performed a continuous incremental walking (3 min up to $8\,km \cdot h^{-1}$) and running test ($1\,km \cdot h^{-1}$ increment every 2 min to exhaustion) on a motorized treadmill (h/p/cosmos mercury, Germany)

with a 1% slope. Ventilation and gas exchanges were measured using a breath-by-breath gas analysis system (Cortex Metamax 3B, Germany). Heart rate was recorded using a telemetric system (Polar Electro S810, Finland). The $\dot{V}O_{2\,peak}$ was determined from the observation of at least two of the following criteria: $\dot{V}O_2$ was increased less than $2\,mL\cdot min^{-1}\cdot kg^{-1}$ after 2 minutes, HR exceeded its age-predicted maximum, and the respiratory exchange ratio (RER) exceeded 1.15.

2.6. Blood Samples and Assays. Blood samples were collected from a forearm vein in K_3EDTA tubes (3 mL) and Li heparin tubes (6 mL) (Vacuette, Greiner Bio-One, Germany) between 7.00 and 9.30 AM after an overnight fast. Heparinized plasma was removed by centrifugation at $3000 \times g$ at 4°C for 15 min within an hour after blood collection for total antioxidant status, lipid peroxidation, and total homocysteine concentration (tHcy) analyses. Heparinized whole blood (0.05 mL) was diluted with 1 mL of diluting agent for glutathione peroxidase (GPx) (Randox laboratories, UK) and kept at −80°C until GPx analysis. The packed red blood cells (RBCs) were washed three times with two volumes of isotonic saline solution at pH 7.0. The washed RBCs were hemolyzed by suspension in double distilled water, centrifuged at $3000 \times g$ at 4°C for 15 min, and then kept at −80°C for erythrocyte GPx and superoxide dismutase (SOD) activity analysis. Each assay of antioxidant was performed on the same day to eliminate variation in assay conditions. The samples were stored in Eppendorf tubes at −80°C and thawed only once before analysis to eliminate a freeze-thaw effect. All assays for each marker were performed with the same conditions (same set of reagent kit, same control, same automate) on the same day, to avoid interassay variations. The automate system was set to randomly repeat the control during the batch to avoid run-to-run variations. The within-run coefficient of variation was less than 2.5% for the biochemical markers measured.

2.7. Biological Assays. Total antioxidant status (TAS) concentration was measured by the radical cation decolorization assay [28] using spectrophotometer (Shidmadzu UV-1601, Japan) at 734 nm. Lipid peroxidation (TBARS) was assayed by measuring the formation of malondialdehyde [29] and measured by spectrophotometer at 530 nm (Shidmadzu UV-1601, Japan). Superoxide dismutase and GPx activities were detected by enzyme kinetic-colorimetric assay (Randox Laboratories, UK) using biochemical automatic analyzer (Vitalab Selectra XL, Flexor Company, The Netherlands). Plasma total homocysteine (tHcy) concentrations were analyzed by Fluorescence Polarization Immunoassay using the AxSYM automatic system (Abbott Laboratories, USA).

2.8. Statistical Analysis. Comparisons between groups (pre- and post-M) and between pre- and post-TC training intervention and investigations of the interaction effect between the TC training intervention and the menopausal status were made by a one-way analysis of variance (ANOVA) with repeated measures. When appropriate, the protected Fisher's Least Significant Difference (LSD) test was performed. When parameters did not follow a normal distribution, we treated them as nonparametric variables using Mann & Whitney or Wilcoxon signed ranks tests. Statistical analyses were made using SPSS (version 15) software. Significance was established at $P < .05$. Values are reported as mean ± standard deviation (SD).

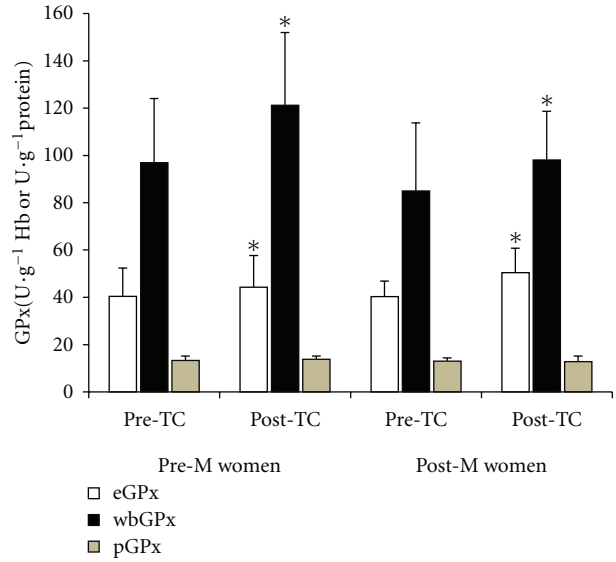

FIGURE 1: Effect of Tai Chi training on erythrocyte (eGPx, unit·g^{-1}Hb), whole blood (wbGPx, unit·g^{-1}Hb), and plasma (pGPx, unit·g^{-1}total protein) glutathione peroxidase activities in pre-menopausal (Pre-M) and post-menopausal menopausal (Post-M) women. *$P < .001$, different from Pre-training.

3. Results

3.1. Baseline Differences between Pre- and Post-M Women. At baseline, post-M women had significantly lower balance and $\dot{V}O_{2\,max}$ compared with pre-M women (Table 1). No difference was found between pre-M and post-M women regarding other selected physical fitness parameters (Table 1). Post-M women had significantly higher systolic blood pressure (Table 1). Daily energy expenditure and daily energy intake were not significantly different in pre-M compared to post-M women (Table 2). Post-M women had lower animal-derived proteins intake compared to pre-M women but the daily intake of macronutrients and of selected micronutrients was not significantly different between groups (Table 2). LDL cholesterol tended to be higher ($P = .08$) in post-M women compared to pre-M women. No difference between groups was shown in antioxidant status and in other selected biochemical parameters (Table 3, Figure 1).

3.2. Tai Chi Training Effect. Compared to pretraining data, balance, flexibility, and leg extension strength, were significantly improved in both pre-M and post-M women after the TC training protocol (Table 1). No significant change was observed on systolic and diastolic blood pressure,

Table 2: Daily energy expenditure and daily nutrient intake of pre- and post-menopausal women before and after the Tai Chi training period.

	Pre-training		Post-training	
	Pre M	Post M	Pre M	Post M
EE ($kCal \cdot d^{-1}$)	1770 ± 206	1821 ± 185	1868 ± 285*	2024 ± 318*
EI ($kCal \cdot d^{-1}$)	1579 ± 364	1311 ± 260	1576 ± 566	1617 ± 140
Carbohydrate ($g \cdot d^{-1}$)	216 ± 38	190 ± 36	208 ± 101	209 ± 26
% EI	55.3 ± 5.4	57.9 ± 4.8	51.5 ± 7.2*	51.6 ± 5.2*
Fat ($g \cdot d^{-1}$)	50 ± 19	40 ± 11	55 ± 19*	58 ± 10*
% EI	27.5 ± 4.5	27.1 ± 4.0	31.6 ± 6.2*	32.3 ± 4.1*
Protein ($g \cdot d^{-1} \cdot kg^{-1}$)	1.246 ± 0.318	0.826 ± 0.400	1.141 ± 0.216	1.068 ± 0.205
% EI	17.1 ± 2.0	15.0 ± 3.3	16.9 ± 3.6	16.0 ± 1.6
Animal protein ($g \cdot d^{-1} \cdot kg^{-1}$)	0.690 ± 0.172	0.405 ± 0.288#	0.597 ± 0.152	0.562 ± 0.156#
Vegetal protein ($g \cdot d^{-1} \cdot kg^{-1}$)	0.322 ± 0.137	0.282 ± 0.195	0.310 ± 0.138	0.306 ± 0.129
β-Carotene ($\mu g \cdot d^{-1}$)	1150 ± 834	867 ± 765	803 ± 572	887 ± 585
Vitamin C ($mg \cdot d^{-1}$)	175 ± 156	107 ± 81	96 ± 155	145 ± 199
Vitamin E ($mg \cdot d^{-1}$)	6.91 ± 11.80	9.00 ± 15.93	10.06 ± 13.91	6.58 ± 11.87

Pre M: pre-menopausal women group; Post M: post-menopausal women group; EE: energy expenditure; EI: energy intake. Values are expressed as mean ± standard deviation; *$P < .05$, different from pre-training; #$P < .05$, different from Pre M.

Table 3: Hematological and biochemical parameters of pre- and post-menopausal women before and after the Tai Chi training period.

	Pre-M women		Post-M women	
	Pre-training	Post-training	Pre-training	Post-training
Hemoglobin ($g \cdot dL^{-1}$)	13.06 ± 0.94	13.00 ± 0.86	13.76 ± 0.56	13.31 ± 0.63
Hematocrit (g%)	39.0 ± 3.1	38.4 ± 2.7	40.9 ± 1.9	40.1 ± 2.3
Leukocytes ($\times 10^9\ L^{-1}$)	5.93 ± 1.34	5.90 ± 1.13	5.93 ± 1.06	5.27 ± 1.07
Platelets ($\times 10^9\ L^{-1}$)	290 ± 110	295 ± 125	254 ± 42	227 ± 46
Uric acid ($mg \cdot dL^{-1}$)	3.19 ± 0.59	3.24 ± 0.66	4.09 ± 1.41	4.44 ± 1.27
Triglycerides ($mg \cdot dL^{-1}$)	57 ± 18	65 ± 33	99 ± 50	88 ± 29
Total cholesterol ($mg \cdot dL^{-1}$)	212 ± 32	203 ± 30	226 ± 24	217 ± 33
HDL cholesterol ($mg \cdot dL^{-1}$)	71 ± 34	72 ± 35	54 ± 6	56 ± 7
LDL cholesterol ($mg \cdot dL^{-1}$)	129 ± 19	118 ± 19*	152 ± 25	143 ± 33*
TAS ($mmol \cdot L^{-1}TE$)	1.513 ± 0.133	1.697 ± 0.122**	1.573 ± 0.087	1.662 ± 0.097**
TBARS (μM)	2.44 ± 2.07	3.46 ± 4.27	2.12 ± 1.21	2.38 ± 2.29
eSOD ($unit \cdot g^{-1}Hb$)	1370 ± 286	1275 ± 107	1270 ± 174	1371 ± 96
tHcy ($\mu\ mol \cdot L^{-1}$)	10.85 ± 2.06	8.87 ± 1.88*	11.44 ± 1.88	9.51 ± 1.81*

Values are expressed as mean ± standard deviation; Pre-M: premenopausal women group; Post-M: postmenopausal women group; TAS: total antioxidantstatus; TE: troloq equivalence; TBARS: plasma thiobarbituric acid reactive substance concentration; eSOD: erythrocyte superoxide dismutase activity; tHcy: plasma total homocysteine; *$P < .05$, different from Pre-training; **$P < .001$, different from Pre-training.

resting heart rate and $\dot{V}O_{2\ max}$ (Table 1). A slight but significantly higher total daily energy expenditure (+3% in pre-M and +6% in post-M women) was recorded after the TC training protocol (Table 2). Daily fat intake was recorded to be higher after the TC protocol (Table 2) but no significant difference was shown for other macronutrients and for total daily energy intake (Table 2). Moreover, the intake of antioxidant micronutrients remained unchanged (Table 2).

Compared to pre-training data, LDL cholesterol was lower ($P = .02$; $F = 7.7$) after the TC training protocol (Table 3). Total cholesterol, HDL cholesterol, triglycerides, uric acid and other routine blood parameters remained unchanged (Table 3). Concerning the antioxidant status, plasma TAS concentration ($P < .001$; $F = 25.1$) (Table 3), erythrocyteGPx activity ($P = .001$; $F = 19.0$) and whole blood GPx activity ($P = .001$; $F = 21.3$) were significantly higher after the TC training protocol compared to pre-training data (Figure 1). However, erythrocyte SOD (Table 3) and plasma GPx activities (Figure 1) remained unchanged. Plasma tHcy concentration was significantly lower ($P < .001$; $F = 44.6$) after the TC training intervention compared to pre-training data (Table 3).

3.3. Tai Chi Training and Menopausal Status Interaction Effect. As shown by ANOVA tests, TC training effects were not different among groups (pre-M women versus post-M women).

4. Discussion

The loss of the protective effect of estrogen in postmenopausal women is known to contribute to the increase in oxidative stress markers and to increase the risk of cardiovascular diseases [1]. This study investigated, whether a TC training protocol (1) would not only improve selected health-related fitness parameters but also the antioxidant capacityof pre- and post-M women, and (2) would reduce oxidative damages and cardiovascular risks of post-M women.

In agreement with previous reports [16], our TC training program improved functional balance, muscle strength and flexibility of both pre- and post-M women. Plasma tHcy level, which is used as a risk marker of cardiovascular diseases, has been shown to increase after menopause [30]. Thus, we expected that TC training would reduce the level of this marker in post-M women. The TC program produced an 18% and 17% reduction in plasma tHcy level in pre-M and post-M groups, respectively, but this effect did not depend on menopausal status. In addition, we have shown that our TC training program was able to improve erythrocyte and whole blood GPx activities in both pre-M and post-M women. Cellular GPx plays a major role in the cellular defense against oxidative stress. The deficiency of cellular GPx in mice induced endothelial dysfunction and significant structural vascular and cardiac abnormalities [31]. Our previous reports showed that endurance exercise training improves erythrocyte GPx activity and that the elderly can also benefit from this adaptation [6, 12, 32]. Tai Chi exercises are performed at low to moderate intensity but seem to induce similar effects on this marker. We have paid very close attention to the breathing rate during TC movements (6 breathes/min or 10 sec/breath). In comparison with a normal breathing frequency (15 breathes/min), this slower breathing frequency is synchronized to endogenous circulatory rhythms and improves cardiovascular and respiratory functions [17]. Respiration and physical activity can influence the autonomic control system, which in turn modify the rhythmic fluctuations in heart and blood pressure. This fluctuation may induce the activation of redox-sensitive transcription factors such as NF-κB and AP-1, which mediate the cellular mechanisms that initiate adaptive responses by changes in the GPx gene expression [33]. Some yogic rhythmic breathing training has been shown to improve endogenous antioxidant capacity [17] and to increase the expression of the glutathione S-transferase gene [34].

The relation between the increase in blood GPx activity and tHcy level is unclear but Hcy has been shown to decrease the ability of cells to detoxify hydrogen peroxide by impairing intracellular antioxidant enzymes, specifically GPx [35]. Moreover, the overexpression of cellular GPx can compensate for homocystemia effects [36, 37]. Thus, it is possible that an increase in GPx activity with TC training directly or indirectly decreases the level of plasma tHcy.

The peroxyl radical scavenging capacity in plasma—also called plasma total antioxidant status (TAS)—was determined before and at the end of the training period. Although the difference between pre- and posttraining was very small (0.184 mM (+12%) in pre-M women and 0.089 mM TE (+6%) in post-M women), the significance ($P < .001$; $F = 25.1$) was strong. Values did not seem to depend on plasma uric acid concentrations and evaluated dietary intakes, which remained unchanged. We used extremely controlled conditions (randomisation, standardisation, analysis performed on the same day, automatic analyzer, etc.) but the lack of control group remained a limit in the interpretation of our data changes. Thus, statistical power, particularly for TAS, was high despite the small number of subjects.

Although TAS and erythrocyte GPx activity were increased in our study, we failed to observe any significant change in the lipid peroxidation marker (TBARS), which nevertheless showed high interindividual variability. As already observed [6, 11, 12, 32], this marker may not be sensitive enough to detect variations in lipid peroxidation when it is measured in basal state (i.e., at rest), in a non-challenging situation.

We failed to evidence significant interaction effect between menopause status and TC training. However, the increase in erythrocyte GPx showed in response to TC training, tended ($P = .09$) to be of lower magnitude in pre-M compared to post-M women. Given the condition of inclusion, sample sizes were smaller than expected (15 subjects per groups for a statistical power of 80 percent). This suggests that post-M women would benefit more from this adaptation than pre-M women.

The clinical relevance of the improvement of erythrocyte GPx activity shown in our study is unknown. However, especially with aging, erythrocyte GPx activity may be a sensitive marker of the reinforcement of the endogenous antioxidant potential induced by regular physical activity training, as previously suggested in men [12]. The present study showed that it might be also the case for middle age and post-M women with Tai Chi training that is performed at a lower intensity and confirm our previous data on this marker obtained from a cross-sectional study [19].

5. Conclusion

The 8-week design TC training (2 sessions in class; 2 sessions at home, 1-1:15/session) is beneficial on functional balance, flexibility and muscular strength, not only for pre-menopausal women, but also for postmenopausal women. Besides the low-velocity, low-impact, and safety benefits, the main finding of this pilot study was that rotational movements of TC postures with slow and deep breathing increased erythrocyte GPx activity and reduced tHcy concentrations, in both pre- and postmenopausal women. Tai Chi would be a good physical activity design for aged women in order to increase their antioxidant protection and to prevent oxidative stress-related metabolic diseases. Further studies with larger groups are needed to confirm our presented results. Investigating breathing effects during TC movements would be an interesting area for further research in diseases prevention.

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Research Article

Subjective and Objective Appraisal of Activity in Adults with Obstructive Sleep Apnea

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Objective. This study examined the association between obstructive sleep apnea (OSA), daytime sleepiness, functional activity, and objective physical activity. *Setting.* Subjects ($N = 37$) being evaluated for OSA were recruited from a sleep clinic. *Participants.* The sample was balanced by gender (53% male), middle-aged, primarily White, and overweight or obese with a mean BMI of 33.98 (SD = 7.35; median BMI = 32.30). Over 40% reported subjective sleepiness (Epworth Sleepiness Scale (ESS) ≥10) and had OSA (78% with apnea + hypopnea index (AHI) ≥5/hr). *Measurements.* Evaluation included questionnaires to evaluate subjective sleepiness (Epworth Sleepiness Scale (ESS)) and functional outcomes (Functional Outcomes of Sleep Questionnaire (FOSQ)), an activity monitor, and an overnight sleep study to determine OSA severity. *Results.* Increased subjective sleepiness was significantly associated with lower scores on the FOSQ but not with average number of steps walked per day. A multiple regression analysis showed that higher AHI values were significantly associated with lower average number of steps walked per day after controlling patient's age, sex, and ESS. *Conclusion.* Subjective sleepiness was associated with perceived difficulty in activity but not with objectively measured activity. However, OSA severity was associated with decreased objective physical activity in aging adults.

1. Introduction

The increased prevalence of persons in the USA who are overweight or obese has been accompanied by a parallel increase in the prevalence of obstructive sleep apnea (OSA) [1]. Data from multiple studies suggest that excessive body weight is a primary risk factor for type 2 diabetes, cardiovascular disease, and OSA [2–5]. Increased physical activity has significant health benefits that include not only improved weight control but also an independent reduction in the risk for diabetes, hypertension, cardiovascular disease, depression, and osteoporosis [6–8]. Unfortunately, many adults who are obese also have sedentary lifestyles, a factor that further increases their risk for developing chronic illness. Therefore, promotion of physical activity is especially important for adults to help prevent the development of chronic illness.

Physical activity, defined as any movement that involves physical effort, is not synonymous with exercise but includes lifestyle activity. The current recommendation by the U.S. Department of Health is that adults obtain at least 150 minutes of physical activity of moderate-intensity activity or 75 minutes a week of vigorous-intensity activity each week [8]. However, another measure of adequate physical activity, walking at least 10,000 steps a day, is considered indicative of an "active" lifestyle [9]. Although data suggest that intense physical activity is most efficacious for increased health benefits, results from population-level studies suggest that even walking at a moderate pace has positive health benefits of decreased obesity, improved insulin resistance, and reduced mortality [10–12].

Findings from several studies using subjective measures of activity indicate that increased OSA severity is associated with decreased physical activity [13, 14]. In addition, excessive daytime sleepiness, a frequent symptom of OSA, has been associated with both increased obesity and decreased functional activity in areas sensitive to sleep disruption [15]. However, it remains unclear if OSA or excessive daytime

sleepiness affects objectively measured physical activity. The purpose of this study is to examine the relationship between subjective daytime sleepiness, OSA severity, functional activity, and objectively measured physical activity in order to obtain a multidimensional perspective of the association between nighttime sleep and daytime activity.

2. Methods

2.1. Participants. Participants were recruited from patients evaluated for sleep disorders at the University of Pittsburgh Medical Center Sleep Medicine Center. The sample was limited to individuals scheduled for an overnight sleep study for the evaluation of possible OSA. The eligibility criteria excluded persons already treated for OSA, coexistence of other sleep disorders such as insomnia or restless leg syndrome, regular use of sedative, hypnotic, or alerting medications, rotating shift or night-shift work, or pregnancy. The study had Institutional Review Board approval by the University of Pittsburgh. For this paper, we conducted analyses on baseline data from 37 participants having complete data on the study variables of interest.

2.2. Measures. Questionnaires developed at the University of Pittsburgh's School of Nursing were used to obtain data on sociodemographic factors including age, gender, race, marital status, years of formal education, and comorbid diseases. Weight was measured on a digital scale with the subject wearing light clothing and without shoes. Height was measured on a wall-mounted stadiometer. BMI was computed using the following formula: BMI = weight (kg)/height (meters^2).

Objective sleep disorders were determined by the diagnostic overnight polysomnography (PSG) to determine the presence and severity of suspected OSA. Scoring of the PSG was performed according to the criteria of American Academy of Sleep Medicine [16]. Apnea was defined as the complete cessation of airflow associated with a 4% oxygen desaturation that persisted for >10 seconds; hypopnea was a decreased airflow of at least 30% associated with a drop of at least 4% in oxygen saturation. The PSG study recorded the electroencephalogram (EEG (C3A2 with C4A1 as backup, O2A1 with O1A2 as backup)), bilateral electrooculograms (EOG (right and left outer canthi referenced to A2 and A1)), bipolar submental and bilateral tibialis anterior electromyograms, chest and abdominal expansion by inductance plethysmography, airflow via nasal pressure and oral thermistor recording, pulse oximetry, and electrocardiogram. The apnea + hypopnea index (AHI) was the endpoint used to determine OSA severity.

Subjective daytime sleepiness was quantified by the Epworth Sleepiness Scale (ESS) [17], an 8-item questionnaire that asks the respondent to rate the possibility of their dozing in eight soporific situations. Sleepiness was graded on a 4-point Likert scale ranging from 0 "no chance of dozing" to 3 "high chance of dozing". The ESS is a validated single-factor instrument with test-retest reliability (r = .82) and internal consistency (Cronbach's alpha = .88). At a cut-point of ≥10, the ESS has a sensitivity of 93.5% and a specificity of 100% for distinguishing normal from pathological sleepiness [18–20]. The total score on the ESS was the endpoint to determine subjective daytime sleepiness.

Functional activity was determined by the Functional Outcomes of Sleep Questionnaire (FOSQ) [21], a questionnaire designed to assess if sleepiness makes performing certain activities difficult. An example of FOSQ questions is "Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?" This 30-item questionnaire (Total Scale alpha = .95) contains five subscales: General Productivity (alpha = .86), Vigilance (alpha = .87), Social Outcomes (alpha = .88), Activity Level (alpha = .91), and Intimacy and Sexual Relationships (alpha = .87). Test-retest reliability for the total scale was r = .90, for subscales, r = .81 to .90. The total score and subscale scores were used as endpoints in this analysis.

Objective activity and energy expenditure were evaluated with the Bodymedia SenseWear Pro Armband activity monitor. This activity monitor is a two-axial accelerometer device that measures the duration and intensity of activity. The activity monitor was worn on an adjustable Velcro armband worn on the right upper arm for a 7-day period. Subjects were instructed to wear the activity armbands around-the-clock except for showering or engaging in any activity that could make the activity monitor wet. The primary endpoint for activity was summarized on each subject as the mean daily activity counts for steps walked: additional endpoints include total estimated energy expenditure and mean metabolic equivalent units (MET).

2.3. Procedure. Human subjects' approval was obtained at the University of Pittsburgh for both the Sleep Disorders Registry and the current study. Patients at the sleep center are routinely asked if they are willing to participate in a Sleep Disorders Registry. People who consented to the registry were sent a letter explaining the study and informing them they would be contacted by telephone by study personnel. Over 30% of those people contacted (n = 119) by telephone screening were eligible and enrolled in the study. The primary reason people were excluded during phone screening was that the person had already been diagnosed with sleep apnea and treated with continuous positive airway treatment.

At the baseline visit, we obtained informed consent and measured subject's height and weight. The evaluations were conducted in the Center for Translational Research Center at the University of Pittsburgh. A prepaid mailer was given to the subjects to return their physical activity monitor and the questionnaires. Results of the overnight sleep study were obtained from the medical record.

2.4. Statistical Analyses. Data analyses were conducted using SPSS v. 17 (SPSS Inc., Chicago, IL). All continuous variables were checked for normality. Because some continuous variables were skewed, summary statistics were presented as the median and interquartile range (IQR) as well as the mean

and standard deviation and as frequencies and percentages for categorical variables. Bivariate relations between continuous variables were examined with Pearson product-moment correlation for approximately bivariately normally distributed data. The Spearman rank-order correlation was used to examine the bivariate association between variables that were either ordinally scaled or with skewed distributions. Two sample t-test or Mann-Whitney U test, if data were ordinally scaled or nonnormally distributed, were used to examine differences in age, AHI, BMI, and self-reported daytime sleepiness between men and women. Predictors for the hierarchical regression analyses for mean daily number of steps walked were selected based on previous associations of age, gender, and ESS with AHI and measures of physical activity [22–25]. Age, gender, and ESS were entered in the first block of the hierarchical regression analysis; AHI was then entered on the second block of the regression analysis.

3. Results

3.1. Sample Characteristics. The demographic characteristics of the sample ($N = 37$) are presented in Table 1. Overall, our sample was evenly distributed by gender, predominantly white, and middle age. Most subjects were married and well educated (median years of formal education = 16) but only 54% of the sample was employed full- or part-time. The majority of the sample was overweight or obese. This sleep clinic-based sample had a high prevalence of both objective sleep disordered breathing and excessive daytime sleepiness. Over 78% of the sample had diagnosable OSA (AHI $\geq$ 5) and 24% of the sample had severe OSA (AHI $\geq$ 30). Excessive daytime sleepiness (ESS $\geq$ 10) was reported by 41% of the sample. Analysis of mean Bodymedia activity data found that many people in the sample were sedentary (40%, $n = 13$) with <5000 steps walked on average daily and few (19%, $n = 6$) were active with $\geq$10,000 steps/day.

3.2. Demographic Characteristics, Sleep, and Activity. There was no statistically significant difference in age, ESS scores, FOSQ total and subscale scores, or objectively measured activity levels between male and female subjects. Based on BMI, female subjects were typically more obese than male subjects (female: median = 38.95, IQR = 12.65; male: median = 31.00, IQR = 5.40; Mann-Whitney $U = 68$, $P = .001$). Male subjects in the study had more severe OSA based on AHI (median = 19.34, IQR = 52.43) compared to female subjects (Median = 8.57, IQR = 6.68), although there was no statistically significant difference in this small sample (Mann-Whitney $U = 157$, $P = .690$). Females in the sample were less active (median daily steps = 4195, IQR = 4832) than males (median daily steps = 7352, IQR = 6004); however, it was again not statistically significant (Mann-Whitney $U = 87$, $P = .13$).

Age and BMI were not significantly associated with subjective sleepiness (ESS), OSA severity (AHI), or subjective activity (FOSQ total and subscale scores). Results of correlational analyses using Spearman rank-order correlations suggest that increased age is associated with decreased physical activity as measured by mean number of steps walked per day ($r_s = -.35$, $P = .051$) and decreased total daily energy expenditure ($r_s = -.47$, $P = .007$). Although BMI was not significantly associated with the mean number of steps walked, an increase in BMI was associated with decreased activity intensity (mean MET, $r_s = -.48$, $P = .006$).

Table 1: Demographic and clinical characteristics of sample ($N = 37$).

Characteristics	Measures of central tendency dispersion, or frequency
Age (years)	Median = 51.00, IQR = 15, Mean = 49.51 ± 11.45,
Male % (n)	53 (19)
White % (n)	78 (29)
Married/living with partner% (n)	62 (23)
Education >12 years% (n)	76 (28)
Body Mass Index (kg/m^2)	Median = 32.30, IQR = 10.90, Mean = 33.98 ± 7.35,
Epworth Sleepiness Scale (ESS)	Mean = 9.43 ± 4.94,
Functional Outcomes of Sleep Questionnaire (FOSQ) Total Score	Median = 17.66, IQR = 5.87,
Apnea + hypopnea index (AHI)	Median = 9.94, IQR = 27.80, Mean = 21.74 ± 25.40,
Steps walked daily	Median = 5881, IQR = 5896, Mean = 6,988 ± 3,852

3.3. Daytime Sleepiness, OSA Severity, and Activity. Table 2 reports the results of correlation analyses examining the relationships between daytime sleepiness, OSA severity, functional activity, and objectively measured activity. Excessive sleepiness was associated with increased difficulty to conduct normal activities measured by all five FOSQ subscale scores (General Productivity, Social Outcomes, Activity Level, Vigilance, and Sexual and Intimate Relationships) and the FOSQ total score. No statistically significant associations were found between daytime sleepiness and average daily measures of objective physical activity (mean steps walked, total energy expenditure, or average METS). Difficulties in performing functional activities because of sleepiness (FOSQ total and subscale scores) were not significantly associated with any objective measure of physical activity.

OSA severity was not statistically significantly associated with either daytime sleepiness or functional activity (FOSQ total or subscale scores). Data suggest that increased OSA severity may be associated with decreased physical activity. There were negative associations between AHI and total energy expenditure ($r_s = -.32$, $P = .07$), steps walked ($r_s = -.29$, $P = .11$), and average METS ($r_s = -.29$, $P = .10$) that approached statistical significance.

A multiple regression model (Table 3) with the daily mean number of steps as the dependent variable, controlling for gender, age, ESS and AHI, was found to be statistically significant overall ($F = 3.91$, $R^2 = .38$, $P = .01$).

Table 2: Correlations among study variables.

Variable pairs	Spearman's r_s	P value
Mean steps and AHI	−.29	.11
ESS and total FOSQ	−.73	<.001
ESS and FOSQ General Productivity	−.67	<.001
ESS and FOSQ Social Outcomes	−.63	<.001
ESS and FOSQ Activity Level	−.62	<.001
ESS and FOSQ Vigilance	−.80	<.001
ESS and FOSQ Intimacy and Sexual Relationships	−.80	.001

Table 3: Regression results of objective physical activity (mean daily steps walked).

Variable	Beta	P value
Age	−98.81	.07
Gender (male)	3434.13	.01
Epworth	−110.07	.35
AHI	−64.25	.01

R^2 = .38 (Adjusted R^2 = .28).

The strongest predictors of number of steps were gender (t = 2.79, P = .01) and AHI (t = −2.72, P = .01). Age approached statistical significance (t = −1.90, P = .07). ESS was not statistically significantly associated (t = −.95, P = .35) with number of steps. An extra year of age was estimated to translate to a decrease of 98.81 steps per day. An extra point in AHI was found to result in a drop of 64.25 in mean daily steps. Male gender in this multiple regression analysis was associated with an additional 3434 steps per day.

4. Discussion

We found that increased OSA severity was associated with decreased objectively measured physical activity while controlling for age, gender, and daytime sleepiness (Table 3). In addition, while complaints of subjective sleepiness were strongly associated with increased self-reported difficulty in being active, there was no significant association between either sleepiness or self-reported difficulty because of sleepiness in performing functional activity and objectively measured activity.

The United States Department of Health and Human Services has set 150 minutes a week of moderate-intensity activity or 10,000 steps a day of walking as the goal [8]. Although the 2008 Physical Activities Guidelines and other study acknowledge that the goal of 10,000 steps a day may not be sustainable with elderly persons or persons with chronic illness, it is considered appropriate for most adults [7–9]. Increased activity is especially beneficial in persons who are moving from middle age into old age to promote healthy aging. In this study we found that OSA, a treatable sleep disorder, is associated with more sedentary lifestyles. Assessment and treatment of OSA is important not only because it is a harmful disease, but also because of its mediating effect on physical activity, an essential part of every adults program for healthy aging.

The sample (Table 1) of middle-aged, obese, sedentary persons is fairly representative of the aging population. The results of our study (Table 2) are consistent with previous research showing a significant association between decreased moderate to moderately vigorous physical activity and increased severity of OSA in the Sleep Heart Health Study (SHHS (N = 4275)) [14]. The evaluation of physical activity in the SHHS was based on self-report, which might have affected the measurement of physical activity. In addition, the SHHS used different instruments for the assessment of physical activity in the five cohorts in the study which might have interfered with the precision of the findings. Our findings are important because they validate this relationship using an objective measurement of physical activity.

The finding that women are likely to be more obese and have less severe OSA than men is consistent with previous research among patients being evaluated in a sleep clinic for possible sleep apnea [22–26]. Women in the study were more likely to be sedentary than men, again a finding that agrees with the results of previous studies that utilized questionnaires to evaluate physical activity [22]. Although premenopausal women have a decreased risk for OSA, the risk of OSA increases in both men and women as they age. Unfortunately, OSA in women is frequently underdiagnosed because of a common misconception that OSA is a "male" disorder [27, 28].

The FOSQ is a validated questionnaire that has been used in multiple clinical trials to assess the impact of sleepiness on the ability to conduct daily activities [29–32]. The FOSQ questionnaire evaluates the degree of difficulty caused by sleepiness on functional outcomes such as being active and productive, able to maintain vigilance during a task like driving, watching a movie, being active in the morning/afternoon/evening, or being interested in engaging in intimate relationships. It is important to remember that the FOSQ was not developed as an indirect measure of physical activity. The strong association between daytime sleepiness on the Epworth Sleepiness Scale and the FOSQ (Table 2) might have resulted because the instruments measure subjective difficulty rather than objective behavior. This incongruity between objective physical activity and subjective report of difficulty in performing functional activity is similar to the well-known discordance between self-reports of medication adherence and objective medication behavior [33].

There are several limitations of the present study. Since this study had a cross-sectional observational design, we can only report associations and cannot infer causation. Sleepiness was evaluated only by subjective self-assessment by subjects and there was no objective assessment of excessive sleepiness such as with a multiple sleep latency test. Therefore, future evaluation of the effect of objective sleepiness on physical activity is warranted. The small sample size and resultant lack of statistical power resulted in several tests possibly having a type-2 error. Because there was a small convenience sample that consisted exclusively of sleep clinic patients, the findings of this study need to be considered

as preliminary and cannot be generalized to the general adult population. Finally, although we attempted to control potential confounders, we cannot dismiss the possibility that important variables might not have been included in the analyses.

5. Conclusions

An active lifestyle with regular physical activity is essential for health promotion and disease prevention for healthy aging. While exercise of longer duration and greater intensity is optimal, an active lifestyle is fundamental to health promotion across the lifespan. Although previous studies found that sleepiness and OSA were associated with decreased self-reported activity, this study's utilization of an objective activity monitor helped quantify the effect of OSA severity and sleepiness on physical activity.

Evidence from previous studies has strongly implicated the role of daytime sleepiness in negatively affecting participation in functional activities [13, 15]. Excessive daytime sleepiness is not benign, and as also found in the current study, has a negative effect on quality of life. Because excessive sleepiness is nonspecific, a comprehensive evaluation of this important symptom is important for health promotion and disease prevention in the aging adult. This is relevant for both men and women because of the importance of physical activity for healthy aging and the implication that untreated OSA may negatively impact the ability to have an active lifestyle.

Authors' Contributions

E. Chasens is responsible for concept and design, interpretation of data, and preparation of manuscript. S. Sereika is responsible for interpretation of data, preparation of manuscript. M. Houze is responsible for interpretation of data and writing of results. P. Strollo reformed medical management, interpretation of data, and preparation of manuscript.

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Research Article

Physical Performance Is Associated with Executive Functioning in Older African American Women

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An older adult's ability to perform physical tasks is predictive of disability onset and is associated with declines in cognition. Risk factors for physical performance declines among African Americans, a group with the highest rates of disability, remain understudied. This study sought to identify demographic, health, and cognitive factors associated with lower-extremity physical performance in a sample of 106 African American women ages 56 to 91. After controlling for global cognitive functioning (Mini Mental State Exam), physical performance was associated with executive functioning (Stroop Color/Word), but not visuospatial construction (WASI Block Design) or processing speed (Trail Making Test, Part A). Executive functioning remained associated with physical performance after entry of demographic variables, exercise, depression, disease burden, and body mass index (BMI). Age, and BMI were also significant in this model. Executive functioning, age and BMI are associated with lower-extremity physical performance among older African American women.

1. Introduction

Impairments in physical and cognitive functioning, as well as onset of chronic diseases, are often feared in later life as such changes lead to dependence in tasks of daily living, depression, and hospitalization. Compared to white elders, African American older adults experience a greater number of years exposed to the negative impacts of chronic disease and functional disability [1] making disability intervention especially important for this minority group. The field of gerontology has identified lower-extremity physical performance measures as key for identification of early changes that may lead to disability in older adults. Lower-extremity measures of physical performance are predictive of several outcomes in later life including declines in activities of daily living (ADLs), hospitalization, risk for death, nursing home placement, and hip fracture [2, 3]. Reflecting the observed racial and socioeconomic discrepancies in rates of disability among older adults, African American elders score more poorly on performance-based measures of physical function than both white adults [4] and suburban African Americans [5].

While much evidence exists for the relationship between cognitive functioning and ADL declines [6–8], fewer studies have focused on the associations between physical performance and cognition, specifically executive functioning, in minority populations. Executive functioning encompasses a broad range of cognitive abilities such as the planning, sequencing, and execution of complex goal-directed behaviors characteristic of IADLs (instrumental activities of daily living) [9, 10]. Amongst cognitive domains such as memory, language, visuospatial ability, and psychomotor speed, executive functioning is deemed as essential to preserved functional status [11, 12]. Prior studies have found that executive functioning is related to mobility and balance among older adults [13–15]; however, this relationship may be attenuated after accounting for disease burden in African American elders [16]. Additionally, it remains unclear whether performance of physical tasks may involve executive functioning more than other domains of cognition

and whether screening measures of global cognitive functioning, such as the Mini Mental Status Exam (MMSE), which are commonly used in disability risk assessments, may adequately predict physical performance declines [14, 17, 18].

Neuroimaging studies and clinical observation of age-related cognitive disorders such as Parkinson's disease and vascular dementia, provide evidence that changes in brain structures result in impairments in both cognitive functioning [9] and physical performance [19]. The frontal subcortical region, implicated in tasks of executive functioning, is particularly sensitive to effects of cardiovascular risk factors (CVRFs) such as atherosclerosis, hypertension, stroke, and diabetes [20–24]. Vascular burden is associated with presence of white matter hyperintensities (WMHs), brain atrophy and infarcts. Older adults with compromise to the white matter pathways connecting subcortical and frontal regions secondary to vascular processes demonstrate poor executive functioning, slow gait speed and depression [15, 25]. The co-occurrence of these symptoms is associated with greater functional dependency [19], poorer physical performance [15], and mortality [26].

African American adults have higher body mass index (BMI), and a greater number of health conditions, particularly CVRFs such as hypertension and diabetes, when compared to their white, same-gender peers [27, 28]. Both obesity and inactivity are associated with disability [29]. Exercise interventions have been shown to improve scores on measures of lower-extremity functioning [30] and decrease risk for mortality, frailty, disease [31] and obesity [29]; however, it remains unclear what level of exercise is needed to decrease disability risk. In order to develop interventions and delay disability onset within African American elders, a high-risk group of older adults, further work is needed to understand the impact of medical conditions and the potential benefit of exercise to prevent early disability.

The goals of this study are to (1) identify whether a specific domain of cognition versus global cognitive functioning may be uniquely associated with physical performance; and (2) to examine relationships between physical performance and a range of factors associated with disability risk including cognition, depression, exercise, disease burden, BMI and demographics in a sample of community-dwelling African American older women. Based on previous research it was predicted that executive functioning would be significantly associated with physical performance while other domains of cognition would not and that physical performance would be related to demographics, depression, exercise, health, and cognition.

2. Methods

2.1. Sample. Participants were drawn from the Health, Disability and Cognitive Function in Urban African American Older Adults dataset, which includes 130 community-dwelling African American adults between the ages of 55 and 100 who resided in the city of Detroit. This project received approval from the Institutional Review Board, Human Investigation Committee of Wayne State University. Prior to participation, all participants provided signed consent. Subjects were recruited from independent living centers, community centers and senior apartments through presentations within the community given by the PI. Fliers stating that the aim of the study is to understand "health and cognitive functioning in older African American adults" were also given to potential participants. Individuals were excluded if they (1) did not self-report as African American or black; (2) were unable to speak English fluently; (3) had major hearing or vision loss; and/or (4) were below age 55. Because the dataset contained a significantly greater proportion of females (87.7%), male participants were excluded from these analyses.

A summary of participant characteristics is presented in Table 1 and mean raw scores on cognitive measures for the final sample are presented in Table 2. The final sample was comprised of 106 African American women ages 56 to 91 (mean = 71.83; SD = 7.73), and with 6 to 18 years of formal education (mean = 12.74; SD = 2.45).

2.2. Measures and Procedures. Measures reported in this study were administered as part of a larger evaluation that involved data collection on demographics, physical health, cognition, health behaviors, and mental health in urban African American elders for a dissertation project. Data was collected in an individual interview session format by three trained interviewers who were supervised by a research psychologist (PL). Participants were informed of the length of the test battery prior to participation. However, due to participant time restraints leading them to leave early or arrive late, as well as slowness in completing the measures, the battery occasionally had to be shortened or terminated before all measures were completed. This led to slight differences in sample size across measures. The average time to complete the battery was two hours.

2.3. Cognitive Measures. Fuld object memory evaluation (FOME) [32]. The FOME is a measure of verbal memory that involves recall of 10 common objects. Recall trials are separated by a distraction task to minimize the effects of short-term memory.

Mini Mental Status Exam (MMSE) [33]. The MMSE is an 11-item screening tool used to obtain an estimate of an individual's global cognitive functioning and orientation to date, time, and place. Scores range from 0 to 30 with higher scores indicating better cognitive functioning.

Stroop Color/Word subtest (Stroop C/W) [34]. The Stroop C/W test is a measure of processing speed and mental flexibility. The Stroop test is comprised of three subtasks: color word naming, color naming, and naming the color of ink a color name is printed in. For example, saying "green" when the word "red" is printed in green ink. Third subtask is an interference trial that requires inhibition and mental flexibility. Time to completion was recorded for each trial.

Trail Making Test, Part A (TMT-A) [35]. Part A of the TMT is a measure of attention and psychomotor processing speed in which participants are asked to connect numbers in numerical order (1-2-3 and so on) as quickly as possible. Scores are based on the time to completion.

Table 1: Demographic, exercise, BMI and mood characteristics of sample.

(Overall $N = 106$)	Mean	SD	Range
Age	71.83	7.73	56–91
Education	12.74	2.45	6–18
GDS-15	1.78	1.89	0–9
Exercise	2.75	2.61	0–7
BMI	31.39	7.91	15.7–56.7

Note: GDS: Geriatric Depression Scale-15 item; BMI: body mass index.

Table 2: Descriptive statistics for cognitive measures.

Measure	Mean	SD	Range
FOME	39.84	5.31	24–50
MMSE	27.05	2.18	19–30
Stroop Color/Word	25.15	9.63	2–49
TMT-A	56.21	27.02	20–136
WASI BD	16.05	10.35	2–43

Note: FOME: Fuld Object Memory Evaluation; MMSE: Mini Mental Status Exam; TMT-A: Trail Making Test, Part A; WASI BD: Wechsler Abbreviated Scale of Intelligence, Block Design subtest.

Wechsler Abbreviated Scale of Intelligence (WASI), Block Design subtest [36]. The WASI Block Design subtest is a timed measure of visuoconstructional abilities in which participants use blocks to construct three-dimensional figures from a two-dimensional drawing in the stimulus book.

2.4. Geriatric Depression Scale-15 Item (GDS) [37]. The GDS-15 is a shortened version of the original 30-item screening questionnaire that is presented verbally to the participant. Respondents answer yes or no to questions regarding how they have felt over the last two weeks. Items for which a respondent indicates pathology are given a score of 1. Total scores range from 0 to 15, with higher scores indicating greater depressive symptomology.

2.5. Exercise. Participation in exercise was obtained from self-reported answers to the following questions: (1) "Do you participate in a regular program of exercise?" and if yes, then "How many days per week". Participants were asked to provide an estimated number of days between 0 and 7.

2.6. Health. Participants were asked whether a doctor had ever told them that they have health conditions that were grouped into two disease categories: (1) cardiovascular (i.e., hypertension, stroke, myocardial infarct, congestive heart failure, vascular disease, and diabetes), or (2) general health (i.e., arthritis, chronic obstructive pulmonary disease, gastrointenstinal conditions, kidney disease, and liver disease). Table 3 shows the number of participants that reported each of these health conditions. Participants were also asked to report their estimated current height and weight.

2.7. Short Physical Performance Battery (SPPB). The SPPB used in this study was replicated from methodology used in the Established Populations for Epidemiologic Studies of the Elderly (EPESE) studies that examined physical functioning in over 5,000 mostly white older adults [38]. This methodology is described in detail elsewhere [3, 38]. Lower-extremity function was assessed through the performance of three tasks: standing balance, walking, and chair stands.

Table 3: Frequencies of health conditions.

(Overall $N = 106$)	Frequencies	Percentage
Hypertension	71	67%
Myocardial infarct	11	10%
Peripheral vascular disease	8	7%
Diabetes	23	22%
Stroke	11	10%
Congestive heart failure	11	10%
Arthritis	76	72%
Gastrointestinal disease	25	24%
Kidney disease	7	7%
Liver disease	1	.9%
COPD or emphysema	9	8%

Balance was assessed by recording the amount of time each participant could maintain each of the following three poses: semitandem (heel of one foot to the side of the first toe of the other foot), tandem (heel to toe), and side-by-side. Timing stopped when the participant lost balance, grasped for the examiner, or ten seconds had elapsed. According to the Guralnik et al.'s criteria [38], participants received a score of a 1 if they were able to hold a side-by-side position for 10 seconds, but were unable to hold a semi-tandem position; a score of a 2 if they could hold a semi-tandem position for 10 seconds but were unable to hold a full tandem for more than 2 seconds; a score of a 3 if they could stand in full tandem for 3 to 9 seconds; and a score of a 4 if they could stand in full tandem for 10 seconds.

Gait speed was assessed by two 3-meter walks, at a normal everyday pace, which was marked out for each subject in advance. The faster of their two walks was used as their final score which was recorded in quartiles such that a score of 1 = ≥ 5.6 seconds; a score of 2 = 4.4–5.5 seconds; a score of 3 = 3.8–4.3 seconds; and a score of 4 = ≤ 3.7.

The final task, chair stands, required the participants to fold their arms across their chest and to stand up from a sitting position once. Upon successful completion of this task, participants were asked to stand up and sit down with their arms across their chest five times as quickly as they could. Times were then recorded into quartiles such that a score of a 1 = ≥ 16.1 seconds; a score of a 2 = 12.9 to 16.0 seconds; a score of a 3 = 9.9 to 12.8 seconds; and a score of a 4 = ≤ 9.8 seconds.

Summing the scores for each subtask (standing balance, gait speed, and chair rises) creates a summary performance score that was used in the analyses.

2.8. Statistical Methods. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc., 2009). Participants who were missing data on variables of interest ($n = 6$)

were excluded from the analyses. All variables were examined to ensure they met assumptions of normality. All variables except BMI were within acceptable ranges; a logarithmic transformation was performed on BMI. The transformed variable was used in all analyses. To initially ascertain the relationships between the SPPB and predictor variables, Pearson product moment correlations were obtained. To examine the relationship between physical performance and specific domains of cognition, a multiple regression analysis was conducted in which SPPB total score was regressed on age, education, and MMSE. Each individual cognitive test (Stroop C/W, TMT-A, MMSE and WASI Block Design) was entered into separate regression analyses. Raw scores were used for all cognitive measures of interest. Next, to examine the relationship between physical performance and demographic variables (i.e., age, and education), cognition, exercise, mood, disease burden and BMI, a hierarchical regression analysis was conducted. In Block 1, SPPB total score was regressed on age and education. To examine the incremental variance accounted for by other variables of interest, Stroop C/W raw score was entered in Block 2, exercise was entered in Block 3, GDS total score was entered in Block 4, total number of both vascular health and general health conditions were entered in Block 5, and BMI was entered in Block 6. For both sets of analyses, a P value of less than .05 was considered significant.

3. Results

Examination of preliminary analyses revealed significant bivariate relationships between the SPPB and age ($r = -.34$; $P < .00$), education ($r = .20$; $P < .04$), BMI ($r = -.27$; $P < .00$), exercise ($r = .20$; $P < .05$), vascular health ($r = -.29$; $P < .00$), general health ($r = -.25$; $P < .01$), and the GDS ($r = -.26$, $P < .01$). All cognitive variables were also significantly correlated with SPPB performance (MMSE, $r = .29$, $P < .00$; WASI BD, $r = .24$, $P < .01$; TMT-A, $r = -.33$, $P < .00$; Stroop C/W, $r = .36$, $P < .00$), except the FOME ($r = .18$, $P = .07$).

To examine our first hypothesis, a multiple regression was conducted to determine the association of each cognitive domain (i.e., attention, visuospatial skills, and executive functioning) with physical performance after accounting for age, education, and general cognitive functioning (MMSE). In Block 1, age ($P < .00$) and MMSE ($P < .05$) significantly contributed to SPPB scores. Upon entry of each cognitive measure individually in Block 2, only Stroop C/W was significantly associated with physical performance ($P < .05$). MMSE was nonsignificant with the entry of Stroop C/W. This model accounted for 18.8% of the variance in physical performance scores; see Table 4 for results.

Next, a hierarchical regression was conducted to ascertain the amount of variance in physical performance accounted for by demographics, cognition, exercise, depression, vascular health, general health and BMI. Based on results of the initial analyses, only Stroop C/W was used to represent cognition in this model. R^2 change was significant at Block 1 with entry of demographics, $R^2 = .15$, $F(2, 103) = 9.39$, $P < .00$. Age ($P < .00$) and education ($P < .05$) were both significant predictors in Block 1. In Block 2, Stroop C/W significantly improved prediction of SPPB scores ($P < .00$); $\Delta R^2 = .05$, $F(1, 102) = 7.01$, $P < .00$. With the addition of Stroop C/W, education became nonsignificant. In Block 3, exercise did not significantly improve prediction ($P > .05$); $\Delta R^2 = .02$, $F(1, 101) = 2.74$, $P = .10$. GDS significantly improved prediction ($P < .05$) in Block 4; $\Delta R^2 = .04$, $F(1, 100) = 5.36$, $P < .05$. In Block 5, both vascular health ($P < .05$) and general health were significant ($P < .05$); $\Delta R^2 = .08$, $F(2, 98) = 5.93$, $P < .00$. With the entry of the health variables in Block 5, the GDS became non-significant ($P = .21$). In Block 6, BMI was significant ($P < .05$); however, vascular and general health became non-significant ($P > .05$); $\Delta R^2 = .03$, $F(1, 97) = 4.84$, $P < .03$. In the final model, age, Stroop C/W, and BMI were significant contributors, and accounted for 32.8% (Adj. R^2) of the variance in SPPB scores. Block 6 results are reported in Table 5.

Table 4: Association of cognition with the SPPB.

Variable	Beta	SE Beta	β	Sig.	ΔR^2
Stroop C/W	.07	.03	.21	.04	.03
WASI BD	.03	.03	.10	.32	.01
TMT-A	−.02	.01	−.17	.09	.09

Note: Results are based on separate hierarchical regression models for each cognitive test. Block 2 adjusted for age, education and MMSE score. WASI BD: Wechsler Abbreviated Scale of Intelligence, Block Design subtest; TMT-A: Trail Making Test, Part A.

4. Discussion

Confirming our hypothesis, among cognitive domains of memory, attention, and visuospatial construction, only executive functioning was significantly associated with physical performance after controlling for general cognitive functioning. A secondary analysis demonstrated that among a range of factors shown to contribute to disability onset, age, executive functioning, and BMI were associated with physical performance scores. These findings have clinical implications for improving gerontology's understanding of disability and helping clinicians and researchers to design and implement interventions aimed at delaying disability onset among African American women.

Foremost, this study provides further evidence that executive functioning contributes not only to ADL disability onset, but also to declines in physical performance, an early indicator of disability, in African American older adults [1, 17, 39]. Executive functioning accounted for a small, yet significant, proportion of variance in physical performance, and our findings suggest that performance of basic physical tasks included in the SPPB involve executive processes such as inhibition and mental flexibility. An older adult's ability to inhibit attention to extraneous information in the environment and to make appropriate responses is involved in the successful performance of physical tasks. Executive functions may become even more important in complex scenarios older adults face in daily life, such as when avoiding obstacles in their home or when attempting to multitask (i.e., walking and talking).

Table 5: Contribution of demographics, cognition, depression, exercise and health variables to SPPB.

Block 6	Beta	Std. Error	β	t	Sig.
Age	−.16	.04	−.32	−3.80	.00
Education	.09	.12	.07	.76	.45
Stroop C/W	.06	.03	.19	2.06	.04
Exercise	.10	.11	.09	.97	.33
GDS	−.20	.15	−.12	−1.33	.19
General health	−.49	.30	−.15	−1.63	.11
Vascular health	−.46	.26	−.15	−1.75	.08
BMI	−6.24	2.83	−.20	−2.20	.03

Note: BMI: Body Mass Index; GDS: Geriatric Depression Scale.

These findings are supported by and expand upon our previous work using a separate dataset of African American elders from the Detroit area [16]. In this study, two of three measures of executive functioning (Trail Making Test, Part B and Animal Naming) were significantly associated with SPPB scores after controlling for general cognitive functioning. The current study demonstrates that even after examination of four other domains of cognition, only executive functioning is associated with physical performance. Providing convergent evidence of this relationship in a similar study of African American older adults, Nieto and colleagues [13] report that after adjusting for age, gender, comorbidity, global cognition, education levels, and global memory, individuals with poor executive function were four times more likely to have impaired lower-extremity functioning. These results are congruent with several other studies reporting relationships between executive functioning and physical performance in samples of predominantly white older adults [14, 15, 40]. Executive functioning measures such as the Stroop are brief, easy to administer and are well tolerated by older adults. Disability assessment traditionally includes some measure of general cognition, often the MMSE. However, we argue that the addition of executive function measures would improve assessment of disability risk.

Our second analysis provides further information about mechanisms potentially underlying the relationship between physical performance and executive functioning. Along with executive functioning, age and BMI were significantly associated with physical performance while mood and exercise were not. Although both vascular and general health conditions were significantly associated with physical performance, they became non-significant after entry of BMI. BMI is a well-established risk factor for disability in older adults [41]. Outcomes of and contributors to BMI and obesity are difficult to separate; however, obesity is highly associated with medical burden, particularly cardiovascular conditions and arthritis, as well as frailty and decreased exercise tolerance and mobility [42]. Reciprocal influences of several processes lead to greater BMI and increase risk for disability. Associations between vascular burden, obesity, and both physical and cognitive declines is of particular interest [43–45].

Our results support the idea that vascular disease in later life increases an older adult's risk for physical declines, and that physical performance is associated with executive dysfunction. Brain insult to shared neuroanatomical pathways secondary to CVRFs may partially explain mutual declines in cognition and physical performance. Supporting this hypothesis, Leung and colleagues [46] found that Stroop performance was related to activation in the anterior cingulate gyrus, as well as inferior and middle frontal regions; areas implicated in physical performance tasks and sensitive to the impact of vascular burden. Because the frontal lobe integrates informational input from multiple regions of the brain, WMHs and atrophy to shared pathways in the frontal region could result in both physical performance declines and executive dysfunction.

Exercise was not associated with physical performance in our study. Previous work has demonstrated that exercise interventions yield better performance on the SPPB [31, 47] when participants were engaged in moderate exercise for approximately 150 minutes per week. Our ability to find a relationship between exercise and the SPPB may have been attenuated by the amount and intensity of exercise of our participants. Also, physical activity is difficult to accurately measure via self-report as older adults often participate in unstructured, low-intensity physical activities that can be difficult to recall [48]. One final consideration is that exercise is a health behavior, while the variables that were significant in the model, namely BMI and cognition, are the outcome of cumulative lifelong processes. BMI in particular likely reflects lifelong health behaviors, including exercise.

Though depression was not significantly related to physical performance in the final model, it was a significant predictor prior to the entry of vascular and general health, and is related to poorer physical performance in other studies [15]. As such, disease burden may mediate the relationship between depression and physical performance [49]. The relationship between physical performance and depression within samples of African American elders requires further clarification.

There are several limitations to this study. Foremost, due to our small sample size ($N = 106$), our findings should be considered exploratory in nature. Further work is needed to extend and support these findings within a larger sample of African American elders drawn from various geographic regions. Secondly, only single measures were used to represent each cognitive domain. Because the Stroop involves processing speed, as do SPPB tasks, it may be questioned whether the processing speed factor accounts

for its association with the SPPB. Though three of the five cognitive measures were timed (i.e., Stroop C/W, TMT-A and WASI Block Design), and two involved a motor component (i.e., TMT-A and WASI Block Design), none involved lower-extremity physical performance. Only the Stroop C/W was significantly associated with physical performance while other measures that involved speeded processing were not, suggesting that the executive functioning components, mental flexibility, and inhibition, account for its association with physical performance rather than processing speed. In the future it would be of interest to use a broader range of executive functioning measures to determine whether a relationship between executive functioning and physical performance would remain, specifically, for untimed measures.

Because the SPPB is designed to measure only lower-extremity function, this may be viewed as a limitation of our study. However, measures of lower, versus upper, extremity performance are more predictive of future disability because lower extremity function has a greater impact on an older adult's ability to remain independent [2]. Additionally, performances on lower-extremity measures decline across time more than performances on upper-extremity measures suggesting that they are a more sensitive indicator of change in functional status [50]. Self-reported disability is also more strongly correlated with lower-extremity than upper-extremity tasks [51].

Finally, many studies fail to examine racial differences or race-specific relationships with regard to risk factors for disability. Though not directly compared, the risk factors in this study are similar to those identified in previous studies that used primarily white older adults. Differences in comorbidity account for African American/white disparities in disability rates, suggesting that disease burden may contribute to disability differently in African Americans versus whites. Though there is generally greater variance among individuals in a group than between groups, disease burden may present an exception. African American older adults experience greater comorbidity at an earlier age of onset of chronic diseases, and have a greater average BMI than their white counterparts [28, 52]. Additionally, many social factors contribute to differences in healthcare seeking and health behaviors in African Americans versus whites. These factors suggest that pathways to disability may operate differently in African Americans.

5. Conclusions

Study results provide further information regarding correlates of physical performance, an indicator of predisability, in older African American women. Foremost, they support previous work demonstrating that executive functioning is related to physical performance and may serve as an indicator of disability risk within African American elders. BMI, which is highly associated with disease burden and health behaviors, was also related to physical performance. Disease processes may underlie the relationship between physical performance and executive function and serve as an important target for interventions.

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