Cardiology Research and Practice

Cardiovascular Disease-Related Lifestyle Factors and Longevity

Guest Editors: Christina Chrysohoou, Christodoulos Stefanadis, Christos Pitsavos, Demosthenes Panagiotakos, Undurti N. Das, and Dario Giugliano

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Editorial Board

Contents

Contents

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Editorial

Cardiovascular Disease-Related Lifestyle Factors and Longevity

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Cardiovascular disease is one of the leading causes of death in the developed world. Understanding trends in cardiovascular disease prevalence and identifying factors associated with its development are important, since they provide information to define the burden and the mechanisms of the disease, which is the first step before population-based interventions. This special issue is devoted to highlight lifestyle factors and behaviors associated with the development of cardiovascular disease. According to the World Health Organization, sedentary lifestyle, smoking habits, and unhealthy dietary habits, are the most important factors associated with the development of cardiac diseases; and the main reason for classifying these factors as the most significant is because they can be prevented.

In their paper, G. S. Metsios et al. presented current scientific evidence about the role of passive smoking in the development of cardiovascular disease in children. The authors identified a total of 42 articles (i.e., 30 reviews and 12 observational), and they revealed that passive smoking may be implicated in deteriorating cardiovascular status in children in terms of unfavorable high-density lipoprotein levels and deteriorated vascular function. In another article based on a middle-aged population of the Ikaria island in Greece, C. Chrysohoou et al. reported that short-term depressive symptoms are related to a worse 30-day prognosis of ACS patients; however, this relationship was mediated by Mediterranean diet adherence. It is well known that depression is an independent risk factor for cardiac diseases. Due to a significant increase of the incidence of depression during the past decades, there has been a growing interest regarding the mechanisms underlying its pathogenesis, including the parameter of nutrition. Y. Ma et al. reported that chronic depression is associated with inflammatory response in women, but not in men. Previous studies have also observed the positive relationship between depression and inflammation. It seems that Mediterranean diet, due to its antioxidant role, may mediate the adverse effect of depression on cardiac system; the majority of studies suggest the beneficial effects of omega-3 PUFAs, a main constituent of Mediterranean diet, in the treatment of clinical depression, with eicosapentaenoic acid (EPA) being more effective than docosahexaenoic (DHA). Another lifestyle factor that has received much attention concerning the prevention of cardiovascular diseases is physical activity status. In the paper by S. A. Kavouras et al., from the ATTICA study, the investigators revealed another mechanism about the protective role of physical activity in atherosclerosis, the improvement in total antioxidant capacity of the study's participants. Moreover, under the context of the IKARIA study, the authors observed that frequent fish intake (i.e., >3 times per week) seems to moderate depressive mood. In addition to the latter, Tyrovolas et al. reported that nutrition services provided in Greek islands played a significant role in modifying dietary habits of older adults. M. M. Pryde and W. B. Kannel resumed that dietary modifications about polyunsaturated fat intake, processed meat consumption, fish choices and preparation, trans fatty acids, low carbohydrate diets, egg consumption, coffee, added sugar, soft drink beverages, glycemic load, chocolate, orange juice, nut consumption, vitamin D supplements, food portion size, and alcohol drinking may preserve cardiovascular health and longevity.

In this special issue, the role of lifestyle, mainly represented by diet, smoking, and physical activity, has been extensively studied in relation to cardiovascular disease development. The scientific evidence strongly supports the protective role of healthy diet, abstinence of smoking, and engagement in physical activities for the prevention of cardiovascular disease. Public health policy makers should target on these lifestyle behaviors which seemingly can cost-effectively reduce the burden of the disease at population level.

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Review Article

Systematic Review of the Effect of Diet and Exercise Lifestyle Interventions in the Secondary Prevention of Coronary Heart Disease

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The effectiveness of lifestyle interventions within secondary prevention of coronary heart disease (CHD) remains unclear. This systematic review aimed to determine their effectiveness and included randomized controlled trials of lifestyle interventions, in primary care or community settings, with a minimum follow-up of three months, published since 1990. 21 trials with 10,799 patients were included; the interventions were multifactorial (10), educational (4), psychological (3), dietary (1), organisational (2), and exercise (1). The overall results for modifiable risk factors suggested improvements in dietary and exercise outcomes but no overall effect on smoking outcomes. In trials that examined mortality and morbidity, significant benefits were reported for total mortality (in 4 of 6 trials; overall risk ratio (RR) 0.75 (95% confidence intervals (CI) 0.65, 0.87)), cardiovascular mortality (3 of 8 trials; overall RR 0.63 (95% CI 0.47, 0.84)), and nonfatal cardiac events (5 of 9 trials; overall RR 0.68 (95% CI 0.55, 0.84)). The heterogeneity between trials and generally poor quality of trials make any concrete conclusions difficult. However, the beneficial effects observed in this review are encouraging and should stimulate further research.

1. Introduction

The World Health Organisation has stated that, since 1990, more people worldwide have died from coronary heart disease (CHD) than any other cause [1]. Further, they reported that 80% to 90% of people dying from CHD had one or more major risk factors associated with lifestyle.

In the UK, more than 90,000 deaths per year are due to CHD, and although death rates are falling they are still among the highest in western Europe [2].

Cardiac rehabilitation (CR) programmes were initiated in the 1960s when the benefits of mobilisation and physical activity (PA) following lengthy hospital stays for CHD became known [3]. Since then, secondary prevention has become an essential aspect of care of the patient with CHD [4]. Research has shown that lifestyle change, including PA, a healthy diet, and smoking cessation, alters the course of CHD [5–7], and so disease prevention measures have been designed to focus on a range of lifestyle factors. Indeed, cardiac rehabilitation and secondary prevention programmes have developed from focusing on exercise alone to becoming multidisciplinary and encompassing baseline patient assessments, nutritional counselling, risk factor management (i.e., lipids, hypertension, weight, diabetes, and smoking), psychosocial and vocational counselling, and PA advice and exercise training, in addition to the appropriate use of cardioprotective drugs [4].

Multidisciplinary measures are advocated by governments around the world, and in the UK the National Institute for Clinical Excellence (NICE) set out a series of guidelines in 2007 for care of patients who had had a myocardial infarction (MI) [8]. The guidelines covered secondary prevention in primary and secondary care and were not focused solely on lifestyle interventions. They did, however, incorporate PA, diet, smoking, and drug therapy and were based on systematic reviews of the best available evidence. Priority

recommendations, considered to have the most important effect on patient care and outcomes, included that on discharge from hospital every MI patient should have had a confirmed diagnosis of acute MI, results of investigations, future management plans, and advice on secondary prevention. Also, NICE highlighted the importance of advice being given regarding regular PA in the form of 20–30 minutes of exercise per day to the point of slight breathlessness. Patients should also be advised to stop smoking, eat a Mediterranean style diet rich in fibre, fruit, vegetables, and fish, and follow a treatment regime with a combination of ACE (angiotensin-converting enzyme) inhibitors, aspirin, beta-blockers, and statins.

However, despite the evidence that positive lifestyle changes bring about improved outcomes, results from a number of secondary prevention initiatives have been disappointing. In a systematic review of multidisciplinary secondary prevention programmes McAlister et al. [9] reported that although some beneficial impact was achieved on processes of care, morbidity, and mortality, questions remained regarding the duration and frequency of interventions and the best combination of disciplines within an intervention.

The EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) surveys by the European Society of Cardiology have shown that the adoption of cardiovascular disease prevention measures as part of daily clinical practice was wholly inadequate [10] and that unhealthy lifestyle trends are continuing. The authors commented on the difficulty experienced by adults in changing behaviour despite having a life threatening disease and that continued professional support was imperative if this was to be achieved.

Few previous reviews of secondary prevention interventions have been published. McAlister et al. [9] carried out a systematic review of RCTs of secondary prevention interventions, published in 2001, and analysed 12 studies. Jolliffe et al. [11] analysed only exercise interventions in secondary prevention, and Rees et al. [12] reviewed psychological interventions. To our knowledge no comprehensive systematic review has been undertaken since 2001 of the effects of diet, exercise, and other lifestyle factors in the secondary prevention of CHD. We therefore performed a systematic review of randomised controlled trials to determine the effectiveness of lifestyle interventions for the secondary prevention of CHD.

2. Methods

This was a systematic review carried out using Cochrane Collaboration methodology [13].

2.1. Participants. We included male and female adults of all ages (aged 18+) with a diagnosis of CHD. Patients included those who had experienced a myocardial infarction (MI), coronary artery bypass graft (CABG), or percutaneous transluminal coronary angioplasty (PTCA) and those with angina pectoris and coronary artery disease defined by angiography. For the purposes of this review we excluded patients who had had a heart transplant, heart valve surgery, or heart failure, unless it was clearly specified that the cause related to CHD.

2.2. Interventions. We have included interventions with a lifestyle and/or behaviour change focus designed for the secondary prevention of CHD, incorporating one or a combination of exercise and diet. Interventions may be categorized as follows.

(1) Dietary.

(2) Exercise.

(3) Psychological.

(4) Educational.

(5) Multifactorial.

(6) Organisational (e.g., case management).

2.3. Exclusions. We have excluded from this review studies which were not randomized controlled trials, focused on primary prevention, involved patients with multiple diseases and/or outcomes which were related to diseases other than CHD, involved patients in a hospital in-patient setting, focused on drug therapy, had short (less than three months) or no follow-up, or reported outcomes which were not the focus of this review (see "Types of outcome measures" section) such as depression, cost-effectiveness, or service delivery.

2.4. Study Duration. Trials were included in this review if they reported a minimum postintervention follow-up of three months to allow some change to take place.

2.5. Settings. For the purposes of this review, interventions have been considered to have been delivered in primary care according to the definition of primary care as stated by the Committee on the Future of Primary Care at the Institute of Medicine in the United States: "Primary care is the provision of integrated, accessible healthcare services by clinicians who are accountable for addressing a large majority of personal healthcare needs, developing a sustained partnership with patients, and practicing in the context of family and community" [14]. Interventions are delivered in primary care by clinicians who are "generally considered to be physicians, nurse practitioners and physical assistants" and "a broader array of individuals in a primary care team" [14]. In the care of CHD patients, the primary care team may include general practitioners, practice nurses, community pharmacists, community and public health nurses, dieticians, occupational therapists, and physiotherapists.

(i) Interventions have been included in the review if they have been delivered in primary care or community settings by primary care clinicians or clinicians whose normal roles may be within secondary care, for example, community hospitals, or tertiary care, for example, general hospitals.

(ii) We have excluded from this review studies of interventions undertaken primarily within secondary or tertiary care settings by clinicians or care teams whose relationship with patients is not long term or ongoing.

2.6. Comparators. In the included studies, the comparators are "normal care" or "usual care," meaning standard clinical care or standard care given by a general practitioner (GP).

2.7. Types of Outcome Measures. All or any number of the following.

Primary Outcomes

(i) All-cause mortality.

(ii) Cardiac mortality.

(iii) Nonfatal cardiac events.

(iv) Hospital admissions (cardiac related/and all-cause if available).

Secondary Outcomes

(i) Diet (e.g., measured by fibre, fruit, and veg quantity).

(ii) Exercise (e.g., frequency, duration).

(iii) Blood pressure (BP); systolic BP (SBP); diastolic BP (DBP).

(iv) Blood lipid levels (high density lipoprotein cholesterol (HDL-chol), low density lipoprotein cholesterol (LDL-chol)).

(v) Smoking behavior.

(vi) Health related quality of life (QOL).

(vii) Self efficacy.

(viii) Medication adherence.

Only outcomes measured using a validated instrument were included.

2.8. Search Methods for Identification of Studies. We searched electronic databases Medline, Cinahl, and Embase for English language randomized trials in humans published since 1990. The search method for Medline is detailed below; it was modified as appropriate for Cinahl and Embase. Reference lists of review articles were also searched.

2.9. Medline Search Method. Selecting an Advanced Ovid search, the keyword "lifestyle" was inserted and the box ticked to select "Map term to subject heading." After selecting "Search" a new page was presented entitled "Mapping Display." Options indicating the Subject Headings "Life Style" and "lifestyle.mp. search as keyword" were chosen and "Continue" selected. This allowed further keywords to be entered.

The same process was followed for the keywords "exercise," "physical activity," and "diet." In each case only the keyword as a subject heading and as a keyword were selected on the Mapping Display page.

A fifth search was commanded by using all four keywords above separated by the Boolean operator "OR." This was done by selecting "click to expand" the "Search History" box, ticking each of the four boxes relating to the keywords, and selecting "Combine selections with OR."

A sixth search term "secondary prevention" was added as a keyword in same way as above. A seventh "coronary heart disease" was inserted, then its abbreviation "CHD" and four conditions related to it and their abbreviations, where appropriate, all as separate keywords: "myocardial infarction," "MI," "coronary artery bypass graft," "CABG," "percutaneous transluminal coronary angioplasty," "PTCA," and "angina pectoris." This group incorporating coronary heart disease and related conditions involved a total of nine separate searches, and they were together inserted as a 16th search, with each term separated by "OR." This was done, as above, by expanding the search history, selecting the relevant boxes beside keywords and selecting "Combine selections with OR."

The three components of the search were put together in the following way.

On the search history page, search five was selected by clicking on the box beside it (Lifestyle.mp. or Life Style/OR Exercise.mp. or Exercise/OR Physical activity.mp. OR Diet/or diet.mp.). Search six was then selected (Secondary prevention.mp. or Secondary Prevention/), and search 16 (Coronary heart disease.mp. or Coronary Disease/OR CHD.mp. OR Myocardial infarction.mp. or Myocardial Infarction/OR MI.mp OR Coronary Artery Bypass/or coronary artery bypass graft.mp. OR CABG.mp. OR Percutaneous transluminal coronary angioplasty.mp. or Angioplasty, Transluminal, Percutaneous Coronary/OR PTCA.mp. OR Angina pectoris.mp. or Angina Pectoris/). The option "Combine selections with AND" was selected.

This gave search 17. Search 17 was selected by ticking the box, and limits were imposed in an effort to narrow the search. Below the search results, within the "Limits" options, "English language," "Humans," and "Publication Year-1990 to Current" were selected. "Additional Limits" was then selected, search 17 was selected, and in the "Age Groups" options "All Adult (19 plus years)" was selected. No other limits were imposed. Then, "Limit A Search" was selected.

To refine the search further, terms relating to a randomized controlled trial study design were inserted. The terms entered were randomized controlled trial.mp. or Randomized Controlled Trial/, controlled clinical trial.mp. or Controlled Clinical Trial/, random allocation.mp. or Random Allocation/, double blind method.mp. or Double-Blind Method/, single blind method.mp. or Single-Blind Method. Each of these terms was combined with "OR," giving search 24.

Selecting search 18 and search 24, and combining them with "AND" gave the final selection. The Medline search strategy is detailed in the Appendix.

2.10. Data Analysis. From the searching, titles and abstracts were screened by two reviewers (MC, JC), and potentially relevant references were retrieved. The two reviewers (MC,

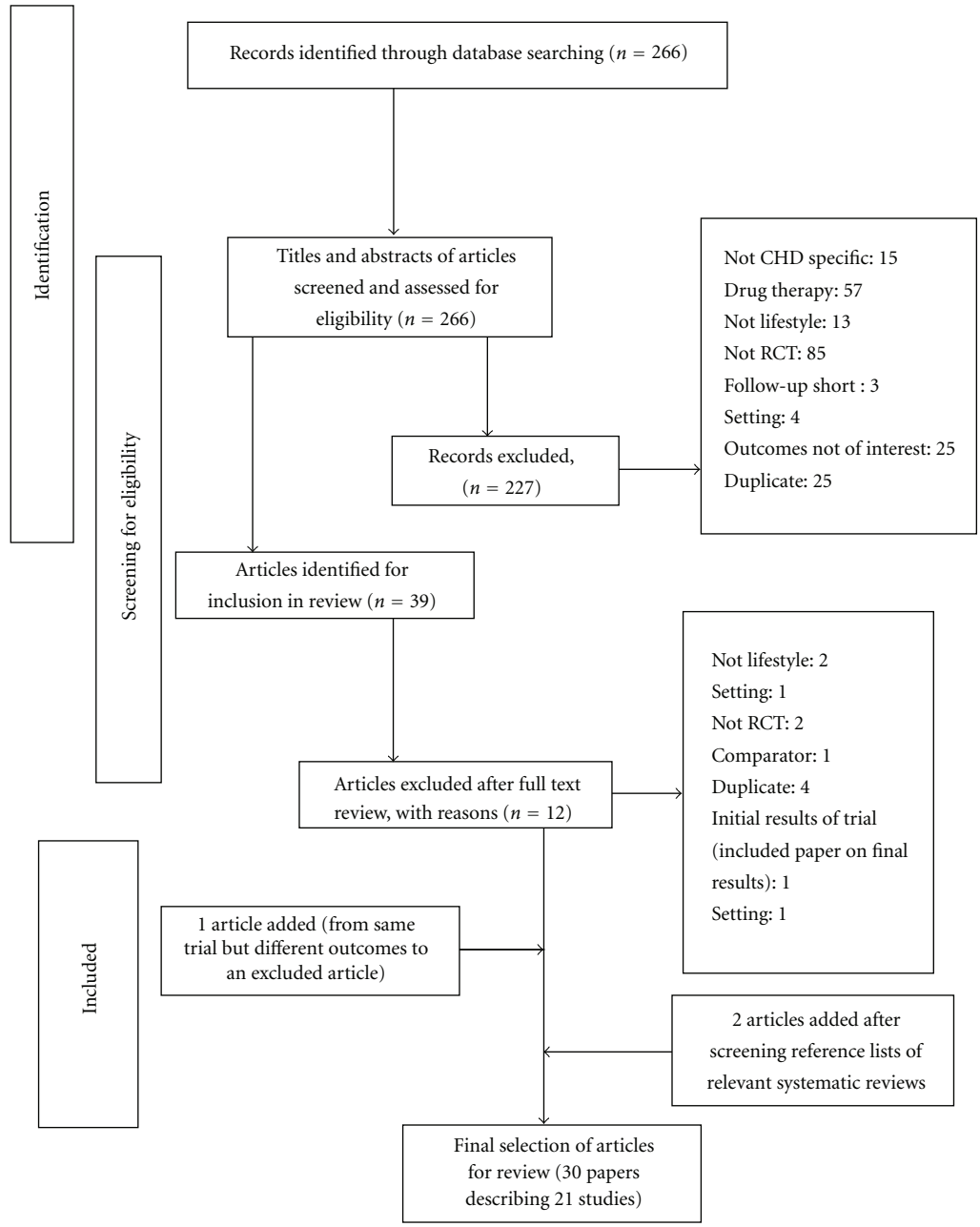

Figure 1: Screening and selection of studies of interventions for secondary prevention of coronary heart disease.

JC) then independently selected trials to be included in the review. Reference lists of relevant systematic reviews were also screened for potential papers to include.

After the final selection of trials was agreed upon, data including study characteristics, outcome measures and results were extracted.

In addition, the quality of trials was assessed in relation to randomization method, loss to follow up, intention to treat analyses, and blinding measures.

Dichotomous outcomes for each study have been expressed as risk ratios, where appropriate, and 95% confidence intervals (CIs). Meta-analyses were performed using random effects models, and data were presented as forest plots using Revman software [15]. We were only able to perform meta-analysis on three outcomes—total mortality, cardiovascular mortality, and nonfatal cardiac events.

Continuous variables have been expressed as the difference between intervention and control groups at study completion and the standard deviation difference where reported.

3. Results

3.1. Study Selection and Evaluation. Figure 1 shows the selection, screening, and identification of studies for this review. Of the 266 papers originally identified through

searching the three electronic databases, we identified 39 that were potentially eligible for inclusion, and full text versions of these studies were retrieved and assessed. Twelve of the 39 papers were excluded because they included diseases other than CHD, were drug trials, did not focus on lifestyle, were not randomized controlled trials, had a short follow-up period, were conducted within a hospital in-patient setting, had outcomes which were not of interest, or were retrieved more than once from the three search engines. Two papers were added after screening reference lists of relevant systematic reviews, and one trial was added which reported different outcomes of an identical study which emerged in our searches (Figure 1).

3.2. Description of Studies. Table 1 shows summary data of 30 papers from the 21 randomised controlled trials (RCTs) found to be eligible for this review [16–45]. We have presented them in the six categories described in the "Methods" section (exercise, dietary, psychological, educational, multifactorial, and organisational). The category which had the largest number of trials was multifactorial (10 in total). We also found one which focused on exercise only, one dietary intervention, three which had a psychological approach, four educational, and two organisational.

In all the trials except where stated, patients randomised to the control group received usual care, which was not defined by every study but usually meant standard clinical care or standard care given by a GP.

3.2.1. Study Characteristics. The studies varied greatly in terms of sample size, duration, and intervention elements; however all involved patients of a similar age group (older adults) with CHD.

The sample size of trials ranged from 48 [41] to 3241 [21], and study duration ranged from three months [19, 43] to four [33] and five years [41]. Follow-up analyses varied too, ranging from three months [19] to 15 years [45].

3.2.2. Settings. We found much variation in study setting. Astengo et al. [16] reported a home-based exercise intervention while two studies incorporated initial short residential stays to deliver an intensive educational programme. Lisspers et al. [26] conducted a four-week stay at an intervention unit located in a rural part of northern Sweden, followed by a structured 11-month programme consisting of self-recording of lifestyle behaviours and contact with the patients' personal coaches. It was not clear whether the intervention unit was part of a hospital. Ornish et al. [41] organised a week-long residential stay at a hotel to educate patients on diet, exercise, and stress, followed by twice-weekly group support meetings for five years. The Vestfold Heartcare Study Group [28] conducted an initial six-week "Heart School" at a hospital rehabilitation centre, although it was unclear whether this was residential. Heart School involved physiotherapist-led PA, stress reduction education and lifestyle counselling followed by nine weeks of twice-weekly exercise, and then meetings every three months for two years. No other trial contained a residential element.

3.2.3. Intervention Intensity. Some studies were of intensive interventions. Salminen et al. [25] delivered nurse-led lectures, lasting up to two hours each, once a month for 16 months. In addition, eight group meetings were organised throughout this period, six exercise sessions, and three social events.

Less intensive programmes, in which patients were encouraged to self-manage their lifestyle behaviour change, included those reported by Murphy et al. [17] and Cupples and McKnight [22, 23], in which patients were seen every four months.

Another less intensive intervention, the Lyon Diet Heart Study [32, 33], involved a one-hour education session with a cardiologist and dietician, followed by a repeat visit at eight weeks and annually thereafter.

3.2.4. Professional Involvement. The interventions included in this review involved a range of clinical and other healthcare staff including doctors, nurses, physiotherapists, psychologists, dieticians, and social workers. Seven of the 21 trials were led by nurses, mainly based in primary care. De Lorgeril et al. [32, 33] reported a trial conducted by a cardiologist and dietician. Four studies were GP-led, one conducted by a physiotherapist and one nutritionist-led. Other studies involved a variety of professional input.

3.3. Risk of Bias in Included Studies. The methodological quality of the included studies is presented in Table 2. The quality of the trials, in terms of the method of randomisation, whether groups were similar at baseline, losses to follow up, whether intention to treat analyses were used and blinding of outcome assessors, is as reported in the papers.

In seven of the 21 original studies (excluding follow-up papers), the randomisation method was not clearly described. In six of these trials, the method was not stated at all [16, 25, 26, 39, 43, 45]. The majority of the remaining studies described various randomisation techniques including the use of computer-generated random numbers, random numbers tables, and sealed envelopes. Lewin et al. [29] used block randomisation, while Carlsson [42] allocated patients in groups of 20. Murphy et al. [17] used cluster randomisation because their intervention was aimed to alter practitioners' behaviour which could contaminate their interactions with control patients.

Loss to follow up was not reported by some authors. Where it was reported, it was defined differently. Some authors included as losses to follow up deaths and withdrawals due to poor health, while others defined it as people who could not be accounted for or contacted at follow-up. Follow-up as a quality marker relates only to original studies and varied considerably for longer-term follow-up studies as would be expected.

Thirteen of the 21 studies stated that analyses were conducted using intention to treat principles. The Vestfold Heartcare Study Group [28] used the last recorded value of a variable from the previous visit if there were missing data.

Only seven out of 21 studies reported that outcome assessors were blind to group allocation. Overall, the quality

Table 1: Studies (all RCTs) included in analysis of secondary prevention programmes in coronary heart disease.

Source	Study population	Mean age (years)	% Men	Outcomes	Follow-up	Intervention
Exercise						
Astengo et al. [16] (2010), Sweden	62 patients with stable angina who had percutaneous coronary intervention (PCI).	Intervention (I) group ($n = 32$): 62 (SD 7); Control (C) group ($n = 29$): 65 (8).	I: 79% C: 76%	PA (cycle ergometer test), glucose, and lipid metabolism.	At completion of 8-month intervention.	8-month intervention: I group patients exercised at home on a bicycle ergometer for ≥30 minutes on ≥5 days/week of 250 day (eight months) study period; resistance exercises; monthly motivational meetings with physiotherapist.
Dietary						
De Lorgeril et al. [32] (1996), France	605 subjects <70 years who had survived a MI within 6 months of enrolment.	I ($n = 302$): 53.5. C ($n = 303$): 53.5.	I: 89.4%; C: 92.1%	All-cause and cardiovascular (CV) mortality, nonfatal CV events, diet (24 hour diet recall, Food Frequency Questionnaire).	27 months. De Lorgeril et al. [33] (1999): 46 months	5-year intervention: initial 1-hour advice session from research cardiologist and dietician to adopt Mediterranean type diet of more bread, root and green vegetables, more fish, less meat, fruit every day and butter and cream replaced with margarine; patients seen at 8 weeks from baseline and annually thereafter.
Psychological						
Lewin et al. [29] (2002), UK	142 patients with angina diagnosed within previous 12 months randomised to Angina Plan or educational session.	I ($n = 68$): 66.7 (9.4); C ($n = 74$): 67.6 (9).	I: 57%; C: 62%.	Frequency of angina attacks, physical limitations (Seattle Angina questionnaire), anxiety, depression, use of drugs.	At completion of 6-month intervention.	6-month intervention: nurse-led Angina Plan: 70 page "workbook" and audio-taped relaxation programme introduced to patient and partner during a 30–40 minute structured interview; nurse sought to correct any misunderstanding of illness. Risk factors discussed; how to reduce these through goal setting and pacing; patients asked to practice relaxation using the tape each day. Nurse contacted patient by phone at end of weeks 1, 4, 8, and 12 and praised the achievement of reaching goals, discussed extending goals.
Lisspers et al. [26] (1999), Sweden	87 patients with at least 1 significant coronary stenosis suitable for PCI and at least 1 additional clinically insignificant coronary lesion.	I ($n = 46$): 53 (7); C ($n = 41$): 53 (7).	I: 80%; C: 88%.	CV mortality, nonfatal CV events, diet (questionnaire), PA (questionnaire), smoking (questionnaire), QOL (questionnaire:AP-QLQ).	At completion of 12-month intervention. Lisspers et al. [27] (2005): 24, 36 and 60 months from baseline.	12-month intervention: nurse-led. 4-week residential stay at intervention unit: intense group and individual health education and training; stress management, diet, exercise, smoking; followed by 11-month structured maintenance phase; regular contact with specially assigned nurse through mail and phone calls. Personal lifestyle goals set, diaries kept of everyday lifestyle behaviour.

Table 1: Continued.

Source	Study population	Mean age (years)	% Men	Outcomes	Follow-up	Intervention
Salminen et al. [25] (2005), Finland	227 patients with CHD.	I ($n = 118$): males 72.5 (5.3), females 75.5 (6.6); C ($n = 109$): males 72.6 (5.5), females 75.3 (6.5).	I: 49%; C: 50%.	Diet (patient interviews), PA (self report), smoking (patient interviews), BP, total, LDL and HDL cholesterol.	At completion of 16-month intervention.	16-month intervention: nurse-led. 16 lectures: 90–120 minutes each; prevention of CHD, diet and weight control, exercising, financial concerns. 8 group discussions: small groups, 8 meetings 90–120 minutes each; treatment of elevated serum lipids, healthy eating, CHD risk factors. 6 light exercise sessions: 60–90 minutes each; walking, gymnastics, relaxation. 3 social activities: picnic at national park, visit to spa, 24-hour cruise.
Educational						
Carlsson et al. [42, 43] (1997), Sweden	50–70 years with acute MI, CABG or PTCA less than 2 weeks before study.	Carlsson A [42]: 121 AMI patients: I = 61; C = 60; mean age 62.1.56 CABG patients: I = 27; C = 29; mean age 61.5. Carlsson B [42]: 142 AMI patients: I = 75; C = 67; mean age 62.0. 63 CABG patients: I = 31; C = 32; mean age 61.3. Carlsson C [43]: 168 patients with AMI: I ($n = 87$): 62.2; C ($n = 81$): 61.9.	A: AMI patients: 75%; CABG patients: 84%. B: AMI patients: 77%; CABG patients: 84%. C: 75%	Diet (questionnaire), PA (questionnaire), smoking (questionnaire), total, LDL and HDL cholesterol, use of drugs.	At completion of 1-year intervention.	3-month nurse-led education programme: individual and group counselling: 9 hours/patient: 1.5 hours smoking cessation, 5.5 hours diet, 2 hours PA. Exercise training: 2/3 times/week for 10–12 weeks, 40 minutes PA including interval training with cycling and jogging. Education continued by nurse for 1 year. Individual exercise schedules.
Cupples and McKnight [22] (1994), UK	688 patients who had had angina for ≥6 months.	I ($n = 342$): mean age 62.7 (7.1). C ($n = 346$): 63.6 (6.8).	I: 59.4% C: 59.2%	All-cause and CV mortality, diet (Department of Health and Social Services), PA (patient interviews), smoking (patient interviews), BP, cholesterol, QOL, use of drugs.	At completion of 2-year intervention. Cupples and McKnight [23] (1999): 5 years from baseline.	Patients given practical advice relating to CV risk factors and reviewed by health visitors at four monthly intervals for two years.

Table 1: Continued.

Source	Study population	Mean age (years)	% Men	Outcomes	Follow-up	Intervention
Heller et al. [44] (1993), Australia	450 subjects admitted to hospital with suspected MI.	I ($n = 213$): 59 (8); C ($n = 237$): 58 (8).	I: 76% C: 68%	Nonfatal CV events, hospital admissions, diet (fat intake), PA (questionnaire), total cholesterol, QOL (Oldridge et al. 1989), use of drugs.	At completion of 6-month intervention.	6-month intervention: GP-delivered educational intervention. Initial letter to GP on benefits of aspirin and beta-blockers plus first of 3 posted packages for patient. Package 1: Step 1 of "Facts on Fat" kit; quiz, patient target for fat reduction; walking programme and smoking cessation advice. Package 2: Steps 2 and 3; questions on previous week's PA. Package 3: Steps 4 and 5; information on local walking groups. Monthly newsletters posted over next 4 months containing recipes, dietary and PA information, and National Heart Foundation booklet. Two telephone calls attempted, patients urged to telephone if requiring information.
Southard et al. [31] (2003), USA	104 subjects with CHD, congestive heart failure or both.	I ($n = 53$): 61.8 (10.6); C ($n = 51$): 62.8 (10.6).	I: 68% C: 82%	Nonfatal CV events, diet (MEDFICTS dietary survey), PA (min/wk), BP, total, LDL and HDL cholesterol, triglycerides.	At completion of 6-month intervention.	6-month intervention: Internet based educational programme for nurse case managers to provide risk factor management training and advice. Patients accessed internet programme at least once a week for 30 minutes, communicating with case manager via website's internal email system, completing educational modules (with interactive multiple choice self-tests), entering data (at any time) to monitor progress. Optional discussions with other participants, rewards given (worth \$0.50 to \$1.50) for active participation on website. Dietician available to analyse 24 hour diet recalls. Case managers and dietician also available via telephone and post if necessary.
Multifactorial						
Allen et al. [30] (2002), USA	228 patients with hypercholestero-laemia who had CABG or PCI.	I ($n = 115$): 61.1 (10.3); C ($n = 113$): 59.6 (9.6).	I: 70%; C: 73%.	Diet (Block Health Habits and History), PA (Aerobics Centre questionnaire), total, HDL, and LDL cholesterol, triglycerides.	At completion of 1-year intervention.	1-year intervention: nurse case management: plan devised 4–6 weeks after hospital discharge including lifestyle counselling and review of drug therapy. Follow-up telephone calls to reinforce counselling and adjust drug therapy (each patient contacted average 7 times during follow-up year); ongoing plan sent regularly to doctor. Diet advice: <30% of total energy as fat, <7% saturated fat, <200 mg per day cholesterol; PA: participation in moderate intensity home-based exercise programme; referral to CR; smoking cessation advice and relapse prevention.

Table 1: Continued.

Source	Study population	Mean age (years)	% Men	Outcomes	Follow-up	Intervention
Campbell et al. [34] (1998)A (Heart)	1343 patients with CHD. At 1 yr: I = 593; C = 580.	66	58.2%	Diet (Dietary Instrument for Nutrition Education (DINE) questionnaire), PA (Health Practitioners Index Questionnaire), smoking (Health Practitioners Index Questionnaire), BP, lipid management, aspirin management.	At completion of 1-year intervention.	1-year intervention: Nurse-led clinics to promote medical and lifestyle aspects of secondary prevention. Clinics: 4 stages: (1) Review of symptoms to identify poor control and refer accordingly. (2) Review of drug treatment; encourage aspirin use. (3) BP and lipid assessment. (4) Assessment of exercise, diet, smoking, and behaviour changes suggested. Follow-up visits every 2–6 months; 20 minutes.
	Murchie et al. [36] (2003) A: at 4-year follow-up: I = 564; C = 534.	I: 65.4 (8.2); C: 65.7 (8.6).	As above	As above plus: All-cause mortality, CV events.	4 years from baseline.	As above.
	Campbell et al. [35] (1998) B: as Campbell A	As Campbell A	As Campbell A	QOL (Short Form (SF) 36 questionnaire)	At completion of 1-year intervention.	As Campbell A
	Murchie et al. [37] (2004) B: as Murchie A	As Murchie A	As Murchie A	QOL (SF 36)	4 years from baseline	
	Delaney et al. [38] (2008): at 10-year follow-up 531 of 1343 original cohort had died.			All-cause mortality and coronary events (nonfatal MIs and coronary deaths).	10 years from baseline.	
Giallauria et al. [18] (2009), Italy	52 patients with acute myocardial infarction (AMI).	I ($n = 26$): 58.2 (7.8); C ($n = 26$): 57.4 (9.7).	I: 85%; C: 85%.	Nonfatal CV events, PA (cycle ergometer test), BP, total, LDL and HDL cholesterol, triglycerides.	At completion of 2-year intervention.	2-year intervention: educational and behavioural; individual and group. Each patient given booklet on exercise, diet and smoking cessation, and ideal targets. Monthly hospital visits: dietary advice, reinforcement of healthy lifestyles, exercise training session to 60–70% of VO_2 peak.
Gianuzzi et al. [21] (2008), Italy	3241 patients with recent MI (within past 3 months).	57.9 (9.2)	86.3%	All-cause and CV mortality, nonfatal CV events, diet (knowledge/habits), PA (questionnaire), smoking (questionnaire), BP, total, HDL and LDL cholesterol, self/stress management, use of drugs.	At completion of 3-year intervention; Data collected at 6 months, 1, 2 and 3 years.	3-year intervention: multifactorial, continued educational and behavioural; monthly sessions from months 1 to 6, then every 6 months for 3 years. Each session: 30 minutes supervised aerobic exercise; lifestyle and risk factor counselling lasting at least 1hour; reinforcement of preventive interventions. Booklet on how to deal with exercise, diet, smoking cessation, and stress management. Targets: cease smoking, adopt Mediterranean diet, increase PA to at least 3hours/week at 60–75% of mean max heart rate, maintain BMI of <25, BP 140/85, total cholesterol <200 mg/dL, LDL chol <100 mg/dL, blood glucose <110 mg/dL. Drug treatments positively recommended.

Table 1: Continued.

Source	Study population	Mean age (years)	% Men	Outcomes	Follow-up	Intervention
Hamalainen et al. [45] (1995), Finland	375 subjects with MI.	I ($n = 188$): mean age men 53.4, women 58.8. C ($n = 187$): mean age men 53.0, women 58.4.	I: 80% C: 80%	All-cause and CV mortality, PA (cycle ergometer test), smoking (patient interviews), BP, cholesterol, triglycerides.	15 years from baseline.	3-year intervention: optimal medical care, physical activation, antismoking, dietary, psychosocial counselling led by social worker, psychologist, dietician, physiotherapist, and doctors. Intervention most intensive for 3 months after AMI, close contacts with team maintained over 3 years.
Murphy et al. [17] (2009), Northern Ireland and Republic of Ireland	903 subjects with CHD recruited from 48 general practices.	I ($n = 444$): 68.5 (9.3); C ($n = 459$): 66.5 (9.9).	I: 70%; C: 70%.	BP, total cholesterol, hospital admissions, QOL (SF 12), diet (DINE questionnaire), PA (Godin questionnaire), smoking (Slan National Survey of Health and Lifestyles in Ireland).	At completion of 18-month intervention.	GP and nurse-led tailored care plans for practices: training in prescribing and behaviour change, administrative support, quarterly newsletter; Tailored care plans for patients: motivational interviewing, goal setting, target setting for lifestyle change, info booklet given to each patient, progress reviewed every 4 months. (Social cognitive theory used to develop training in behaviour change, design patient info booklet, and inform development of tailored patient care plans.)
Ornish et al. [41] (1998), USA	48 patients with moderate to severe CHD.	I ($n = 20$): 57.4 (6.4); C ($n = 15$): 61.8 (7.5).	I: 100% C: 80%	CV mortality, nonfatal CV events, hospital admissions, diet (diaries), PA (questionnaire on type, frequency, duration), BP, total, LDL and HDL cholesterol, triglycerides, apolipoproteins.	At completion of 5-year intervention.	5-year intervention: week long educational residential stay at hotel (Ornish et al., 1990).Group support meetings, 4 hours twice a week. Diet: low fat vegetarian, for at least a year: fruit, vegetables, grains, legumes, soybean products; no animal products except egg white and 1 cup/day of nonfat milk or yoghurt. Stress management techniques; advised at least 1 hour/day; audiocassette tape to assist. Exercise: individual prescription according to baseline treadmill test results, mainly walking; at least 3 hours/week, 30 minutes per session. Clinical psychologist-led group discussions: social support to encourage adherence.
Redfern et al. [19] (2008) A, Australia	144 acute coronary syndrome (ACS) survivors not accessing standard cardiac rehabilitation (CR).	I ($n = 72$): 62 (1.6); C ($n = 72$): 67 (1.3).	I: 74%; C: 75%.	PA (Physical Activity Readiness Questionnaire (PARQ)), smoking (self report/Airmet Scientific Micro-smokanalyser), BP, total cholesterol.	At completion of 3-month intervention. Redfern et al. [20] (2009) B: 12 months from baseline	GP-led behaviour change intervention; 1 hour initial consultation, 3 months of 5 phone calls (Redfern et al., 2006) for risk factor education, assertiveness training and assessment of lifestyle goals. Mandatory cholesterol lowering module, including healthy eating and pharmacological advice, and choice of 2 other modules including BP lowering, smoking cessation, and PA; choice of management options for risk factors including doctor-directed, such as a PA "script" from GP, hospital programme, for example, exercise class, individual programme, or self-help.

Table 1: Continued.

Source	Study population	Mean age (years)	% Men	Outcomes	Follow-up	Intervention
Vestfold Heartcare Study Group [28] (2003), Norway	197 subjects with acute MI, hospitalisation for unstable angina, PCI, or CABG.	I ($n = 98$): 54 (8); C ($n = 99$): 55 (8).	I: 81%; C: 83%.	Hospital admissions, diet (FFQ), PA (self-report/diaries), smoking (self-report), BP, total and HDL cholesterol, QOL (SF 36), use of drugs.	At completion of 2-year intervention.	2-year intervention: 6-week "heart school" in hospital: PA with physiotherapist: 15 minutes warm-up, 20 minutes walking, 10 minutes cool-down, 10 minutes stretching; advised to exercise on their own every day. Education sessions: twice a week, 2 hours each; dietary advice, smoking cessation, PA counselling, risk factor management, psychosocial management, medication, stress reduction; individual counselling. Followed by 9 weeks' organised PA twice a week at gym supervised by physiotherapist; level increased to jogging; group meetings every 3rd month throughout 2 year follow-up.
Wallner et al. [39] (1999), Austria	60 patients <70 years with angiographically documented CAD and stable angina pectoris; recruited after successful elective PTCA.	I ($n = 28$): 58 (8). C ($n = 32$): 60 (7)	I: 89%; C: 69%.	Nonfatal CV events, diet (7-day weighted food records), PA (Minnesota Leisure Time questionnaire), BP, LDL and HDL cholesterol.	Mean 26 months (range 18–31) after baseline.	12-month intervention: nutritionist-led. All patients at baseline: dietary and lifestyle advice: cholesterol 100–150 mg/day, fibre ≥25 g/day, PA ≥3 times/week for 30 minutes, smoking cessation. I group: 1-hour dietary advice sessions with nutritionist weekly during first month, every 2 weeks until month 3 then monthly until end of intervention.
Organisational						
Jolly et al. [40] (1999), UK	597 patients; 422 with MI and 175 with new diagnosis of angina.	I ($n = 277$): 63 (10); C ($n = 320$): 64 (10).	I: 68%; C: 74%.	Total cholesterol, BP, PA (questionnaire, walking test), smoking (questionnaire), BMI.	At completion of 1-year intervention.	Led by 3 specialist cardiac liaison nurses responsible for coordinating follow-up care, especially transfer of responsibility for care between hospital and GP. Liaison nurses provided support to practice staff by phone and visits to practice every 3–6 months. Practice nurses encouraged to attend training on behaviour change based on stages of change model. Each patient was given a patient held record, which prompted and guided follow-up (at approximately 4 to 6 month intervals).
Munoz et al. [24] (2007), Spain	983 subjects with MI, angina, or ischaemia within previous 6 years.	I ($n = 515$): 64.2 (9.8); C ($n = 468$): 63.6 (10.3).	I: 76.1%; C: 73.2%.	Total mortality, CV mortality, nonfatal CV events, PA (self report), BP, total, LDL and HDL cholesterol, QOL (SF 12), use of drugs.	At completion of 3-year intervention or until an endpoint occurred.	3-year intervention: Postal reminders to see GP every 3 months during 3-year follow-up. GPs strictly followed most recent guidelines on CV prevention, provide patients with healthy lifestyle advice including Mediterranean diet, PA and smoking cessation; adjusted treatments.

I: intervention; C: control

of many trials was poor with a majority not having blinded outcome assessors and many not describing the method of randomisation.

3.4. Effects of Interventions

3.4.1. All-Cause Mortality. Six studies reported total mortality and are presented in Figure 2. Overall, four studies showed benefits for intervention patients compared to controls in relation to total mortality. Because of the large differences in follow-up periods, we have used data from the studies which range from 3 to 5 years to allow easier comparison of studies. For all interventions except two, this constituted their study endpoint.

Murchie et al. [36] reported a significant survival effect for intervention patients compared to controls at their 4.7 year follow-up. Within the same study, Delaney et al. [38] reported that, at 10 years, the observed difference was no longer significant between the groups.

Hamalainen et al. [45] reported a significant survival effect for intervention patients compared to controls at their 4.7 year follow-up.

The I^2 test for heterogeneity combined with the Chi^2 nonsignificant P value suggests that the level of heterogeneity between studies is not important.

3.4.2. Cardiovascular Mortality. Eight studies reported cardiovascular mortality and are presented in Figure 3. Three studies showed significant survival effects. Data were collected at times ranging from 2 to 5 years. Delaney et al. [38] reported a 10-year follow-up study but we have presented their data collected at 4.7 years to allow for easier comparison with other studies. For the same reason we have used data reported by Hamalainen et al. [45] at three years of follow-up instead of the authors' results at 15 years.

The three studies reporting significant survival effects were Cupples and McKnight [22], two-year follow-up results from an educational intervention, De Lorgeril et al. [33], a Mediterranean diet study with four-year follow-up, and Hamalainen et al. [45], a trial of a multifactorial intervention.

Hamalainen et al. [45], who reported coronary mortality, also reported significant survival effects for intervention patients compared to controls in their 15-year follow-up study. Delaney et al. [38] reported CV and coronary deaths at both 4.7- and 10-year follow-up points. However, the mortality figures were combined with nonfatal MI to calculate a proportional hazard ratio. Murchie et al. [36], a paper from the same study at 4.7 years of follow-up, reported an adjusted hazard ratio of 0.76 for coronary events (coronary deaths plus nonfatal MIs) (0.58 to 1.00, $P = .049$).

The I^2 test for heterogeneity indicated a moderate level of heterogeneity across studies.

3.4.3. Nonfatal Cardiac Events. This was reported by nine studies. In Figure 4, we have presented data for major nonfatal events (MI, CABG, PCI, coronary angioplasty). Significant benefits for intervention patients compared to controls were shown by five studies. Four studies reported nonfatal events separately [21, 33, 41, 44] while five reported the number of patients who had an event.

Lisspers et al. [27] included mortality in "event" results, therefore although they reported figures for various events and mortality they did not report a separate statistic for nonfatal events. Delaney et al. [38] reported coronary events which included coronary deaths and nonfatal MIs; however separate figures for each variable were not reported.

Gianuzzi et al. [21] reported nonfatal stroke, heart failure, and angina data but none of the values was significant.

Lewin et al. [29] reported the frequency of angina attack in number of episodes per week. Intervention group patients had a reduction of three attacks per week compared to a reduction of 0.4 attacks among control subjects ($P = .016$).

In addition to nonfatal MI and coronary revascularisation, De Lorgeril et al. [33] reported a number of major and minor secondary endpoints. They calculated risk ratios for nonfatal AMI combined with CV deaths, major secondary endpoints (periprocedural infarction, unstable angina, heart failure, stroke, pulmonary embolism, peripheral embolism) combined with primary endpoints, and primary and major secondary endpoints combined with minor secondary endpoints (stable angina, post-PCTA restenosis, and thrombophlebitis). Separate risk ratios for nonfatal CV events were not reported.

In addition to MI, PTCA, and CABG, Ornish et al. [41] reported the frequency, duration, and severity of angina chest pain at one year and five years. One significant value out of three outcomes reported at the two different time points each was reported: chest pain severity (scale 1–7, baseline to one year: intervention group 1.5 (1.5) to 0.7 (1.2); control group 0.6 (0.8) to 1.4 (1.2); $P < .001$).

The I^2 test for heterogeneity indicated that there may be substantial heterogeneity across studies so results of this meta-analysis have to be interpreted with caution.

3.4.4. Hospital Admissions. Five studies reported results relating to hospital admissions. While there was an overall trend to reduced admissions in intervention groups, only one of these studies reported a significant reduction in intervention patients [17]. The data are presented in Table 3.

3.4.5. Lifestyle Risk Factors. Data relating to lifestyle risk factors for CHD–diet, PA, and smoking are presented in Table 4.

Table 5 shows a summary of lifestyle risk findings from our included studies. For each of the three areas of diet, exercise, and smoking, we have presented the number of studies reporting each outcome, the number of outcomes, and the numbers of significant and nonsignificant values.

Diet. Fifteen studies reported diet as an outcome, with a total of 51 outcomes. Of these, 39 showed significant benefits for intervention patients compared to controls in relation to dietary consumption. These included significant improvement in specific food intake, such as fat, fibre, sugar, and cholesterol [28, 30, 33, 34, 39, 41], diet score, diet

Table 2: Methodological quality of included studies.

Source	Randomisation method	Groups similar at baseline	Loss to follow up	Intention to treat analyses?	Assessors blind?
Exercise					
Astengo et al. [16] (2010)	Unclear. Method of randomisation not stated. Authors state randomised "to training group or control."	Yes Only significant difference was fasting glucose level (higher in intervention (I) group than control (C)).	None. Six patients (9.7%) had major clinical complications and did not complete study.	Unclear	Unclear
Dietary					
De Lorgeril et al. [32, 33] (1996, 1999)	Clear. Consecutive patients with first MI randomised. Inclusion based on modified Zelen design.	Yes Except: smokers (more in I group).	Not clear. Rate of withdrawal from follow-up reported: I = 8% C = 7% (De Lorgeril et al. [46], 1994)	Yes	Yes
Psychological					
Lewin et al. [29] (2002)	Clear. Eligible patients allocated to I or C group by block randomisation, stratifying for age and sex.	Yes	Not clear. 9 dropouts (6.3%), 1 did not return questionnaires (0.7%), and 2 died (1.4%).	Yes	Yes
Lisspers et al. [26] (1999)	Unclear. Method not stated/described.	Yes; Except C group: significantly higher proportion taking beta blockers.	Data missing from exercise tests (4 I patients, 4 Cs), and questionnaires (numbers not stated). 5-year follow-up (Lisspers et al. [27], 2005): data available from 28 intervention patients (39% loss) and 27 control (34% loss). Further detail not reported.	Unclear	Unclear
Salminen et al. [25] (2005)	Unclear. Method not stated/described. Authors stated that patients identified from longitudinal study data and randomly divided into intervention and control groups.	Yes	None. 12 did not wish to take part in study after randomisation (4.5%); 29 died (10.8%).	Unclear	Unclear
Educational					
Carlsson et al. [42, 43] (1997, 1998)	Unclear. Carlsson A and B [42]: patients randomised in groups of 20; no further detail on method given. Carlsson C [43]: patients admitted to coronary care unit who fulfilled inclusion criteria were randomised.	Carlsson A, B, and C: yes	Carlsson A, B, and C: unclear. Carlsson C: 4 (4.9%) of usual care patients lost to follow up; no data given for intervention patients. Authors reported figures for missing data relating to specific variables.	Carlsson A, B, and C: unclear.	Carlsson A, B, and C: unclear.
Cupples and McKnight [22] (1994).	Clear. Patients randomised to one of two groups. A health visitor opened an opaque, sealed, and numbered envelope containing the allocation which had been generated by a computer programme using random permuted blocks.	Yes	2 years: I: 25/342 (7.3%). C: 46/346 (13.3%); reasons given 5 years [23]: I: 92/342 (29.9%). C: 109/346 (31.5%); reasons given.	Yes	Yes

Table 2: Continued.

Source	Randomisation method	Groups similar at baseline	Loss to follow up	Intention to treat analyses?	Assessors blind?
Heller et al. [44] (1993)	Clear. Patients allocated to I or C groups according to name of GP. General practices stratified by number of doctors and randomly allocated to I or C.	Yes I = 213, C = 237: nos. not similar because randomisation was by GP.	Did not return follow-up questionnaires: I: 45/213 (21.1%) C: 30/237 (12.7%) (no further detail given)	Unclear	Unclear
Southard et al. [31] (2003)	Clear. Patients stratified by ethnic group, CR participation, and acute status, then allocated to I or C groups by computer generated random number.	Yes	4 (3.84%); reasons stated.	Yes	Unclear
Multifactorial					
Allen et al. [30] (2002)	Clear. Consecutive patients randomised with computerised schema.	Yes	Unclear. 158 out of 228 completed follow-up (31% loss); reasons for these losses given.	Yes	Unclear
Campbell et al. [34] (1998)	Clear. Random numbers tables used to centrally randomise patients (by individual after stratification by age, sex, and practice) to I and C groups.	Yes	Unclear. Available at 1-year analysis: I: 593 (88%) out of original total 673; C: 580 (87%) out of 670; reasons for loss given. Murchie et al. [36] (2003): available at 4-year follow-up analysis: I: 500 (74%); C: 461 (69%); reasons for loss given. Delaney et al. [38] (2008): available at 10-year follow-up: I: 385 (57%); C: 365 (54%). These figures include deaths but loss to follow up was reported as 62 patients (4.6%).	Yes	Unclear
Giallauria et al. [18] (2009)	Clear. Patients randomised 1 : 1 using computer generated randomisation.	Yes	None	Unclear	Unclear
Gianuzzi et al. [21] (2008)	Clear. Patients randomised 1-to-1; randomisation centrally determined by fax at coordinating secretariat using computerised algorithm.	Yes	154 (4.7%).	Yes	Yes
Hamalainen et al. [45] (1995)	Unclear. Consecutive patients hospitalised for AMI allocated to I or C group by stratified randomisation. No further detail on method given.	Yes	Unclear	Unclear	Unclear
Murphy et al. [17] (2009)	Clear. Practices: computer generated random numbers; patients: randomly selected at remote site, sent invitation in sequence from lists in random order.	Yes Except: different proportions in control and intervention groups admitted to hospital in previous 12 months. This was adjusted for in analysis.	None	Yes	Yes

Table 2: Continued.

Source	Randomisation method	Groups similar at baseline	Loss to follow up	Intention to treat analyses?	Assessors blind?
Ornish et al. [41] (1998)	Unclear. Method stated; not fully described. After angiography patients randomised using invitational design to minimise crossover, ethical concerns, nocebo effects, and dropout.	Yes Except C group had significantly higher levels of HDL-chol and apolipoprotein A-I.	20 (71%) intervention patients completed 5-year follow-up; 15 (75%) control patients.	Yes	Yes
Redfern et al. [19] (2008)	Clear. Consecutive patients randomised following blinded baseline assessment. Computer generated random allocation sequence was implemented using consecutively numbered envelopes.	Of 15 demographic and clinical characteristics, groups were similar in 9. Statistically different were European and Asian/African origin, employment status, CVD history, and CABG status.	1 (uncontactable). (4 withdrew, 3 died).	Yes	Yes
Vestfold Heartcare Study Group [28] (2003)	Clear. Patients randomised by use of preprepared sealed opaque envelopes containing details on group allocation. Patients opened envelopes so that their group allocation was revealed to them without previous knowledge of study investigators.	Yes	Unclear. Percentages attending follow-up meetings, keeping diaries and adhering to PA levels only given for I group.	Unclear: where there were missing data at 6 months and 2 years, the last recorded value of the variable from previous visit was used.	Unclear
Wallner et al. [39] (1999)	Unclear. Method of randomisation not stated/described.	Yes Except: statistically significant differences in number with previous MI (I group more), SBP (I group higher), exercise/day (I group more).	Unclear. Patients randomised: I = 28, C = 32. At 12 months, analyses performed in 25 I patients (89%), 13 C (40%) (only patients with complete data for 12 months were included at baseline) because all patients did not agree to complete lengthy questionnaires. Cardiological follow-up was completed in all patients recruited.	Yes	Unclear
Organisational					
Jolly et al. [40] (1999)	Clear. Practices randomised (before consent sought) to I or C after stratification by size of practice and distance from district general hospital.	Yes	10% in both groups; reasons given.	Yes	Unclear
Munoz et al. [24] (2007).	Clear. Primary care facilities allocated to I or C by random sequence generated by computer programme.	Yes Except: C group higher proportion had previous hypertension, peripheral vascular disease; higher proportion taking beta blockers, ACE inhibitors; higher BP; I group higher HDL-chol.	11 (1.1%). Also: Withdrew: 28 (2.8%); Unwilling: 2 (0.2%); Died: 59 (6%).	Yes	Unclear

I: intervention; C: control.

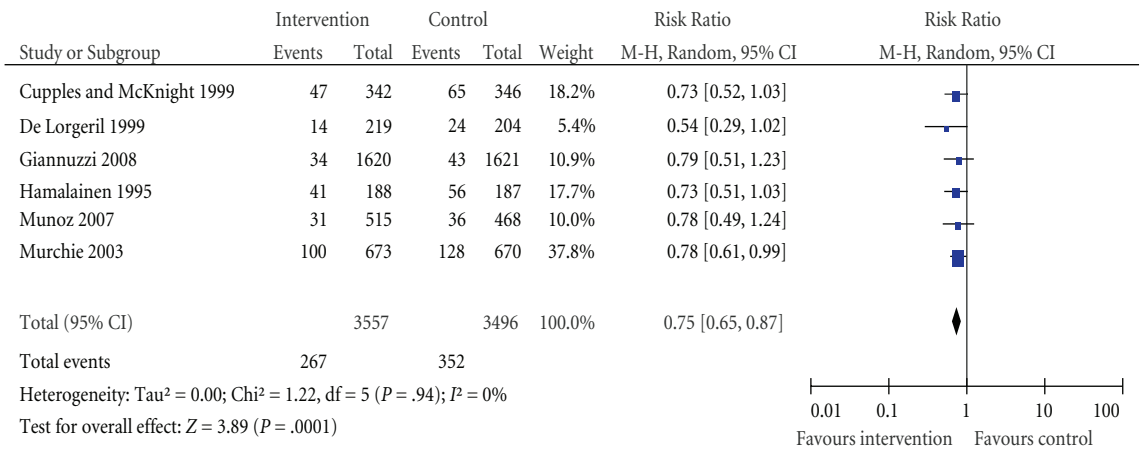

Figure 2: Effect of interventions on all-cause mortality: comparison of intervention versus control groups.

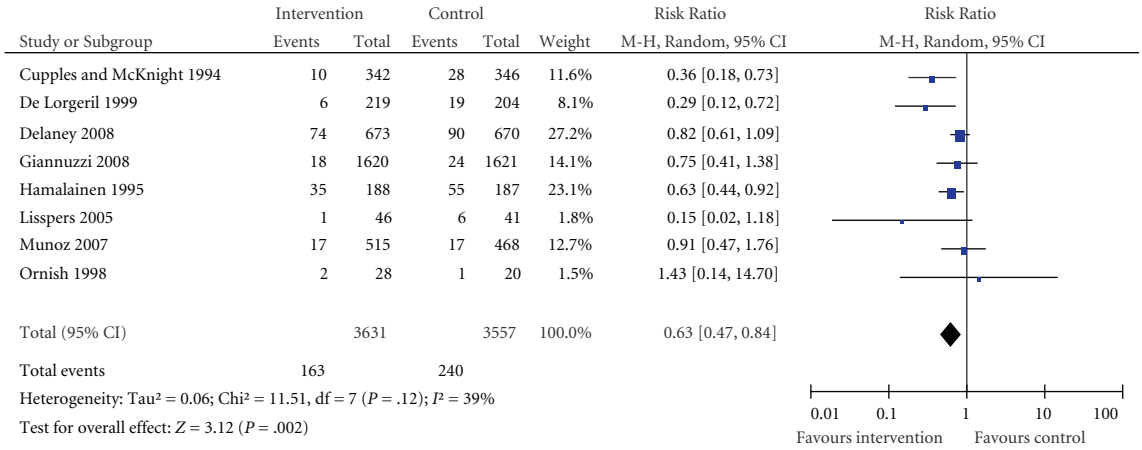

Figure 3: Effect of interventions on cardiovascular mortality: comparison of intervention versus control groups.

knowledge, and habits [21, 27, 44, 47], and for concern about dietary habits [43].

PA. Twenty-one studies incorporated PA, with 37 outcomes. Of these, 20 showed significant improvements for intervention patients compared to controls. These included significant improvements in maximal workload and VO_{2peak} [16, 18, 27]. Eleven studies used validated questionnaires or patient diaries [17, 20, 23–25, 28, 30, 34, 36, 39, 41]. Four conducted patient interviews or used questionnaires which were not reported as validated [21, 40, 43, 44]. Of these, eight studies reported significant improvements [20, 21, 23, 27, 28, 30, 34, 39].

Smoking. While all studies reported proportions of the study populations that smoked, only 13 studies reported smoking as an outcome and five of these reported significant reductions in smoking behaviours in the intervention groups [20, 21, 27, 28, 45]. Hamalainen et al. [45] reported a nonsignificant difference between intervention and control groups at one year, but significant at two and three years.

BP. Thirteen studies reported BP as an outcome, and five reported significant benefits for intervention compared to control patients [18, 20, 34, 39, 45]. Giallauria et al. [18] reported significant improvements in SBP and DBP at 12 months and 24 months. Redfern et al. [20] reported significant difference in SBP among intervention compared to control patients at three months and 12 months. Campbell et al. [34] collected BP data from medical records and classified it as being managed according to British Hypertension Society recommendations if the last recorded measurement was less than 160/90 mmHg or receiving attention. The significant difference between intervention and control groups at one year was no longer observed at four-year follow-up [36].

Wallner et al. [39] found significant improvements in SBP and DBP in intervention patients compared to controls. Hamalainen et al. [45] reported significant benefits for intervention compared to control patients relating to SBP and DBP at one, two, and three years but not at six or 10 years.

Total Cholesterol and/or Lipid Levels. These outcomes were reported by 19 studies and 12 demonstrated significant

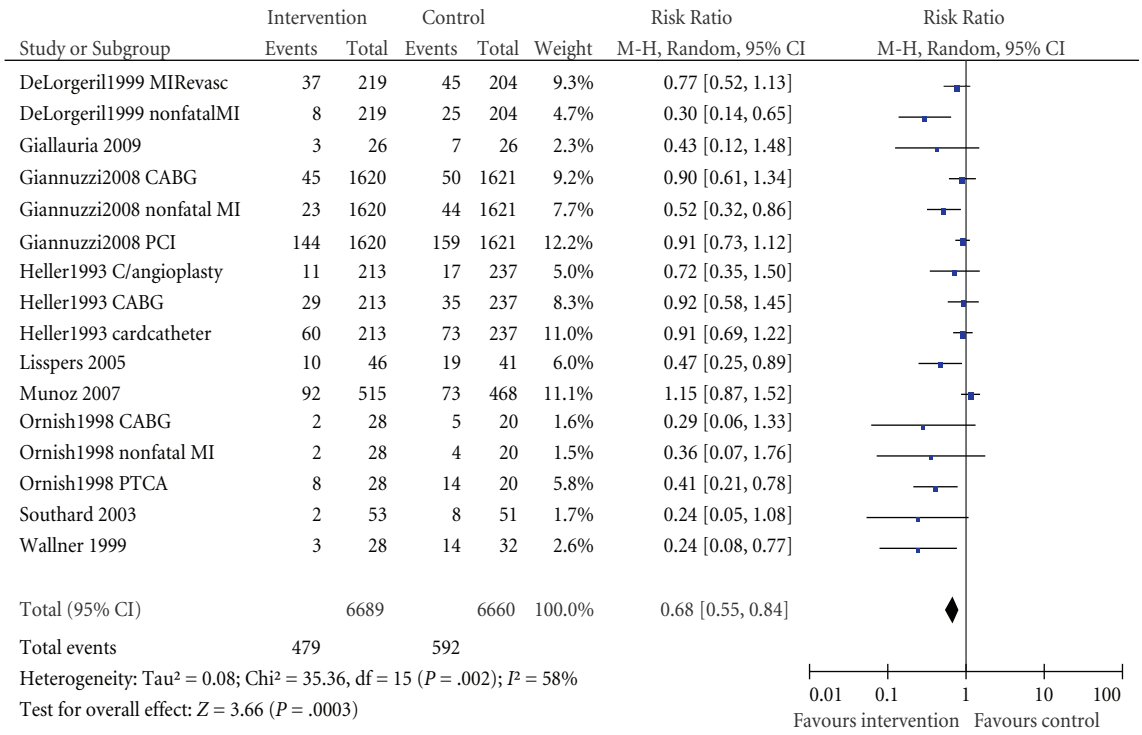

Figure 4: Effect of interventions on nonfatal cardiac events: comparison of intervention versus control groups. MIRevasc = elective myocardial revascularisation, CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention, C/angioplasty = coronary angioplasty, Cardcatheter = cardiac catheter, PTCA = percutaneous transluminal coronary angioplasty.

benefits for intervention patients. Seven of these 12 studies reported significant improvements in total cholesterol for intervention patients compared to controls [18, 20, 21, 30, 41, 42, 45]. Another study found a significant difference in total cholesterol between female intervention and control groups but not male [25].

Low-Density Lipoprotein Cholesterol (LDL-chol). Five studies reported significant improvements in levels of LDL-chol among intervention patients compared to controls [18, 30, 39, 41, 42]. Salminen et al. [25] found significant improvements between female intervention and control groups but not male.

Only one study, that by Giallauria et al. [18], found a significant improvement in levels of high-density lipoprotein cholesterol (HDL-chol) among intervention patients compared to controls.

QOL. 10 studies reported quality of life, and four reported significant benefits for intervention patients—including for "physical activity factor" [26], physical function [28], and emotional [44]. Campbell et al. [35] reported five significant results out of the eight health status domains (physical, social, role physical, role emotional, and pain).

Self Efficacy. This was reported by only one study. Gianuzzi et al. [21] reported a significantly better score in intervention patients compared to controls relating to self/stress management at six month follow-up and throughout their study.

Medication. Nine studies reported use of medications, and six reported significant improvements among intervention patients compared to controls.

Lewin et al. [29] reported the number of glyceryl trinitrate pills or puffs of sublingual spray taken per day which were self-reported in a diary by patients. Intervention patients reported a significant reduction in doses per week compared to control group patients.

Campbell et al. [34] reported proportions taking aspirin which was ascertained by postal questionnaire. A significantly greater number of intervention patients at one-year follow-up was taking aspirin compared to controls.

Carlsson [42] found significant differences between intervention and control patients in use of statins and cholestyramine; however it was unclear how this data was collected.

In the study by Cupples and McKnight [22, 23] trained health visitors assessed the use of prophylactic drugs for angina by interviewing patients. At the two- and five-year follow-ups, a significantly higher number of intervention patients were using prophylactic medication than controls.

4. Discussion

We have conducted a systematic review of lifestyle interventions for the secondary prevention of CHD using Cochrane Collaboration methodology. The review indicates that lifestyle interventions have mixed effects with some benefits in relation to total mortality, CV mortality, and

Table 3: Impact of interventions on hospital admissions.

Study	Intervention	Control	Risk ratio
Murphy*	Overall: Baseline to 18 months:		$P = .03$
	0.3 (0.6) to 0.4 (0.7)	0.4 (0.8) to 0.5 (1.0)	
	CV: At 18 months:		$P = .04$
	0.14 (0.50)	0.23 (0.7)	
	Other:		$P = .22$
	0.24 (0.6)	0.32 (0.7)	
Vestfold**	20	33	NS (not significant)
Ornish***	23	44	0.685 (0.012–13.2), $P = .81$
Heller****	47	60	0.253***** Diff -0.8% (−10.0–8.4); NS
Delaney*****	7647	8642	$P = .998$

*Mean number of admissions per patient (at 18 months).
**20 admissions related to chest pain without evidence of ischaemia among 11 patients in intervention group, 33 admissions among 14 patients in control group (at 2 years).
***Cardiac hospitalisations (at 5 years).
****Patients with ≥1 hospital readmission (at 6 months).
*****Total number of admissions (at 10 years).

nonfatal CV events as well as PA, diet, blood pressure, cholesterol, QOL, and medication adherence. The review was restricted to the period after 1990 because the concept of secondary prevention and methods to promote it are a relatively recent development in healthcare. Nonetheless, we found trials of interventions which were heterogeneous, and this was evidenced by the range of categories into which they could be classified. Few trials evaluated a single component of lifestyle, while many assessed the effects of a complex, multifactorial intervention. Other differences between studies included trial quality, intervention setting, intensity, duration, and length of follow-up.

For all trials the control group was usual medical care. We excluded trials which evaluated the intervention against a different intervention or other programme which could not be defined as usual care.

4.1. Effectiveness of Interventions. Overall, a small number of studies showed a significant reduction in deaths and nonfatal MIs while several reported positive results relating to adherence to lifestyle change. Regarding total mortality, four studies out of the six reporting this outcome showed significant benefits in the relatively short time scale studied (3–5 years). The Lyon Diet Heart Study [33] showed a significant impact on All-cause mortality and fewer deaths from CV causes among intervention patients compared to controls. The protective effect of the intervention was maintained for up to four years. This was a noteworthy result because patients were seen annually, indicating that they were able to maintain the diet for long periods alone and without professional motivation. The other trials showing significant benefits were of an educational intervention [22] and two multifactorial [36, 45]. Only three out of eight studies showed significant results for cardiovascular mortality. These were a dietary intervention [33], educational [22] and multifactorial ones [45], all of which had also shown significant effects on total mortality.

Concerning nonfatal CV events, we presented 16 outcomes from nine studies. There were significant improvements in five of these trials, which were of dietary [33], psychological [27], and multifactorial [21, 39, 41] interventions. Of the five studies which reported hospital admissions, only one, Murphy et al. [17], reported significant benefit for intervention patients compared to controls, both for overall and CV admissions.

In terms of risk factors for CHD, these were assessed by greatly differing methods which made comparison difficult. Diet, PA, smoking status, blood pressure, and cholesterol were widely reported, with varying results. In relation to diet, significant results were reported for the dietary intervention, one psychological, three educational, and six multifactorial interventions. Significant results relating to PA were reported for one exercise trial, one educational, two psychological, and seven multifactorial. Of the five studies which showed significant benefits for intervention patients compared to controls in relation to smoking, four were multifactorial and one psychological. All five interventions which showed significant results relating to BP were multifactorial. Concerning cholesterol and lipid levels, the interventions which showed significant results were one psychological, one educational, and eight multifactorial.

In relation to quality of life, one psychological trial reported a significant benefit for intervention patients compared to controls, as did one educational and two multifactorial.

Few trials reported medication intake or adherence. However, as appropriate therapy is a key aspect of secondary prevention of CHD [8], this should surely be given greater consideration. The trials which reported significant results relating to medication were classified as psychological (one), multifactorial (two), and educational (three).

Likewise, self-efficacy, a patient's ability, and confidence to manage their own condition, was only reported in one study. This multifactorial intervention reported a significant outcome for intervention patients compared to controls.

4.2. Relevance of Lifestyle and Risk Factor Modification. Recent evidence has shown the importance of focusing on lifestyle to effect positive changes relating to CHD. Bennett et al. [48] used the IMPACT CHD model to examine the decline in CHD mortality in Ireland between 1985 and 2000, and possible reasons for this. The mortality rate fell during this period by some 47%, representing 3673 fewer observed CHD deaths. The authors found that 48% of this decrease was due to a reduction in major risk factors including smoking and cholesterol levels. Conversely, an upward trend was seen in obesity, diabetes, and PA which were said to

Table 4: Impact of interventions on lifestyle risk factors.

Source	Diet	Exercise	Smoking
Exercise			
Astengo et al. [16] (2010)	NR	Maximum workload: $P = .02$. Self-reported training (days/week): P value for difference between groups <.001. Self reported training (minutes/session): P <.001. Maximum heart rate: NS.	NR
Dietary			
De Lorgeril et al. [32] (1996).	% calories consumed: Total lipids: $P = .002$. Saturated fats: $P = .0001$. Polyunsaturated fats: $P = .0001$. Oleic: $P = .0001$. Linoleic: $P = .0001$. Linolenic: $P = .0001$. Alcohol: NS. Proteins: NS. Fibre: $P = .004$. Cholesterol: $P = .0001$.	NR	NR
Psychological			
Lewin et al. [29] (2002)	NR	Seattle Angina Questionnaire: physical limitations score for I group reduced; for C group increased: $P < .001$.	NR
Lisspers et al. [26] (1999).	Diet knowledge index: $P < .0005$. Self rated dietary habits: $P < .0005$. Lisspers et al. [27] (2005) calculated overall lifestyle scores incorporating diet, PA, smoking, and stress: I group significantly higher score than C group at 12, 24, 36, and 60 months. P values not given for individual components of score.	PA frequency: $P < .025$. Maximum workload: $P < .0025$. Chest pain ratings during exercise tests: $P < .025$.	Self rated smokers $P < .01$.
Salminen et al. [25] (2005)	Type of milk/type of fat consumed: NS (data not reported).	PA frequency: NS (data not reported).	NS (data not reported).
Educational			
Carlsson et al. [42, 43] (1997, 1998).	A: NR B: NR C: Concern about food habits: $P = .008$	A: work capacity: NS (AMI patients: $P = .08$; CABG patients: $P = .75$). B: NR. C: PA: frequency: NS. Stopped physical training: $P = .43$; started physical training: $P = 0.50$.	A: NR B: NR C: smoking cessation: NS.

Table 4: Continued.

Source	Diet	Exercise	Smoking
Cupples and McKnight [22] (1994).	Intake of poultry ($P = .02$), green vegetables ($P = .002$), high fibre food ($P = .01$), red meat ($P = .005$), fried food ($P = .045$), biscuits and sweets ($P = .0001$), saturated fat ($P = .013$).	PA frequency: $P < .0001$.	Smoking cessation rate: NS ($P = .82$).
Cupples and McKnight [23] (1999)	Diet score: difference between groups: NS	PA frequency: $P < .05$.	Smoking cessation rate: difference between groups: NS.
Heller et al. [44] (1993)	Mean fat score: $P = .002$.	Proportion exercising 3 times weekly: difference between groups NS.	Current smoker: difference in proportions between groups: NS
Southard et al. [31] (2003)	MEDFICTS dietary score: NS	Canadian Angina Grade, Duke Activity Status Score: NS. PA duration: NS.	NR
Multifactorial			
Allen et al. [30] (2002).	1 year: Fat: $P = .009$; Saturated fat: $P = .004$; Cholesterol: $P = .006$; Fibre: NS.	MET, hr/wk ≥6 1 year: $P = .02$.	NR
Campbell et al. [34] (1998) A	Low fat diet: effect size: OR 1.47, CI 1.10 to 1.96, $P = .009$.	Moderate PA: effect size: OR 1.67, CI 1.23 to 2.26, $P = .001$.	Proportion of non-smokers: OR 0.78, $P = .322$.
Giallauria et al. [18] (2009).	NR	VO_{2peak} (increase in oxygen at peak exercise): 3, 12, and 24 months: $P < .001$. VO_{2AT} (anaerobic threshold): 3, 12 and 24 months: $P < .001$. $Watt_{max}$: 3, 12 and 24 months: $P < .001$.	NR
Gianuzzi et al. [21] (2008)	Dietary score 3.9% higher in I group ($P < .001$); maintained throughout study.	Mean score: 6 months: $P < .01$; maintained throughout study.	At 6 months: $P = .02$. 3 years: NS ($P = .60$).
Hamalainen et al. [45] (1995).	NR	Frequency of PA and work capacity: NS (data not reported).	No. cigarettes smoked/day: 1 year: NS; 2 years: $P = .02$; 3 years: $P = .002$; Years 6 and 10: NS.
Murchie et al. [36] (2003) A	NS I group improvements sustained in all areas but at 4 years C group improved and differences no longer significant.	NS	NS

Table 4: Continued.

Source	Diet	Exercise	Smoking
Murphy et al. [17] (2009).	DINE fibre: NS ($P = .06$) DINE fat: NS ($P = .86$).	Godin exercise score: NS ($P = 0.67$).	Self reported smoker: NS ($P = .23$).
Ornish et al. [41] (1998).	Fat intake, g per day: 1 year: $P < .001$. 5 years: $P < .001$. Fat intake, % of energy intake: 1 year: $P < .001$. 5 years: $P < .001$. Dietary cholesterol: 1 year: $P < .001$. 5 years: $P = .002$. Energy intake: 1 year: $P = .64$. 5 years: $P = .86$.	Adherence to exercise: 1 year: NS. 5 years: NS.	NR
Redfern et al. [19] (2008) A Baseline to 3 months	NR	METS/kg/min: $P = .01$.	Smokers: $P < 0.01$.
Redfern et al. [20] (2009) B	NR	METS/kg/min, $P = .001$.	NR
Vestfold [28] (2003).	6 months: I patients significantly lower intake saturated and monounsaturated fat, sugar, and cholesterol, higher fibre than C. 2 years: I group significantly lower total fat intake, saturated fat and monounsaturated, significantly higher fibre, lower sugar and cholesterol.	PA frequency: 6 months: $P < .001$. 2 years: $P < .01$.	6 months: $P < .05$. 2 years: $P < .05$.
Wallner et al. [39] (1999).	Total fat: $P = .001$; SFA: $P = .05$; MUFA: $P = .04$; Carbohydrate: $P = .001$; Fibre: $P = .006$; Cholesterol: $P = .03$; Vitamin C: $P = .006$; Energy intake (kcal), PUFA, protein, vitamin E: NS.	Kcal/day: $P = .001$.	NR
Organisational			
Jolly et al. [40] (1999)	NR	Fitness test (distance walked in 6 minutes, metres): NS.	Quit rate (proportion who stopped smoking): NS.
Munoz et al. [24] (2007)	NR	PA (amount of exercise): both groups increased but difference between groups NS.	NR

NR: not reported; NS: not significant; I: intervention; C: control.

Table 5: Summary of lifestyle risk findings.

Outcome	Number of studies with this outcome	Number of outcomes	Number significantly improved	Number of outcomes with no significant difference
Exercise	21	37	20	17
Diet	15	51	39	12
Smoking	13	20	7	13

Note: we counted Campbell and Murchie as separate studies as the patients in each were not necessarily the same. Other follow-up studies, Cupples, Ornish, Vestfold, and Redfern we counted as one study but counted the outcomes from each time point as different outcomes (hence the 20 outcomes for the 13 studies reporting smoking outcomes).

contribute an additional 500 deaths in 2000. These results were similar to those found by Palmieri et al. [49], who also used the IMPACT model and investigated the decline in CHD mortality in Italy between 1980 and 2000. They concluded that over half of the mortality fall was due to risk factors, mainly blood pressure and cholesterol, and just under half was due to medical therapies.

The Lyon Diet Heart Study [33] was the first clinical trial evidence in support of the Mediterranean diet, which comprises a high intake of fruit, vegetables, nuts, legumes, and grains. Other recent evidence has been found supporting the Mediterranean diet's protective effect in the secondary prevention of CHD [50–52]. O'Connor et al. [6] examined RCTs of cardiac rehabilitation with exercise and found a moderate reduction of 20% in total and CV mortality after one year, with a reduced risk maintained for three years after infarction. In a recent review of interventions incorporating exercise as part of a cardiac rehabilitation programme, Jolliffe et al. [11] also observed a reduction in total mortality. Exercise-only interventions resulted in a 27% reduction in total mortality and 31% reduction in cardiac mortality while comprehensive rehabilitation reduced mortality to a lesser extent (26%).

The psychological interventions included in this review showed small beneficial effects. This is in keeping with similar findings in a recent review of 36 RCTs of psychological interventions by Rees et al. [12] which showed no evidence of effect on total or cardiac mortality, but found small reductions in anxiety and depression.

We included two organisational interventions in this review, and both reported disappointing results. Jolly et al. [40] investigated a programme to improve communication between hospital and GP practices using liaison nurses. The programme was effective in promoting follow-up care of patients in general practice; however health outcomes were not improved. Munoz et al. [24] examined an intervention involving postal reminders sent to patients to encourage them to visit their GP. Blood pressure and HDL-cholesterol levels were improved, but no effect was observed on mortality or morbidity.

4.3. Limitations of the Review. This review has a number of potential limitations. The relatively small number of studies which included mortality as an outcome, the heterogeneity between trials, and poor quality of reporting all arise from the primary data. Further, imprecise descriptions of the interventions and the limited data have made it difficult to determine the benefits of various components of the interventions. The majority of the population of the interventions was male and relatively low risk; however greater benefit could have been derived from the interventions by higher risk patients who were excluded on the basis of comorbidity.

The broad range of trials included, and the subsequent large number discovered in our search, may have made comparisons difficult. Nonetheless this reflects the current lack of clarity in respect of the optimal components of effective interventions for CHD secondary prevention.

4.4. Implications for Practice. We have found that lifestyle interventions promoting regular PA, a healthy diet, and adherence to medication have beneficial effects among patients with CHD. It is therefore reasonable to promote such a healthy lifestyle to patients similar to those included in the RCTs we investigated—mainly older adults who had suffered a coronary event. As practitioners endeavour to achieve target levels of blood pressure and cholesterol by altering their patients' prescribed medication, the potential value of their advice regarding exercise and diet should not be overlooked.

4.5. Implications for Future Research. Overall, the current evidence suggests that lifestyle interventions have some beneficial effects on total and cardiac mortality, morbidity, and on behaviour change in relation to modifiable cardiac risk factors. Even where little or no effect was observed relating to mortality or morbidity, some trials reported benefits in terms of lifestyle behaviour change. That healthcare education and even small-scale interventions can lead to healthier lifestyle choices, as shown in this review and others, should be an encouragement to professionals in practice. Future studies should be designed carefully, with attention given to aspects of study quality, which we addressed in Table 2. For example, RCTs of a cluster design help to avoid contamination of control patients. Further, outcomes should be matched to intervention elements. In addition, it is important to incorporate concealment of allocation and blinding of outcomes. Maximal follow-up should be ensured and more consideration given to the underlying theoretical foundation for the intervention.

However, the fact that more profound and wide reaching benefits were not seen in our review is surprising considering that all guidelines focus on the importance of lifestyle interventions. Future research should perhaps focus on the components of interventions and what the ideal combination of measures, intervention intensity, and duration should be. In addition, investigations into the barriers to lifestyle change among patients with CHD may shed new light on why some well-designed and executed interventions have not resulted in expected benefits.

Appendix

Medline Search Strategy

(1) Lifestyle.mp. or Life Style/

(2) Exercise.mp. or Exercise/

(3) Physical activity.mp.

(4) Diet/ or diet.mp.

(5) 1 OR 2 OR 3 OR 4.

(6) Secondary prevention.mp. or Secondary Prevention/

(7) Coronary heart disease.mp. or Coronary Disease/

(8) CHD.mp.

(9) Myocardial infarction.mp. or Myocardial Infarction/

(10) MI.mp.

(11) Coronary Artery Bypass/or coronary artery bypass graft.mp.

(12) CABG.mp.

(13) Percutaneous transluminal coronary angioplasty.mp. or Angioplasty, Transluminal, Percutaneous Coronary/

(14) PTCA.mp.

(15) Angina pectoris.mp. or Angina Pectoris/

(16) 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15.

(17) 5 AND 6 AND 16.

(18) Limit search 17 by English language, humans, 1990-current and adults all ages (19 plus).

(19) randomized controlled trial.mp. or Randomized Controlled Trial/

(20) controlled clinical trial.mp. or Controlled Clinical Trial/

(21) random allocation.mp. or Random Allocation/

(22) double blind method.mp. or Double-Blind Method/

(23) single blind method.mp. or Single-Blind Method/

(24) 19 OR 20 OR 21 OR 22.

(25) 18 AND 24.

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Review Article

Passive Smoking and the Development of Cardiovascular Disease in Children: A Systematic Review

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Passive smoking may be implicated in the development of cardiovascular disease (CVD) in children because of their partially developed physiological systems. The aim of the present systematic paper is to investigate whether passive smoking is associated with factors that influence the development of CVD in children. Data sources included Medline, Cochrane Library, Cumulative Index to Nursing & Allied Health (CINAHL) research database, Google Scholar, Excerpta Medica database (EMBASE), the 2006 Office of the Surgeon General's report, and the 2005 report from the California Environmental Protection Agency. We identified a total of 42 relevant articles (i.e., 30 reviews and 12 observational). Results revealed that passive smoking may be implicated in deteriorating cardiovascular status in children in terms of unfavorable high-density lipoprotein levels and deteriorated vascular function.

1. Introduction

Active smoking and disease is a research area investigated for many decades. The first ever case-control studies which revealed a strong association between active smoking and lung cancer were conducted in Nazi Germany in 1939 and 1943 [1]. Many other studies, thereafter, have explored the effects of tobacco smoke on human health. It is now an accepted fact that smoking is responsible for the development of chronic diseases as well as increased morbidity and mortality [2].

During the last decades research has also expanded in the area of passive smoking (PS) and its effects on aspects of human health. The first conclusive evidence on the danger of PS arose in 1981 from a study showing that nonsmoking Japanese women married to men who smoked had an increased risk for lung cancer [3]. Since then, a vast number of studies have appeared investigating the unfavorable effects of PS. In line with active smoking, it is now generally accepted that PS leads to increased prevalence of various cardiovascular diseases [4] and increases the risk of death by at least 20% [5]. More importantly, recent methodologically robust data from nonsmoking adults have shown that PS compromises health not only when individuals are exposed frequently for prolonged periods of time—as initially thought—but also after a single brief exposure [6–10]. This novel evidence clearly shows that PS may have a substantive role in the development of chronic diseases [11].

Despite the recent measures adopted in different countries to eliminate indoor smoking, 700 million children globally are still exposed to environmental tobacco smoke [12] while the smoking epidemic continues to increase worldwide [13]. Given that tobacco smoke contains chemicals characterized as carcinogenic (e.g., benzene, chlorinated dioxins, and benzo[*a*]pyrene) and have adverse health consequences on the cardiovascular (e.g., arsenic) and respiratory (e.g., acetaldehyde) systems in adults [14], the physiologically immature children may be more vulnerable to damage as a result of PS exposure because of their partially developed or compromised cardiovascular, endocrine, and immune systems. For these reasons, we conducted a systematic review

of the available literature to investigate the evidence regarding PS and its association with factors that influence the development of cardiovascular disease (CVD) in children.

2. Methods

Five databases [Medline, Cochrane Library, Cumulative Index to Nursing & Allied Health (CINAHL) research database, Google Scholar, Excerpta Medica database (EMBASE)], the 2006 report on second hand smoke by the Office of the Surgeon General [4], and the 2005 report by the California Environmental Protection Agency [15] were searched to identify publications from 1975 to April 2009 in English regarding PS and cardiovascular disease in children (<18 years old). The Medical Subject Heading (MeSH) terms "PS," "second hand smoking," "environmental tobacco smoking", "maternal smoking," and "parental smoking", were searched in combination with "obesity", "diabetes," "hypertension," "blood pressure," "cholesterol," "lipids," and "cardiovascular disease." Editorials and conference proceedings were excluded. If the abstract did not provide sufficient information for this process, then the full-text manuscript was examined. The cited articles of the selected papers were also searched manually in order to identify relevant studies not identified in the original search. A flow diagram of the studies identified from databases and the combination of key words used to identify the observational studies included in the present paper in Figure 1.

3. Results

We identified a total of 77 articles, from which only 42 were relevant; of which 30 were reviews and 12 were observational studies and thus included in the present paper. Table 1 depicts the results of each study included in the present paper ($n = 12$).

From the results of the present paper it appears that newborn children exposed to PS at home are more likely to be overweight and obese, particularly when exposed during the first three years of their life [16]. It was also found that PS is associated with deteriorated blood lipids profiles in children, particularly lower high-density lipoprotein which has been a consistent finding in most studies [17–21]. A randomized controlled trial (RCT) also revealed that in passive smokers the rate of factors associated with the development of CVD, such as body weight, cholesterol, and triglycerides, was higher than that in non-PS smokers [22].

PS in children has also been examined in relation to vascular biological parameters. PS appears to directly affect endothelial function in children via a dose-dependent decrease in the bioavailability of nitric oxide [23]. Two randomized controlled studies (RCTs) found that children exposed to PS have also reduced aortic elasticity possibly via the direct effects of PS on the mechanical properties of the arteries (e.g., impaired nitric oxide production, platelet activation, or adrenalin levels) [23, 24].

The effects of exposure to PS during pregnancy with regards to risks factors associated with CVD were investigated in two separate studies. Results revealed a significantly higher concentration of cotinine in children due to exposure to PS from the mother during pregnancy [25] and that PS increased oxidative stress in cord blood [26]. The effects of maternal PS exposure on absolute red blood counts (RBC) were assessed in newborn infants of 55 mothers exposed and 31 not exposed to PS during the last trimester; data revealed that the counts of absolute nucleated RBCs were significantly elevated in the PS exposed group. Table 1 depicts the results of all studies identified in relation to PS and CVD in children.

4. Discussion

The present systematic review investigated the effects of PS on CVD (classical risk factors and vascular function) in children. The results reveal that PS may be implicated in deteriorating cardiovascular status in terms of unfavorable high-density lipoprotein levels and deteriorated vascular function, whereas the mechanisms by which PS negatively affect the cardiovascular status of children (in terms of classical CVD risk factors) have yet to be elucidated. Perhaps, the significant decrease in cardiorespiratory function, as a result of smoking/PS, leads to a decrease in physical activity in children which may then have a significant unfavorable impact on body fat and cholesterol levels. This is supported by a vast amount of evidence demonstrating that physical inactivity results in worse profile in classical CVD risk factors in both healthy and diseased populations [28–30].

Two RCT studies [23, 24] have consistently revealed that children exposed to PS have reduced aortic elasticity. The significant alterations in vascular biological mechanisms from an early age may lead to a deteriorated health status of children exposed to PS, given that vascular dysfunction precedes atherosclerosis and leads to increased CVD mortality [31, 32]. PS appears to directly affect endothelial function in children via a dose-dependent decrease in nitric oxide [23], a mechanism preceding atherosclerosis [31]. Vascular endothelial dysfunction has been implicated in the progression of atherosclerosis and cardiovascular event rates; hence, its assessment may provide pivotal information, particularly given that it may detect "silent" clinical manifestations leading to ischaemia. This is the reason why this assessment is consistently used in research and clinical setting for both prognostic and diagnostic means. Nitric oxide is a vasoactive factor responsible for dilation of the vessels; the drop in exhaled nitric oxide levels within the first minutes of PS may be caused by decreased production of nitric oxide synthase through a negative feedback mechanism, given the high concentrations of nitrogen oxides inherent in tobacco smoke [33]. Possible other mechanisms comprise an increased breakdown of nitric oxide by PS oxidants or a PS-induced accelerated uptake of nitric oxide [34].

Data from adults have shown that the PS-induced changes in lipoprotein oxidization generate various effects in the vessel wall [35]. Animal experiments have shown a synergistic effect between PS and lipoprotein that influence

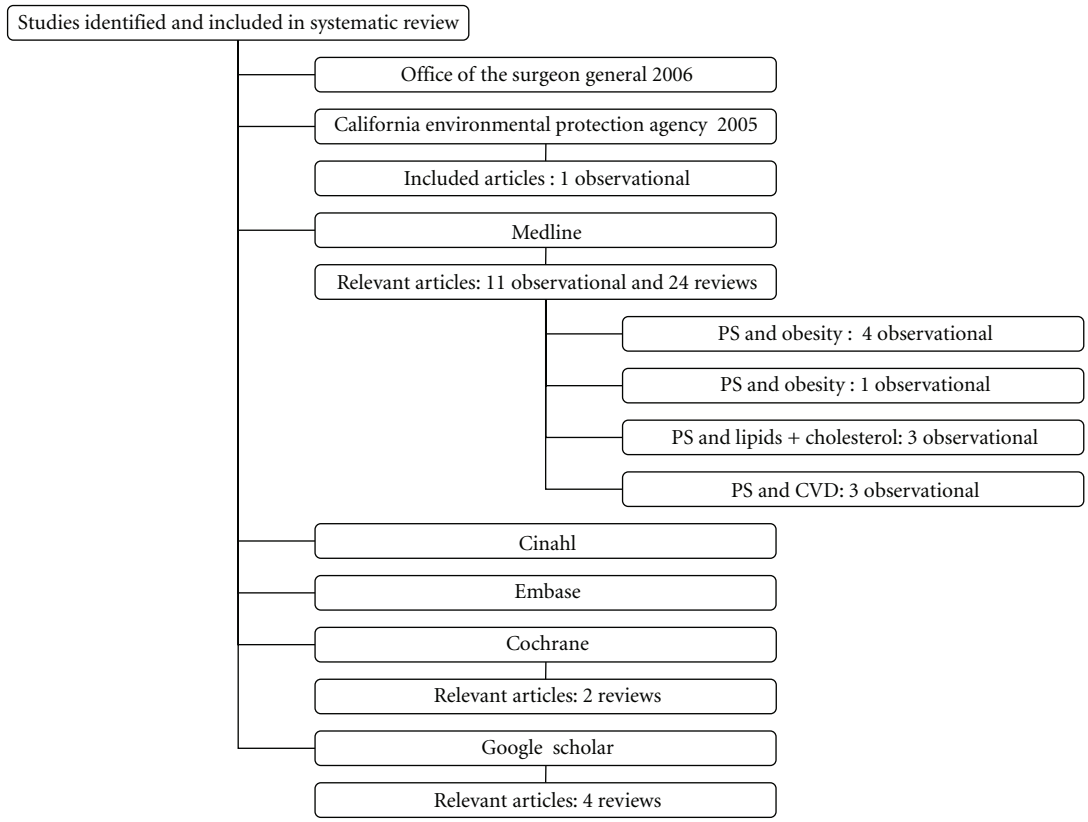

Figure 1: Articles identified and included in systematic review.

the oxidation of lipoprotein in the vessel wall [36]. It is also important to note that polycyclic aromatic hydrocarbons—byproducts of the incomplete combustion of organic material inherent in PS—bind to lipoprotein subfractions and can be integrated into the atheromatic plaques promoting the proliferation of vascular cells and plaque progression [35].

Elevated absolute nucleated RBCs count in the neonate, as observed by Cochran-Black et al. [27], is a marker of fetal hypoxia [15]. Periods of hypoxia may stimulate bone marrow to increase the hematocrit possibly in concert with a more rapid smoke-induced RBC turnover. The findings from this study suggest that maternal PS exposure has similar effects on the fetus as active maternal smoking.

It is of great clinical importance to explore the associations between PS and either pregnancy or early childhood. Clearly, PS has well-established adverse health effects in children [37, 38] whereas the mechanisms by which PS affects the fetus may be different to those that affect the child or adolescent; the deterioration in cardiorespiratory and immune system as well as the toxic substances in tobacco smoke are currently the main suggested mechanisms. Through this systematic review of the current available data, it appears that paternal PS promotes the development of CVD. However, we have previously demonstrated—by using a robust methodological design—that in young adults, even the normal PS exposures (similar to those seen in public places and houses) may significantly compromise health parameters [6–8]. Minimizing children's exposure to PS should therefore be amongst the main aims of interventional studies in order to raise public awareness and improve parent education and counseling.

There are several limitations in the methodological designs of studies conducting research on the effects of PS on children's health. Most of the studies do not take into account very important confounding factors such as the environmental ones (e.g., exposure to other carcinogenic substances) or maternal diet and obesity that may indeed result in increasing CVD prevalence in children. Most importantly, the adopted designs allow only for cross-sectional comparisons, in which the directionality and causality of associations cannot be clearly justified. Also, the vast majority of published studies justify PS on self-reports without an objective measurement of exposure (e.g., cotinine levels). Moreover, it may be possible that PS has indirect effects on CVD outcomes in children, via its immunosuppressive capabilities [37]. For example, it is estimated that PS is equivalent to smoking ~100 cigarettes per year. This number, however, ranges according to the smoking habits of parents [39]. It has been found that even 30 minutes of PS significantly deteriorate cardiovascular outcomes similarly to smoking [40]. Hence, it seems reasonable to suggest that the physiologically undeveloped systems of fetus/children may be more susceptible to damage from the toxic effects of PS, particularly given the fact that the effects of PS may occur at very low levels of exposure [41].

Table 1: The effects of PS on CVD.

Author [reference]	Design	Participants	Results
Apfelbacher et al. [16]	Cohort cross-sectional	35,434 children (50.9% boys), 5–7 years old	PS was a predictor of being overweight and/or obese
Öhrig et al. [22]	RCT	3495 children (age 6.5 ± 2 years)	In passive smokers the rates of body weight, cholesterol, and triglycerides were higher
Hargrave et al. [25]	Controlled Clinical trial	Children-specific numbers not mentioned	Significantly higher concentration of cotinine found in children due to exposure in PS from the mother rather than that from father/friends
Aycicek and Ipek [26]	Clinical trial	Mothers giving birth	PS increased oxidative stress in cord blood
Kallio et al. [23]	RCT	441 children (8–11 years)	PS impairs endothelial function in children
Kallio et al. [24]	RCT	386 children (11 years)	PS impairs aortic elasticity
Neufeld et al. [19]	Cross-sectional (pilot scale)	161 children and adolescence (2–18 years)	High density lipoprotein was significantly lower in passive smokers. PS may increase the risk profile for later atherosclerosis
Moskowitz et al. [17]	Longitudinal	105 PS twin pairs and 111 non-PS twin pairs (all preadolescent children)	HDL was lower in PS children. Also, significant adverse alterations were already present in lipoprotein profiles in twin exposed to PS
Moskowitz et al. [18]	Cohort analytic	408 twins (11 years at baseline)	HDL is significantly lower in passive smokers. White males that have a history of higher CVD, or higher weight, and/or blood pressure may be at increased risk for developing premature CVD
Feldman et al. [20]	Cross-sectional	Healthy adolescents	Lower high density lipoprotein in passive smokers
Işcan et al. [21]	Cross-sectional	194 healthy children (4–14 years)	Total cholesterol, low-density lipoprotein were significantly higher in passive smokers
Cochran-Black et al. [27]	Cross-sectional	55 mothers exposed to PS and 31 not exposed to PS	No significant differences in counts for total red blood cells, white blood cells, platelets, and lymphocytes. Absolute nucleated RBCs significantly elevated in the PS exposed group.

The fact that the majority of the available published paper on this research area were reviews rather than original research investigations demonstrates the difficulty of performing research on PS and CVD in children. We have performed a systematic review of the literature in order to be objective rather than assume causality and report only results that favor directionality of associations, which appears to be the case in many published papers. Based on the available findings, interventions that target the cessation of parental smoking at home and preconception parental smoking, are necessary. Despite that indoor PS has been banned in many countries, PS at home is the most difficult to control and at the moment pulled data from systematic study reveal that interventions to reduce exposure in children are ineffective [42].

The findings of this systematic paper are particularly timely given the emerging experimental evidence on the adverse effects of passive smoking on health [6–8], as well as the shifting global smoking patterns, with an estimated 930 million of the world's 1.1 billion smokers living in developing countries, that also demonstrate increasing smoking rates amongst young individuals [30, 43]. The findings of this paper indicate that public health preventive actions toward minimizing the exposure of children to PS should aim not only at suppressing tobacco use, but should also target family influence as attitudes that reinforce smoking behaviors and increase the exposure of children to PS.

5. Conclusions

We conclude that the current available data reveal that PS in children is linked with deteriorated lipid profile and vascular function whereas data for maternal smoking (during pregnancy and PS after birth) are still inconclusive mainly due to design constrains and lack of adjusting because of important confounding factors.

Conflict of Interests

The Authors have no Conflict of Interests.

Abbreviations

PS: Passive smoking
CVD: Cardiovascular disease
CINAHL: Cumulative Index to Nursing & Allied Health
EMBASE: Excerpta Medica database
MeSH: Medical subject heading.

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Review Article

Does Smoking Act as a Friend or Enemy of Blood Pressure? Let Release Pandora's Box

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In spite of the great number of observations which show the certainty of cardiovascular damage from smoking, the opinions on that are not yet unanimous. There is a discrepancy that could be attributed to the lack of reproducible data particularly in some epidemiological studies. On the contrary, experimental findings conducted on both animals and humans give evidence of exactly reproducible results of cardiovascular alterations and among these the course of Blood Pressure (BP). Findings identify an increase in BP of active smokers or non-smokers exposed to passive smoking, while a lot of others refer a lowering of BP due to smoking. This discrepancy could be explained as follows. Initially, a vasoconstriction mediated by nicotine causes acute but transient increase in systolic BP. This phase is followed by a decrease in BP as a consequence of depressant effects played chronically by nicotine itself. Simultaneously, carbon monoxide is acting directly on the arterial wall causing, in the long run, structurally irreversible alterations. At this time, there is a change in BP that increases again, and often constantly, its levels following chronic exposure. Changes in response to antihypertensive drugs have been observed in hypertensive smokers since smoking influences metabolic steps of the drugs.

1. Introduction

Tobacco smoke is a term indicating cigarette smoking, cigar smoking, and pipe smoking. Usually, the main reports concerning the relationship between smoking and cardiovascular alterations are attributed to cigarette smoking since systematic studies on the harm caused by pipe and cigars are yet lacking.

There are a lot of reports that identify cardiovascular system as one of the major target organs for smoking [1–12]. Either active or passive exposure to smoking causes damage to the heart and blood vessels although pathological mechanisms of damage may differ with regards to the type of action but not for that is concerning chemical toxics responsible of the alterations [13–30].

In spite of the great number of observations which show the certainty of cardiovascular damage from smoking, the opinions are not yet unanimous. There is a discrepancy that could be attributed to the lack of reproducible data particularly in some epidemiological studies. On the contrary, experimental findings conducted on both animals and humans give evidence of exactly reproducible results of cardiovascular alterations.

Adverse effects on the heart and vessels are mediated by many chemical compounds that are usually concentrated and condensed into tobacco mixtures [23]. Over 4000 chemicals have been identified in smoke, and a large majority of these have carcinogenic and/or negative cardiovascular effects in humans and animals. Chemical compounds of smoking cause both structural and functional alterations of heart and blood vessels, although with different results which are depending on several factors related to the type of smoking, environment, and subject exposed.

Worldwide, more than 3 million people currently die each year from smoking, half of them before the age of 70, an enormous human cost, and more than one and third have cardiovascular events that often determine permanent disability of affected subjects [24, 25]. There are more than 1 billion smokers in the world with an increased/decreased/again increased smoking habit.

Main cardiovascular diseases related to cigarette smoking are listed in Table 1.

Table 1: Main cardiovascular diseases related to cigarette smoking.

Coronary artery disease
Stroke and cerebrovascular disease
Peripheral artery disease
Aortic aneurysm
Hypertension
Heart failure
Arrhythmias
Endothelial dysfunction
Atherosclerosis

Among cardiovascular parameters, blood pressure (BP) is adversely influenced by tobacco smoke with a high rate by a mechanism yet under discussion. In addition, it is not clear if smoking exposure causes a rise or reduction of blood pressure and, otherwise, also if the occurrence of hypertension in smokers is a consequence of the greatest number of hypertensive people independently from smoking, or smoking actively contributes to changes in BP.

The purpose of this paper is to discuss those results that have been reached by the analysis on the relationship between smoking and BP in both smokers and nonsmokers who were passively exposed. The possible interference of smoking on the effects of the most used antihypertensive drugs is also treated.

2. Blood Pressure in Active Smokers

Active smokers can display BP values which vary widely according to a great number of individual, racial, and lifestyle factors. Moreover, changes in BP have been documented in the same smoker while he is smoking a cigarette or not. While a smoker is actively smoking, transiently sympathetic responses, which acutely raise BP levels, usually occur.

Reports emphasize that hypertension or hypotension can be associated with cigarette smoking in active smokers but there is no evidence on the BP measures whether smoking was lacking.

Some findings [31, 32] identified that cigarette smoking in males was inversely related to systolic BP with a reduction of 1.3 mmHg in 1.1% of light smokers, 3.8 mmHg in 3.1% of moderate smokers, and 4.6 mmHg in 3.7% of heavy smokers when these individuals were compared to nonsmokers. There was no clear relation with diastolic blood pressure. This finding was conducted in an oriental population enrolled in the study, but also in Western countries blood pressure reduction was observed primarily in young smokers [32].

In addition, epidemiologic surveys [33–41], although not all, demonstrated that individuals who smoked a different number of cigarettes had lower blood pressure than that of non-smokers. Such a characteristic occurred in males, females, adolescents, adults, and different races. However, this observation was attributed primarily to chronic smoking. Associated loss in body weight of active smokers contributes to lowering BP.

Table 2: Cardiovascular parameters particularly involved in smokers.

Systolic BP
Heart rate
Endothelium-dependent vasodilation

Such data contrast strongly with the results obtained in active smokers while they are smoking a cigarette as well as in dated chronic smokers [32, 42–45].

These individuals display an evident increase in blood pressure that seems to be clearly related to the toxic effects of nicotine and carbon monoxide of acute type but, particularly for that concerns carbon monoxide, also of chronic type with structural arterial lesions associated. Structural alterations, in the run, tend to change the behaviour of BP that becomes irreversibly elevated although it was starting from increased levels initially responsive to smoking cessation.

Nowadays, there is evidence that changes in vascular wall begin as early as a smoker begins with smoking but they are of no estimation because of masked damage, as that will be described ahead.

3. Blood Pressure in Passive Smokers

Passive smokers display different levels of BP depending on the type and duration of exposure to environmental tobacco smoke.

Increased levels of BP, particularly systolic BP, usually follow acute but transient exposure [46]. Occasionally, there is evidence of hypotension followed, however, by stable hypertension in those individuals exposed for long time to passive smoking even if exposure occurs irregularly.

Some concepts are worthy to be clarified to better understand this occurrence.

An obvious consideration is that acute but transient exposure to passive smoking of a non-smoker individual makes him susceptible of main smoking compounds, primarily nicotine but also carbon monoxide, which have, initially, hypertensive effects directly or indirectly throughout adrenergic and sympathetic stimulation on arterial bed. Similarly, increased heart rate can, usually, be identified. Prolonging the exposure, these parameters [1–3, 5, 17, 18] meet some changes which depend on a large number of factors related to cardiovascular parameters. They influence differently BP levels at the end of isolated acute exposure. Physiology, biochemical characteristics and lifestyle interfere with BP in exposed individuals. Table 2 shows the main cardiovascular parameters involved.

Baseline levels usually tend to be reached after the exposure in a variable but short time and adrenergic and sympathetic profile of the individual also contributes to that.

Finally, lifestyle is a strong positive or adverse factor to restore cardiovascular parameters, particularly systolic blood pressure, according to respectively regular physical exercise performed by the individual or lacking that.

BP is a clinical parameter of easy assessment and often linked to endothelial dysfunction. Such a statement is particularly true for the essential hypertension [47, 48]. Moreover, smoking and endothelial dysfunction are closely related in passive smokers [19].

The acute response of BP to environmental tobacco smoke would seem to determine an increase in systolic BP levels in some reports [49, 50], whereas others [51] did not conclude for this statement.

The possible hypothesis by which smoking compounds influence BP could be explained as follows. Initially, a vasoconstriction mechanism mediated by nicotine causes acute but transient increase in systolic BP. This phase is followed by a decrease in BP as a consequence of depressant effects played chronically by nicotine. Simultaneously, carbon monoxide is acting directly on the arterial wall causing, in the long run, structurally irreversible alterations. At this time, there is a change in BP that increases again, and often constantly, its levels [29]. Such a hypothesis explains BP changes following chronic exposure. On the contrary, acute exposure to passive smoking determines a transient increase in systolic BP due to a combined effect of nicotine that acts by endothelial dysfunction and sympathetic stimulation, and carbon monoxide which exerts its toxic effects directly [52–55]. Increased systolic BP after acute exposure to passive smoking was found also by Mahmud and Feely [56], whereas Leone and Corsini [57] documented a decrease in BP following repeated acute exposure to passive smoking. Decrease in BP was proportional to the increase in carboxyhemoglobin concentrations. Diastolic BP would seem to be affected weakly by environmental tobacco smoke exposure.

These observations identify no uniform course of blood pressure in both active smokers and non-smokers exposed and that concept needs to be clarified by the hypothesis of masked cardiovascular damage.

4. Masked Cardiovascular Damage

The phenomenon of masked hypertension from smoking was, firstly, described by Leone et al. [32] as an explanatory hypothesis of why no unanimous opinion existed on the relationship between cigarette smoking and BP. In the time, that phenomenon has found scientific support.

From up to here discussed data, a significant observation emerges: a different response characterizes BP in actively or passively exposed smokers due to the fact that the parameter is assessed immediately after an acute exposure to environmental tobacco smoke or after a chronic and prolonged exposure. Acute exposure is followed by a transient but significant increase in systolic BP, whereas chronic exposure may be followed by reduced or increased BP depending on the presence of reversible or irreversible alterations of the arterial wall caused by smoking compounds, particularly carbon monoxide. These alterations are, for a variable time, masked by the paralyzing action exerted by nicotine on ganglionic ends that follows initial stimulation.

Acute exposure to passive smoking influences adversely either blood vessel dilation since there is a reduced release of nitric oxide, or arterial stiffness. Consequently, an increase in BP [33, 45, 47, 48] is observed. These changes on arterial stiffness, and then, BP usually occur before they are clinically manifested [16] and are greater than those seen when a smoker smokes a single cigarette. Although this type of changes affecting BP is, usually, proven lately, there is evidence, however, that it begins acutely while an individual smokes [14].

In conclusion, even if assessing systolic BP immediately after environmental smoking exposure may be difficult unless in experimental findings, one cannot deny its increase and, consequently, its interpretation as a marker of smoking exposure.

As already described, nicotine may mask the effects of carbon monoxide on arterial wall for a long time. Adverse effects, usually, will appear when they will be of structurally severe degree so that to induce stable hypertension.

5. Antihypertensive Drugs

A large number of smoker individuals, primarily aged heavy smokers, use antihypertensive drugs to fight hypertension similarly to that occurs in hypertensive non-smokers.

Often some of these drugs meet a change in their mechanism of action because of a close interaction with the main compounds of tobacco smoke, particularly nicotine and its metabolites.

Of the main classes of antihypertensive drugs (Table 3), beta-blockers feel primarily the adverse effect of smoking since smoking compounds influence adversely the action and efficacy of beta-blocker drugs through a complex number of effects that involve metabolic response of adrenergic and sympathetic system [58–60].

Beta-blockers have been shown to be less effective to fight elevated BP and heart rate in habitual smokers compared with non-smokers in two large-scale epidemiological surveys [61, 62].

Metabolic changes in response to propranolol infusion have been observed particularly in elderly since physiologically autonomic nervous system meets an impairment of different degree and is, also, adversely influenced by exposure to smoking in aged people [63]. In addition, there is evidence that the sensitivity of baroreceptor reflex in elderly is impaired with a decrease in its function [64, 65]. The decrease in sensitivity of baroreceptors is usually interpreted as a consequence of increased aortic stiffness.

A study analyzed the effect of aging on metabolic steps of beta-adrenergic system [66]. It demonstrated that isoproterenol that is able to increase significantly heart rate and BP needed higher concentrations to raise heart rate of 25 beats per minute and the dose of propranolol that reduced usually heart rate response was poorly effective. This effect would seem to be related to a metabolic change in the reactivity of catecholamine receptors [67].

More recent findings [68] have shown that third generation beta-1-adrenoceptor antagonists acting by an endothelium-dependent vasodilatory mechanism, like nebivolol, can reduce the adverse effects of smoking and have a positive

Table 3: Common classes of antihypertensive drugs and their response to smoking.

Drug	Mechanism of action	Response to smoking
Beta-blockers	Inhibition beta 1 receptors	Highly reduced (+++)
ACE-Inhibitors	Blocked conversion Angiotensin 1 to Angiotensin II	Highly reduced (+++)
Calcium Antagonists	Block entry of calcium into vascular smooth cells	Reduced (++/−)
Diuretics	Decreased body sodium and extracellular fluid volume	Highly reduced (+++)
Angiotensin receptor blockers	Block AT1 receptor	not yet known (− −/+ ?)

+++ : strongest reduction
++/− : moderate reduction
+ : mild reduction
− −/+ : increase
? : not yet established.

action on endothelial function that was, however, limited only to light smokers.

ACE-inhibitors are drugs largely used to reduce hypertension since they interfere with the conversion of angiotensin I to artery-constricting angiotensin II, the strongest known vasoconstrictor. Blocking the production of angiotensin II results in arterial vasodilation followed by reduction in BP. ACE-inhibitors currently are recommended as first-line therapy for hypertension in certain patient populations, primarily diabetic individuals, because of their safety and efficacy.

There is evidence that cigarette smoking reduces dramatically the benefits of ACE inhibitors in treated hypertensive people. Moreover, the response to ACE inhibitors of some groups of individuals with hypertension complicated primarily by diabetic renal disease is as strongly impaired as worsening of those symptoms which are usually improved by using these drugs [69]. The onset of microalbuminuria in diabetic patients would be related to smoking and hyperglycemia.

Calcium antagonists are a class of antihypertensive drugs that interfere with calcium metabolism at different levels, primarily calcium channels. They are currently used for treating hypertension.

Usually, calcium deposits are found into the arterial wall with an increase in their content associated particularly with aging. Since cigarette smoking induces vasoconstriction and a major incidence of thrombi formation where calcium plays a strong metabolic role, there is evidence that hypertensive smokers could be usefully treated by vasodilators drugs which antagonize calcium deposit [70]. Therefore, using calcium antagonists in hypertensive smokers could be a rationale intervention even if these drugs also are adversely influenced by cigarette smoking. Preventive effects against the damage from smoking would be identified by using calcium antagonists together with nitroglycerin in coronary artery disease [70].

A strongly adverse metabolic relationship exists between smoking and diuretics.

Diuretics are a complex class of drugs largely used for the treatment of hypertension [71, 72]. With the exception of the antagonists of aldosterone, the main mechanism of action of these drugs consists of inhibiting ion transporters in the luminal membrane of the renal tubule. There is evidence that most of the data concerning the hypotensive action of diuretics may be explained by the analysis of thiazide-type diuretic action. These drugs, which are used in the treatment of hypertension with a major rate than that of other diuretics and often in combination, act by sodium depletion or by a direct vascular effect independent of natriuresis [73].

Smoking influences strongly diuretic treatment of hypertensive smokers since it exerts an adverse effect on BP lowering primarily due to nicotine action. It is known by long time that either intravenous injection of nicotine or smoking one or two cigarettes has similar antidiuretic action in men [74].

Finally, little is known about the relationship between Angiotensin receptor blockers and smoking. Indeed, large-scale findings on this matter are yet lacking.

An experimental study [75] suggests a positive effect of Valsartan, an Angiotensin receptor blocker, on the alterations caused by smoking on vascular endothelium. The drug prevented smoking from impairing acetylcholine vasodilation. There was evidence that acute single-cigarette smoking caused a dysfunction of endothelium-dependent, but not endothelium-independent, vasodilation of rat cerebral vessel in vivo. The effect was not mimicked by intravenous nicotine. Therefore, Angiotensin 1 receptor blockade could prevent smoking-induced impairment of endothelium-dependent vasodilation although large-scale findings are yet missing and experimental data should be obtained.

Described data undoubtedly demonstrate that all the major classes of drugs commonly used for the treatment of hypertension are adversely influenced by smoking and, consequently, the goal of an effective treatment could fail in hypertensive smokers independently by the mechanism of action or choice of antihypertensive drug.

6. Conclusion

Two basic concepts arise from the analysis of exposed data. They match Pandora's box of Greek mythology [76].

Pandora's jar is a box where all existing evils are contained inside, when it is closed by a lid, to do not harm individuals. Therefore, there is an apparently good health. On the contrary, when the lid is removed all evils come out damaging heavily humans.

The first concept to stress is the different response of BP to smoking compounds that depends on the type of smoking, its duration, and onset of BP increase.

Initially, young smokers usually display normal or even low values of BP with no evident signs of vascular damage that, however, are beginning although not well evident clinically. Therefore, it would seem an illogical suggestion to forbid smoking to these individuals who are, apparently, in good health. One can consider this stage as that of closed Pandora's box which masks the damage contained inside the box. This could be also identified as the stage where tobacco smoke acts as an apparent friend of BP because of normal or lower levels.

The phenomenon of masked hypertension by either active or passive smoking well correlates the duration of smoking exposure and onset of BP increase. A growing literature highlights the role of this occurrence [77, 78]. The evidence now suggests that to improve BP, we require to forbid absolutely smoking as early as it has begun. Indeed, masked hypertension seems to be associated particularly with passive smoking in a dose-related manner, and low physical activity, increased heart rate, and postural haemodynamic reaction, all effects similar to those of sympathetic stimulation, may be potential accelerators of that phenomenon. Therefore, masked hypertension causes a type of damage that, pathologically, starts low and goes slow, but in progress, for many years even in case of pharmacological treatment.

When vascular wall alterations are evident and, more often, irreversible, open Pandora's box releases all unmanageable effects which become the structural substrate for hypertensive alterations. This stage represents tobacco smoke that is acting as enemy of BP.

Secondly, when there is evidence of hypertension to be treated, the response to antihypertensive drugs in smokers is usually impaired since biochemical and metabolic interference exists between cigarette smoking and antihypertensive drugs, although some classes of antihypertensive drugs would less the effects of smoking.

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Research Article

Modelling the Role of Dietary Habits and Eating Behaviours on the Development of Acute Coronary Syndrome or Stroke: Aims, Design, and Validation Properties of a Case-Control Study

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In this paper the methodology and procedures of a case-control study that will be developed for assessing the role of dietary habits and eating behaviours on the development of acute coronary syndrome and stroke is presented. Based on statistical power calculations, 1000 participants will be enrolled; of them, 250 will be consecutive patients with a first acute coronary event, 250 consecutive patients with a first ischaemic stroke, and 500 population-based healthy subjects (controls), age and sex matched to the cases. Socio-demographic, clinical, dietary, psychological, and other lifestyle characteristics will be measured. Dietary habits and eating behaviours will be evaluated with a special questionnaire that has been developed for the study.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality at a global level, with a significant impact on quality of life as well as an important economic burden [1]. In fact, in 2002, it is estimated that 7.2 million people died from coronary heart disease and 5.5 million from stroke, while according to the WHO estimates and due to the demographic changes, the number of CVD events is expected to increase further [2]. Therefore, prevention of CVD is now considered of major public health importance. Means for reducing the burden of the disease at population level include lifestyle interventions, and particularly dietary modifications.

During the last decades, studies from all over the world have evaluated the relationship between specific foods and dietary patterns with the development of CVD, and particularly coronary heart disease [3–8]. Healthy dietary patterns, like the Mediterranean, characterized by high consumption of foods of plant origin, fruits, vegetables, whole grain cereals, legumes, as well as poultry and fish, have been associated with decreased risk of the disease. On the contrary, more western dietary patterns, characterized by increased consumption of red and processed meat, sweets and desserts, potatoes, and refined cereal are associated with increased risk. However, the role of diet on the development of ischaemic stroke is not that well established [9, 10]. Moreover, although significant scientific evidence exists regarding the role of specific foods and dietary patterns on the development of CVD, the influence of certain dietary behaviours and practices has not been extensively studied and understood. For example, apart from the type of foods that are actually consumed, meal frequency, breakfast consumption, food consumption in parallel with other activities (such as working or television viewing), systematic consumption of heavy meals or eating alone, as well as sleeping patterns may also play an important direct or indirect role, regarding the development of coronary heart disease and stroke [11–15] (Figure 1).

Thus, the aim of the present study is to evaluate the role of dietary habits and eating behaviours on the likelihood

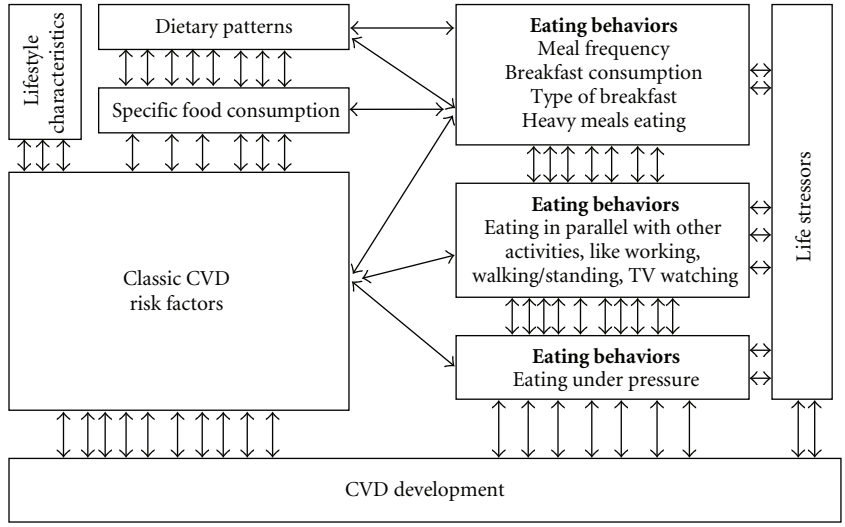

Figure 1: A conceptual model about dietary patterns, eating and lifestyle behaviours, and practices that will be tested in this study regarding the development of CVD.

of developing a first CVD event (acute coronary syndrome or stroke), after taking into account other lifestyle and environmental factors as well as socio-demographic and clinical characteristics.

2. Materials and Methods

2.1. Design. Multicentre, case-control with individual, age (within ±3 years) and sex matching (Figure 2).

2.2. Sampling Procedure. According to the sampling procedure all consecutive patients with a first acute coronary syndrome (ACS) event (acute myocardial infarction (AMI) or unstable angina (UA)) or ischaemic stroke, and without any suspicion of previous CVD, that will enter in the cardiology, pathology clinics, or the emergency units of three major General Hospitals in Greece (i.e., University General Hospital of Ioannina, Korgialeneio-Benakeio Red Cross Hospital, and Alexandra General Hospital, Athens) between October 1, 2009 and December 31, 2010 will be contacted to enrol in the study. Patients with a history of neoplasia or chronic inflammatory disease, as well as individuals with recent changes in their dietary habits, will not be included. Control subjects will be selected on a random, volunteer basis, and they will be without any clinical symptoms or suspicions of CVD in their medical history, as this will be assessed by a cardiologist. The control subjects will be allocated at population basis, and from the same region of the patients. Based on a priori statistical power analysis, a sample size of 500 patients (250 ACS, 250 stroke) and 500 age- and sex-matched healthy subjects, is adequate to evaluate two-sided odds ratios equal to 1.20, achieving statistical power greater than .80 at .05 probability level (P value).

2.3. Diagnosis of ACS or Stroke. At hospital entry clinical symptoms will be evaluated and a 12-lead electrocardiogram will be performed, by a cardiologist. Evidence of myocardial cell death will be assessed with blood tests and measurement of the levels of troponin I and the MB fraction of total creatinine phosphokinase (CPK). According to the Universal Definition of Myocardial Infarction (Joint ESC/ACCF/AHA/WHF Task Force) [16], blood samples will be obtained on hospital admission, at 6 to 9 h, and again at 12 to 24 h if earlier samples will be negative and the clinical index of suspicion is high. Acute coronary syndromes, and particularly myocardial infarction (AMI) will be defined by detection of rise and/or fall of troponin I or CPK with at least one value above the 99th percentile of the upper reference limit as well as with at least one of the following features: (a) compatible clinical symptoms, (b) ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block LBBB), (c) development of pathological Q waves in the ECG, (d) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [16]; unstable angina (UA) will be defined by the occurrence of one or more angina episodes, at rest, within the preceding 48 h, corresponding to class III of the Braunwald classification [17]. Ischaemic strokes will be defined through symptoms of neurologic dysfunction of acute onset of any severity, consistent with focal brain ischaemia and imaging/laboratory confirmation of an acute vascular ischaemic pathology [18].

2.4. Anthropometric Characteristics. Body weight (in kilograms) and height (in meters) will be measured following standard procedures (i.e., height will be measured to the nearest 0.5 cm, without shoes, back square against the wall tape, eyes looking straight ahead, while weight will be measured with a lever balance, to the nearest 100 g, without shoes, in light undergarments). Due to possible difficulties

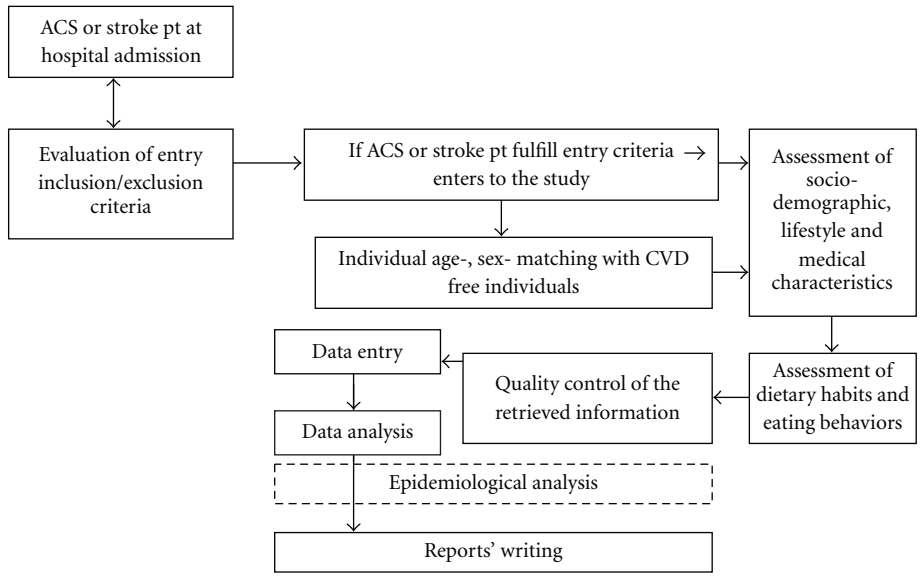

Figure 2: Flowchart of the study.

in the assessment of these anthropometric characteristics for the patients, it will be recorded whether the above values are self-reported or measured. Body mass index will then be calculated as weight (in kilograms) divided by standing height (in meters squared) and overweight and obesity will be defined as body mass index 25.0–29.9 kg/m^2 and >29.9 kg/m^2, respectively. Additionally participants will be asked what their lower and higher body weight was after the age of 20 years (in kilograms). Moreover, the participants will be asked if they have gained or lost weight during the last three months. In case they did, the kilograms gained or lost, and if the gain or the loss were voluntary or not will be recorded.

2.5. Socio-Demographic Characteristics. Socio-demographic variables that will be recorded are age and sex (for the matching procedure), educational level measured by years of school, type of occupation (in the following categories: civil servant, private employee, part-time employee, freelancer, rentier, retired, unemployed, housewife) and occupational skills that will be evaluated through a nine-point scale (values 1–3 refer to manual labour, while values from 7 to 9 refer to intellectual labour). Marital status categorised as single, married, divorced, or widowed and number of children will also be recorded. Financial status will be indirectly evaluated using (a) an index measuring how satisfied the participant is from his/her income (i.e., value 1 means not at all satisfied, to value 9 which means very satisfied), (b) the number of cars in the family, (c) the number of rooms in the house (including kitchen and bathroom), and (d) whether the residence is owned or not.

2.6. Lifestyle Characteristics. Physical activity will be assessed using the International Physical Activity Questionnaire (IPAQ) index [19] that has been validated for the Greek population, too [20]. Subjects will be asked to recall the number of days and hours or minutes they engaged in physical activity of different intensities for at least ten minutes, vigorous intensity and moderate intensity, walking and time spent sitting. According to their physical activity levels, participants will be classified as inactive, minimally active, or health enhancing physical activity (HEPA) active.

Furthermore, sleeping patterns will be assessed and participants will be asked about the hours they sleep at night, if they nap during the day (almost never, only on holidays, sometimes per week, almost every day), and in case they do, for how long (in minutes). They will also be asked about the frequency of night shifts at work (less than once in three months, 1–3 times per month, 2–4 times per week, almost every day). Television viewing will also be assessed by the hours of television viewed daily (less than 1 h, 1-2 h, 3–5 h, more than 5 h) and frequency of food consumption in front of the TV will be recorded (less than once in three months, 1–3 times per month, 2–4 times per week, almost every day).

Current or former smoking habits will be recorded and participants will be classified as (a) current smokers, (b) former smokers, or (c) non-smokers. Particularly, current smokers will be defined as those who smoke at least one cigarette per day, former smokers as those who had stopped smoking more than one year previously, and the rest of the participants will be defined as non-current smokers. Additionally, current and former smokers will be asked about the age they started smoking, the total number of years they smoke, and the number of cigarettes they smoke/smoked daily. Former smokers will be also asked about the number of years they have stopped smoking. Moreover, current and former smokers will be asked about the type of smoke they prefer/preferred (i.e., regular cigarettes, light cigarettes, tobacco), whether they smoke/smoked pipe or cigars, and if they smoke/smoked in their workplace, at home, or in front of their children. For the evaluation of passive smoking,

participants will be asked if other colleagues smoke in front of them in the workplace for more than 30 min daily and if other people in their environment smoke in front of them for more than 30 min per day (partner, parents, children, roommates). If they are not currently exposed to passive smoking, participants will be asked if they were exposed in passive smoking in the past and the years of exposure to passive smoking will be recorded.

2.7. Assessment of Dietary Habits. Dietary habits of the past year will be assessed through a 90-item, validated semi-quantitative food-frequency questionnaire (FFQ). Its validation properties will be briefly presented below. Regarding the dietary assessment, the participant will be asked how often (i.e., less than 3 months, 1-2 times/3 months, 1-2 times/month, 2–4 times/month, 1-2 times/week, 3–5 times/week, almost every day, more than one time per day) he/she consumes the following foods and beverages: red meat, processed meat, poultry, fish (and more specifically baked/boiled fish, fried fish, fresh tuna, or swordfish), legumes, cooked vegetables, pasta and rice (and in particular white pasta, whole wheat pasta, white rice, brown rice), potatoes, salads and fresh vegetables (and more specifically green leafy, cruciferous, coloured or starchy vegetables), eggs, sweets (and in particular baked sweets, honey, marmalade, cakes, white or milk chocolate, dark chocolate), consumption of non-homemade food and type of food (fast-food, sandwich, restaurant), salted nuts, unsalted nuts, canned food, milk and yogurt (and in particular full fat, low fat or skim), the number of milk and yogurt servings consumed in one week, feta-cheese, low fat white cheese, yellow cheese, low fat yellow cheese, and the number of servings of cheese consumed in one week. Fruit consumption will be recorded in fruits per day. The frequency of consumption (rarely, monthly, weekly, daily) of the following sources of fat will also be evaluated: olive oil for cooking or salad dressing, olive oil for frying, seed oil for cooking or salad dressing, seed oil for frying, mayonnaise or other sauce, butter, margarine, milk cream, olives. Additionally, the type of olive oil (packed extra-virgin olive oil, packed virgin olive oil, packed refined olive oil, unpacked olive oil—production by the participant, unpacked olive oil bought from friends) and the weekly amount (in litters) consumed will be assessed. Furthermore, bread as well as rusk consumption will be evaluated according to slices of bread consumed daily (less than half a slice, 0-1, 1-2, 3-4, 5-6, over 7 slices) and according to rusks consumed daily (less than one, 1-2, 3-4, 5-6, 7-8, over 9). The type (white or whole wheat) of bread and rusk consumption will be also recorded (frequency: rarely, monthly, weekly, and daily). Salt consumption in cooking, and the use of table salt or salt substitute will also be assessed. In addition, water, beverages, and juice consumption will be assessed in glasses per day. The type of beverage (cola drink, soda, light) and juice (carbonated, non-carbonated, from fresh fruits) will be evaluated. Frequency of alcohol consumption will be assessed in four categories: rarely, monthly, weekly, and daily. The participant will be also asked if he/she consumed more alcohol in the past as compared with the present consumption. Furthermore, the type of drink consumed will be recorded (i.e., beer, white wine, red wine, whisky, vodka, or ouzo) and the amount of alcohol consumed will be measured in wineglasses per day (i.e., <1, 1-2, 3-4, 5-6, over 7 wineglasses; each wineglass will be equivalent to 12 g of ethanol). Additionally, alcohol consumption patterns will be recorded; in particular, drinking of large quantities of alcohol rarely (for example in the weekends) as well as the frequency of hangover during the last year (i.e., never, 1-2 times/year, 1-2 times/6 months, 1-2 times/month, over twice/month). Coffee consumption will be assessed regarding its frequency (i.e., rarely, monthly, weekly, and daily). The participants will be asked about the type of coffee they prefer to drink (Greek, instant coffee, filtered, espresso, decaffeinated, cappuccino) as well as about the cups of coffee consumed daily (<1, 1-2, 3-4, 5-6, over 7). Additionally, the amount of coffee added in teaspoons in each cup, the type of coffee consumed (light, medium, heavy), and whether sugar or other sweetener is added and if yes, how many teaspoons are added will be evaluated. Frequency (i.e., rarely, monthly, weekly, daily) of tea consumption, the number of cups of tea per day (i.e., 0-1, 1-2, 3–5, over 5 cups) as well as the type of tea consumed (mountain tea, green tea, black tea, chamomile tea) will be also assessed. Additionally, participants will be asked whether they add sugar or other sweetener, and if yes how many teaspoons they add. Furthermore, the participants will be asked if they are on a diet and if they have changed their dietary patterns during the last year. Participants with important recent (i.e., within a year) changes in their dietary habits will be excluded from the study.

Overall assessment of dietary habits will be performed using the MedDietScore [21], an eleven-item composite index that evaluates adherence to the Mediterranean dietary pattern. The range of the MedDietScore is between 0–55. Higher values of this diet score indicate greater adherence to the Mediterranean diet. The validation properties of the MedDietScore have been presented elsewhere in the literature [21–23].

2.8. Validation of the FFQ. As mentioned above, a semi-quantitative FFQ developed for the purposes of this study will be used. For the validation properties, 59 males (40 ± 14 yrs) and 77 females (40 ± 13 yrs) were asked to complete the FFQ presented above, during 2010. Participants were also asked to complete a 3-day food record of what they have eaten. The recording period included two weekdays and one weekend day, over the same time span as the FFQ. This record was used as the reference method for validating the FFQ. Agreement of the FFQ with the 3-day food records was evaluated using the Bland-Altman method and the Kendall's tau-b coefficient. Between the 3-day food records and the FFQ, moderate agreement for coffee (tau-b = 0.56, $P < .001$), fruits (tau-b = 0.48, $P < .001$), fast-food consumption (tau-b = 0.47, $P < .001$), alcohol (tau-b = 0.47, $P < .001$), sweets (tau-b = 0.36, $P < .001$), vegetables (tau-b = 0.32, $P < .001$), and red meat (tau-b = 0.31, $P < .001$) was found, while low, but still significant agreement for greens

(tau-b = 0.22, $P = .004$), cereals (tau-b = 0.21, $P < .001$), and dairy products (tau-b = 0.18, $P = .007$) was observed. According to the Bland-Altman method the level of agreement varied from 90% to 99%. Sensitivity analyses by sex and age category (< or >55 yrs) and obesity status showed similar validity of the FFQ in each subgroup.

2.9. Assessment of Eating Behaviours. As mentioned in the aim of the study, a research hypothesis that will be also tested is whether certain eating behaviours may influence the likelihood of developing ACS or stroke. Thus, a special questionnaire that has been designed for the purposes of the present study will be used to evaluate several behaviours of the participants such as meal frequency, breakfast consumption, consumption of food in parallel with other activities. Frequency of consumption (rarely, 1-2 times/week, 3–5 times/week, and almost every day) of the following meals and snacks will be assessed: breakfast, morning snack, lunch, evening snack, dinner, and bed-time snack. Consumption of any food except water will be considered as a meal or snack. Additionally, potential reasons for skipping a meal will be evaluated. Participants will be asked about how frequently (less than once in three months, 1–3 times per month, 2–4 times per week, almost every day) they skip a meal or snack, because of hard work, because of the will to lose weight, or because they are not hungry. Detailed information will be asked regarding breakfast consumption. In particular, participants will be asked about the time they eat breakfast (earlier than 6 am, 6–8 am, 8–10 am, after 10 am) and the frequency (rarely, 1-2 times/week, 3–5 times/week, almost every day) they consume the following foods for breakfast: coffee or tea without sugar, coffee or tea with sugar, milk and yogurt, juice, fruits, cereals and rusks, sandwiches, bread, marmalade, honey, bakery products (croissants, cakes etc.), eggs, omelettes, and processed meat. Moreover, duration of lunch and dinner (i.e., 0–15 min, 15–30 min, 30–45 min, 45–60 min, and over 60 min), consumption of alcohol with meals (i.e., no alcohol consumption, red wine, white wine, beer, and other) and the time (in minutes) between dinner and night sleep will be recorded.

Additionally, frequency (rarely, 1-2 times per week, 3–5 times per week, almost every day) of food consumption under stress conditions (before the participant has time to relax), while working at the same time (without being on a break), and while walking or standing (not sitting) will be recorded. Furthermore, participants will be asked about how often they consume a more heavy meal that makes them feel full (less than once in three months, 1–3 times per month, 2–4 times per week, almost every day), if they are responsible for the preparation of meals (almost never, sometimes per week, a meal of the day, almost every meal), and how frequently they eat alone (almost never, sometimes per week, a meal of the day, almost every meal).

The last meal consumed before the ACS or the stroke event will be recorded (breakfast, morning snack, lunch, evening snack, dinner, and bed-time snack) and patients will be asked if they have consumed more food than usual the day of the event or the previous day or more heavy food than usually, and which type of food. They will also be asked if they have consumed more alcohol than usually (and how many wineglasses) and if they have consumed more coffee (and how many cups) in the day of the event or the previous day. Time between the last meal consumed and the event will be also recorded. Patients will be asked if they were feeling full or hungry at the time of the event, using a 9-item scale (1: very full, 9: very hungry). Furthermore, they will be asked if the day of the event or the previous day they were feeling: angry or scared, depressed or stressed, if they had exercised more than usual, if they had not slept at night, if they were ill, and if they were exposed to cold. Controls will be asked the same questions, but regarding the day of the interview or the previous day.

To evaluate the participants' health perspectives they will be asked to value the importance of several CVD risk factors using a scale of 1 to 9 (1 means not at all important whereas 9 means very important). The factors that will be evaluated are smoking, passive smoking, sedentary lifestyle, stress, unhealthy dietary habits, overweight and obesity, diabetes, hypercholesterolemia or hypertension, family history.

2.10. Assessment of Medical History. In all participants, family history of CVD as well as personal and family history of hypertension, hypercholesterolemia, hypertriglyceridemia, and diabetes will be recorded. In case of positive responses regarding personal history of the above conditions, the participant will be asked about the way of management (diet and/or drugs) and the frequency of drug use (daily, weekly, monthly, rarely) in case they do not adhere to the drug prescription. Participants will be also asked if they have renal failure (and if yes for how many years), peripheral artery disease and thyroid disease (hypothyroidism, hyperthyroidism, way of management, years of thyroid disease). Women will be asked about their menopause status (premenopausal, menopausal less than 2 years, or menopausal more than 2 years) and also about potential hormone use (oral contraceptive pills, menopause hormone replacement therapy) and for how many years. Finally, angiographic data and the following clinical and biochemical values will be recorded from the latest participants' record: blood pressure, heart rate, fasting glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, TSH, hematocrit, white blood cells count, platelets count, urea, creatinine, and uric acid.

2.11. Psychological Evaluation. A previously translated and validated version of the Zung Depression Rating Scale (ZDRS) will be used for the assessment of depressive symptoms [24, 25]. The ZDRS is a self-rating scale consisting of 20 items that cover affective, psychological, and somatic symptoms for the measurement of depression, and was originally developed in order to assess depression symptoms without the bias of an administrator affecting the results. The individual specifies the frequency a symptom is experienced (i.e., little = 1, some = 2, a good part of the time = 3, or most of the time = 4). Total theoretical range of the score is 20–80, with higher scores indicating more severe depression

[24]. Scores 20–49 are considered normal, scores of 50–59 indicate mild depression, scores of 60–69 moderate to marked depression, while scores of 70–80 severe depression [25].

Moreover, the State-Trait Anxiety Inventory form Y is a brief self-rating scale for the assessment of state and trait anxiety. In the present study anxiety will be assessed only with the also previously translated and validated version of Spielberger Trait Anxiety Inventory (STAI form Y-2), which is a 20-item self-reported questionnaire evaluating how the respondent feels generally [26, 27]. The 20 items are rated from 1 to 4 according to frequency of their feelings (i.e., almost never, sometimes, often, almost always). Total theoretical range of the score ranges from 20 to 80.

2.12. Bioethics. The study has been approved by the Ethics Committee of the University Hospital of Ioannina and will be carried out in accordance to the Declaration of Helsinki (1989) of the World Medical Association. Prior to the collection of any information, participants will be informed about the aims and procedures of the study and will provide their written signed consent.

2.13. Statistical Analysis Plan. Normally distributed continuous variables will be presented as mean values ± standard deviation, skewed variables as median and quartiles and categorical variables as frequencies. Associations between categorical variables will be tested by the calculation of chi-squared test. Comparisons between normally distributed continuous variables will be performed by the calculation of Student's t-test. In case of skewed continuous variables, the tested hypotheses will be evaluated using the nonparametric U-test suggested by Mann and Whitney. Correlations between continuous variables will be evaluated using the Pearson's r or Spearman *rho* coefficients. Normality of the variables will be tested using P-P plots. Estimations of the relative probabilities of developing CVD (ACS, stroke or combined) will be performed by the calculation of the odds ratio and the corresponding 95% confidence intervals through multiple logistic regression analysis. Hosmer-Lemeshow statistic will be calculated to test goodness-of-fit. All reported P values will be based on two-sided tests. SPSS 18.0 software (SPSS Inc., Chicago, Il, USA) will be used for all the statistical calculations.

3. Study's Expectations

The findings of this case-control study will provide novel information and valuable explanations and answers on how dietary choices, from specific food consumption to eating behaviours and practices, influence the development of ACS and ischaemic strokes. Prevention of CVD is of considerable public health importance as it constitutes a major public health problem, especially in westernised world, and less than 50% of its variation has been explained by the up-to-date known risk factors. Lifestyle characteristics, like diet, smoking, and physical activity are considered to play a crucial role for the prevention of the disease, because they can be modified. However, in spite of the nutritional guidelines and recommendations for a healthy diet and lifestyle, dietary habits in the developed world, in developing countries at "nutrition transition", and even around the Mediterranean basin are changing towards the opposite direction [28, 29]. Thus, understanding of the role of dietary habits and eating behaviours on the development of CVD could offer other means to focus on prevention through emphasis on these factors. The results of the present study may suggest other possible ways to emphasize when targeting on the prevention of CVD, giving attention not only on types of food consumed and dietary guidelines, but also on eating behaviours, like meal frequency, breakfast consumption, heavy meal consumption, eating alone, activities to be followed or not while consuming a meal, like working, walking, or television viewing. Finally, attention might be needed regarding other lifestyle behaviours like hours of night sleep and napping, as they could also have an effect on the development of cardiovascular disease directly or indirectly (meaning that they could influence as well food choices).

Authors' Contribution

C. M. Kastorini is the principal investigator of the study and wrote the paper, H. Milionis, J. Goudevenos contributed to the design of the study, and reviewed the paper and D. B. Panagiotakos had the concept, designed the study, and reviewed the paper.

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Research Article

Physical Activity and Adherence to Mediterranean Diet Increase Total Antioxidant Capacity: The ATTICA Study

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We studied the association of physical activity and adherence to the Mediterranean diet, in total antioxidant capacity (TAC). A random sample of 1514 men and 1528 women was selected from Attica region. Physical activity was assessed with a translated version of the validated "International Physical Activity Questionnaire" (iPAQ), and dietary intake through a validated Food Frequency Questionnaire (FFQ). Adherence to the Mediterranean diet was assessed by the MedDietScore that incorporated the inherent characteristics of this diet. TAC was positively correlated with the degree of physical activity ($P < .05$). TAC was also positively correlated with MedDietScore ($r = 0.24$, $P < .001$). Stratified analysis by diet status revealed that the most beneficial results were observed to highly active people as compared to inactive, who also followed the Mediterranean diet ($288 \pm 70\,\mu$mol/L, $230 \pm 50\,\mu$mol/L, resp.), after adjusting for various confounders. Increased physical activity and greater adherence to the Mediterranean diet were associated with increased total antioxidant capacity.

1. Introduction

Physical activity has been evolved as a significant factor towards the prevention of cardiovascular and metabolic diseases as well as some kinds of cancer [1–5]. From early studies, however, it has been reported that strenuous physical activity induces a decrease in antioxidant levels and a concomitant increase in the markers of lipid peroxidation in target tissues and blood [6]. It is also known that vigorous exercise induces mitochondrial generation and/or leakage of superoxide and hydrogen peroxide with or without reduction in tocopherol (vitamin E) content in both muscle and liver [7]. Furthermore, from animal studies it has been found that exercise could accelerate the development of mammary tumors linked to exercise-induced oxidants production [8]. Simultaneously, the impact of a high fat diet has shown to reverse the beneficial effect of caloric restriction in oxidative stress in the muscle tissue of rats [9]. Moreover, a recent study in experimental animals fed with high fat diet showed that physical exercise did not provide any beneficial effect on oxidative stress and antioxidant defenses [10]. Lastly, in a group of 30 sportsmen, antioxidant supplements offered protection against exercise-induced oxidative stress [10].

Likewise, it is well documented from numerous epidemiological studies that diets rich in vegetables, fruits, whole grains, legumes, fish, and low-fat dairy products are associated with lower incidence of various chronic diseases [11, 12]. The dietary characteristics found in the olive growing areas of the Mediterranean region (i.e., Greece, Spain, Italy, and France) have been also associated with lower incidence of cardiovascular diseases, metabolic disorders, and several types of cancer [13–18]. Furthermore, a recent meta-analysis showed that greater adherence to a Mediterranean diet is associated with a significant improvement in health status, as seen by a significant reduction in overall mortality (9%), mortality from cardiovascular diseases (9%), incidence of or

mortality from cancer (6%), and incidence of Parkinson's disease and Alzheimer's disease (13%). These results seem to be clinically relevant for public health, in particular for encouraging a Mediterranean-like dietary pattern for primary prevention of major chronic diseases [19]. These benefits have been associated with higher ability to cope with daily oxidative stress [20].

The determination of antioxidant capacity is a well-established tool in medical diagnosis and treatment of several diseases, such as cardiovascular disease, diabetes mellitus, cancer, and aging [21]. One of the most widely accepted index of whole body antioxidant ability is the total antioxidant capacity (TAC). Evaluation of TAC is one of the most common procedures employed to evaluate the hydrosoluble antioxidant status of biological fluids. Total antioxidant capacity (TAC) considers the cumulative action of all antioxidants that are present in plasma and body fluids and provides an integrated measurement rather than the simple sum of measurable antioxidants. A wide range of evidence indicates the importance of TAC in plasma and tissues, and of its practicability as a tool for investigating the association between diet and oxidative stress [22]. In a recent study, investigating the relation between TAC and obesity in children and adolescences, TAC was inversely associated with body mass index, standard deviation score of body mass index, and total body fat, only in obese subjects. These data suggest that TAC can also be used as a potential indicator of the risk to develop obesity-related features [23]. Furthermore, data from the same group suggest that dietary TAC may be also a potential early estimate of the risk to develop metabolic syndrome features [24]. Finally, in a crossover trial where 24 subjects received a two-week diet high in antioxidant capacity, the results indicated that this type of diet improves significantly endothelial function in the volunteers at low cardiovascular risk, and may further reduce their risk of CVD [25].

Summarizing, the effect of exercise on oxidative stress seems not to be clear and the exercise effects might be modulated by other important factors like diet. Therefore, the purpose of the present study was to examine the separate and combined effect of physical activity and adherence to the Mediterranean diet on TAC.

2. Materials and Methods

The "ATTICA" epidemiological study has been carried out in the province of Attica (including 78% urban and 22% rural areas). The sampling was random, multistage by city, and stratified by age and gender group according to the gender-age distribution of the province of Attica (2001 census). From May 2001 to December 2002, 4056 inhabitants from the above area were randomly selected to enrol into the study (via mail or telephone). However, 3042 of them agreed to participate (75% participation rate). Each participant gave informed written consent and the protocol was approved by the Medical Research Ethics Committee of Athens Medical School. All participants were interviewed by trained personnel (cardiologists, general practitioners, dieticians, and nurses) who used standard questionnaires that evaluated lifestyle habits and various sociodemographic, clinical and biological characteristics. Five percent of men and 3% of women were excluded from the study because they had history of cardiovascular or other atherosclerotic disease, as well as chronic viral infections, as it was ascertained by their medical records. Moreover, participants did not have cold or flu, acute respiratory infection, dental problems, or any type of surgery during the past weeks.

Power analysis showed that the number of enrolled participants is adequate to evaluate two-sided standardised differences greater than 0.5 between diet subgroups and the investigated biochemical parameters, achieving statistical power greater than 0.90 at 5% probability level (P-value).

The study was approved by the Medical Research Ethics Committee of Athens Medical School and was carried out in accordance with the Declaration of Helsinki (1983) of the World Medical Association.

2.1. Physical Activity Ascertainment. A translated version of the validated "International Physical Activity Questionnaire" (iPAQ), suitable for assessing population levels of self-reported physical activity was used [26]. The short version of iPAQ provided information on weekly time spent walking, in vigorous, moderate-intensity, and in sedentary activity. Participants were instructed to refer to all domains of physical activity during a usual week of the past year. Both continuous and categorical indicators of physical activity status were assessed. In particular, the continuous indicator was calculated as a sum of weekly MET-minutes per week of walking, moderate- and vigorous-intensity exercise. Furthermore, the categorical analysis grouped the subjects in three levels that were developed based on a key concept in current public health guidelines for physical activity [27], that is, (a) inactive, (b) minimally active, and (c) HEPA active (health enhancing physical activity, a high active category). The criteria of grouping in each category have been previously described [28].

2.2. Dietary Assessment. Consumption of unrefined cerealsand products, legumes, fruits, poultry, vegetables, olive oil, nonfat or low-fat dairy products, fish, nuts, potatoes, eggs, sweets, red meat, and meat product, was measured as average amounts consumed per week during the past year, with the use of a validated food frequency questionnaire (FFQ) from the department of nutritional epidemiology of Athens Medical School [29]. The frequency of consumption was then quantified approximately in terms of the number of times per month that a food was consumed. Alcohol consumption was measured by daily ethanol intake, in wine glasses (100 mL and 12 g ethanol concentration). Based on the Mediterranean diet pyramid [30], we calculated a special diet score ranging from 0 to 55 [31]. Higher values of this score (MedDietScore) indicate adherence to the Mediterranean diet, whereas lower values indicate adherence to the "Westernized" diet.

2.3. Sociodemographic and Lifestyle Variables. Additionally to the physical activity and dietary status, the study's questionnaire included demographic characteristics such as, the financial status of the study's participants which was recorded as the mean annual income during the past three years and their educational level (as a proxy of social status) which was measured in years of school. Information about smoking habits was also collected using a standardized questionnaire developed for the study. Current smokers were defined as those who smoked at least one cigarette per day and former smokers were characterized as those who had stopped smoking for at least 1 yr. All other individuals were classified as nonsmokers. Occasional smokers (<7 cigarettes per week) were recorded and combined with current smokers due to their small sample size. For a more precise evaluation of smoking habits, the pack-years (cigarette packs per day multiplied by years of smoking) were calculated. In order to take into account various types of cigarettes consumed (i.e., light, heavy, very heavy), we used as a unit 1 cigarette with nicotine content of 0.8 mg.

2.4. Anthropometrics, Clinical, and Biochemical Characteristics. Standing height and weight were recorded, and body mass index (BMI) was calculated as weight (kg) divided by standing height (m^2). Arterial blood pressure was measured three times, at the end of the physical examination with subject in sitting position. All participants were at least 30 minutes at rest. Patients whose average blood pressure levels were greater or equal to 140/90 mmHg or were under antihypertensive medication were classified as hypertensive. Blood samples were collected from an antecubital vein between 8 to 10 AM, with the subjects in a sitting position after 12 hours of fasting and avoiding of alcohol.

TAC was measured through colorimetric test in serum (ImAnOx, Immunodiagnostik AG, Bensheim, Germany). In particular, the determination of antioxidant capacity was performed by the reaction of antioxidants in the sample with a defined amount of exogenously provided hydrogen peroxide. The intra-, interassay coefficients of variation of TAC did not exceed 2% and 5%, respectively. Further blood lipid examinations, that is, serum total cholesterol, and low-density lipoprotein cholesterol, were measured using chromatographic enzymic method in an automatic analyzer (RA-1000, Mecon Ltd, Athens, Greece). The intra- and interassay coefficients of variation of all cholesterol levels did not exceed 4%. Hypercholesterolemia was defined as total serum cholesterol levels greater than 200 mg/dL or the use of lipid lowering agents.

2.5. Statistical Analysis. Continuous variables are presented as mean values ± standard deviation. Categorical variables are presented as absolute and relative frequencies. Associations between categorical variables were tested by the calculation of chi-squared test, while differences between categorical and several biochemical, clinical, and nutritional variables were tested by the use of Student's *t*-test and Mann-Whitney test (for the normally distributed and the skewed variables, resp.). Comparisons between TAC and tertiles of the diet score were performed using one-way Analysis of Variance, after adjusting for sex. However, due to multiple comparisons, we used the Bonferroni correction in order to account for the increase in Type I error. Multiple linear regression was applied to test the association between the MedDietScore and TAC, after controlling for several potential confounders. Colinearity between independent variables was evaluated through the condition index, while model's goodness-of-fit was graphically evaluated (standardized residuals against fitted values).

All reported *P*-values are based on two-sided tests and compared to a significance level of 5%. SPSS 14 (SPSS Inc., Chicago, IL, USA) software was used for all the statistical calculations.

3. Results

The descriptive characteristics of the participants are presented separately in men and women according to the MedDietScore in Table 1. TAC was positively correlated with diet score (rho = 0.24, $P < .005$), indicating that greater adherence to the Mediterranean diet was associated with increased TAC levels. In particular, people in the highest tertile of diet score had higher TAC levels as compared to people in the lowest tertile. Both men and women that were grouped in the higher tertile of the diet score had greater levels of physical activity as assessed by the METs min/week. Furthermore, both male and female participants in the highest tertile of the diet score were older, had lower body mass index, lower systolic blood pressure, and lower prevalence of hypertension. No associations were found between diet score and the other blood lipids measured, current smoking, and financial status (Table 1).

Figure 1 confirms the previous relationships by presenting the correlation of physical activity categories with TAC levels, as well as the combined effect that exercise and compliance to the Mediterranean diet has on TAC. It is shown that highly active people (HEPA active) have higher TAC levels compared to less active ones. The highest TAC levels were observed among people that have both the greater adherence to the Mediterranean diet and the highest level of physical activity.

However, residual confounding may exist. Thus, the unadjusted analyses were repeated after controlling for age, sex, and body mass index (factors that are known to influence both physical activity status and TAC levels). Table 2 illustrates the association of physical activity status on TAC levels, by dietary habits, after various adjustments made. The results demonstrate that people with increased physical activity combined with close or very close adherence to the Mediterranean diet had higher levels of TAC compared to those who were inactive.

4. Discussion

In a sample of 3042 free-living people, it was revealed that increased physical activity in combination with greater adherence to the Mediterranean diet was associated with increased TAC levels.

Table 1: Lifestyle, clinical, and biochemical characteristics of the participants, according to Mediterranean diet score.

	Men ($n = 1514$)			Women ($n = 1528$)			
	Tertile of diet score						
	1st (0–20)	2nd (21–35)	3rd (36–55)	1st (0–20)	2nd (21–35)	3rd (36–55)	$P^{\perp}$
	$n = 504$	$n = 505$	$n = 505$	$n = 509$	$n = 509$	$n = 510$	
Age (years)	44 ± 11	42 ± 8	48 ± 7**	43 ± 7	45 ± 7*	47 ± 6**	.01
Years of education	11 ± 4	13 ± 4	14 ± 5	9 ± 4	10 ± 4	13 ± 3	.001
Current smoking (%)	49	46	44	40	39	38	.21
Physical activity status							.001
Inactive (%)	63	26**	11**	70	22**	8**	
Minimally active (%)	64	26**	10**	71	21**	8**	
HEPA (%)	59	25**	16**	65	25**	10**	
METs min/week	965 ± 1512	976 ± 1495	1429 ± 2023**	728 ± 1262	688 ± 1027*	901 ± 1281**	.03
Body mass index (kg/m^2)	27 ± 5	26 ± 4	25 ± 5*	26 ± 3	24 ± 4*	24 ± 3*	.04
SBP (mm Hg)	129 ± 17	125 ± 18*	125 ± 17*	129 ± 18	120 ± 18**	120 ± 19**	.003
DBP (mm Hg)	83 ± 11	81 ± 14	80 ± 11	80 ± 11	75 ± 12	75 ± 10	.25
Hypertension (%)	51	27**	20**	50	36**	10**	.001
Total cholesterol (mg/dL)	197 ± 43	194 ± 41	194 ± 43	196 ± 40	190 ± 42	188 ± 47	.14
LDL-cholesterol (mg/dL)	134 ± 43	124 ± 38	124 ± 42	126 ± 39	120 ± 37	120 ± 41	.07
Hypercholesterolemia (%)	45	39	36	51	47	25	.08
TAC (μmol/L)	225 ± 33	242 ± 31**	251 ± 32**	231 ± 26	239 ± 29*	255 ± 44**	.002

TAC: total antioxidant capacity; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low density lipoprotein.
Data are presented as mean ± SD and percentages.
No significant interactions were observed between tertile of diet score and sex.
$^{\perp}$ Probability values are derived from ANOVA and evaluate the association between tertiles of diet score and the investigated variables, after adjusting for sex.
*P-value < .05; **P-value < .01 for the comparisons between 2nd, 3rd tertile versus 1st tertile of diet group.

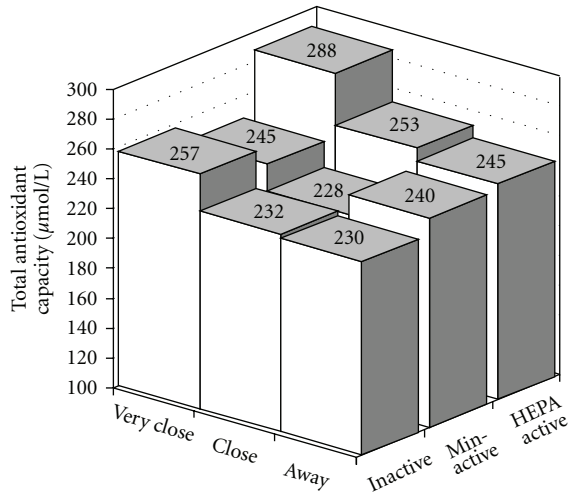

Figure 1: TAC levels and physical activity status (inactive, min-active, and HEPA active) by MedDietScore that assessed adherence to the Mediterranean diet (away, close, and very close).

These findings suggest that regular exercise in combination with this specific dietary pattern may have beneficial effect on cardiovascular system through another pathophysiological mechanism, that is, their ability to modulate oxidation process. Moreover, the results had clearly shown that highly active people who exercise several days per week enjoyed greater protection from the oxidative process due to higher TAC levels. The degree of physical activity was positively correlated with TAC, and another interesting finding of the study was that both men and women who belonged to the highly active group (HEPA active) were also those, who followed dietary patterns closer to the Mediterranean diet.

A large number of observational studies have suggested that people with greater adoption of the Mediterranean diet (i.e., high intakes of fruits, vegetables, and olive oil) experience lower risk of coronary heart disease events [3, 14, 16, 17, 32, 33]. However, the data in changes of total antioxidant capacity (TAC) in humans is conflicting. Some investigators observed that in patients with coronary heart disease, α-tocopherol treatment significantly reduces the rate of nonfatal myocardial infarction, while others reported that although vitamin E supplementation increased blood vitamin concentrations, it did not produce any significant reductions in the morbidity or mortality of any type of cardiovascular disease and cancer. In addition, based on a systematic review in the literature, Blomhoff [34] concluded that although observational studies have suggested that antioxidants may reduce oxidative stress, clinical trials do not support these benefits. Therefore, the scientific research

Table 2: Results from multiple linear regression analysis that evaluated the association of physical activity status (independent) on TAC levels (dependent), by dietary habits.

Mediterranean diet status	Physical activity status	$b \pm$ SE	P
Away	*HEPA versus Inactive*	13.47 ± 5.7	.21
	Minimally active versus inactive	3.34 ± 2.6	.48
	Age (years)	−0.14 ± 0.2	.58
	Males versus females	−4.36 ± 6.7	.52
	BMI (kg/m^2)	−0.32 ± 0.64	.62
Close	*HEPA versus Inactive*	15.7 ± 9.4	.05
	Minimally active versus inactive	2.82 ± 4.3	.09
	Age (years)	−0.76 ± 0.3	.03
	Males versus Females	−4.85 ± 8.2	.56
	BMI (kg/m^2)	−1.79 ± 1.33	.18
Very close	*HEPA versus Inactive*	19.7 ± 7.4	.03
	Minimally active versus inactive	2.4 ± 9.6	.06
	Age (years)	−0.16 ± 0.3	.65
	Males versus females	−21.8 ± 10.7	.04
	BMI (kg/m^2)	−0.35 ± 1.30	.78

needs to clarify whether other plant antioxidants, or their combination, or whole dietary patterns that induce the endogenous antioxidant defense, can reduce pathogenesis of cardiovascular disease. Moreover, since there is some evidence that exhaustive exercise may have negative impact on the body's antioxidant capacity, it seems necessary to determine the level of physical activity that in combination with adaptation of a specific dietary pattern, like the Mediterranean diet, has optimal effect on TAC.

In this work it was observed that almost a 20% increment in the diet score (that assessed greater adherence to the Mediterranean dietary pattern) was associated with about 6% rise in TAC irrespective of various potential confounding factors. The high content of the Mediterranean diet in vegetables, fresh fruits, cereals, and olive oil, as well as the moderate intake of wine, guarantee a high intake of β-carotene, vitamins B_6, B_{12}, C, and E, folic acid, polyphenols and various minerals, known for their antioxidant effect. However, the influence of the Mediterranean dietary pattern on antioxidant capacity of human body has been rarely investigated. To the best of our knowledge, only Leighton et al. [35] based on an intervention study, reported that total antioxidant reactivity increased by 28% above basal levels in the Mediterranean diet group, compared to the high fat diet group. In this study, we expanded the previous results since we were able to study a "free eating" population. Thus, these findings could be applicable to the general population, since the "doses" of this dietary pattern were not excessive even in the high consuming group.

From this work, it can be concluded that the combination of certain dietary patterns with an increased level of physical activity is essential for the protection of the cardiovascular system.

5. Limitations

Due to the cross-sectional design of the study, we cannot establish causal relations but only generate hypothesis for the association of a dietary pattern on TAC of human body. In addition, although diet is a lifelong habit and usually pre-exist a pathological condition, inverse causation may still exist. Another limitation is the misreporting of food items consumed and especially alcohol consumption, due to recall bias or social class of the participants. Moreover, the food frequency questionnaire has been validated in a sample of school teachers, while we have applied it into the general population. This may hide over- or underestimation of various nutrients estimated. However, in this work we have not used nutrient intake that may be influenced by the validation of the questionnaire.

6. Conclusions

Until recently, traditional analyses in the fields of nutritional epidemiology usually relate health status to a single or a few nutrients or foods. However, it is evident that people do not eat isolated nutrients, but meals consisting of a variety of foods with complex combinations of nutrients. Furthermore, the level of physical activity seems to interact with diet and both affect health status. Under this concept, the combined effect of increased physical activity with greater adherence to Mediterranean diet, on TAC was examined. It was observed that the Mediterranean diet as well frequent exercise, enhanced antioxidant defences. Alternatively, the combination of a sedentary lifestyle and a high fat diet, rich in saturated fats, induced oxidative stress.

Based on these findings, we underline the need for actions from public health care professionals, towards prevention of the development and progression of atherosclerotic diseases, through the adoption of an active lifestyle and a dietary pattern, low in fat, rich in fruits, vegetables and legumes, like the Mediterranean diet.

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Research Article

The Impact of Demographic Characteristics and Lifestyle in the Distribution of Cystatin C Values in a Healthy Greek Adult Population

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Background. The aim of the present study was to examine sources of variation for serum cystatin C in a healthy Greek population. *Methods*. Cystatin C together with basic clinical chemistry tests was measured in a total of 490 adults (46 ± 16 yrs, 40% males) who underwent an annual health check. Demographic, anthropometric, and lifestyle characteristics were recorded. *Results*. Higher values of cystatin C were observed among males ($P = .04$), participants aged over 65 years ($P < .001$), current smokers ($P = .001$) and overweight/obese participants ($P = .03$). On the contrary, alcohol consumption and physical activity seemed to have no influence on cystatin C levels ($P = .61$; $P = .95$, resp.). *Conclusions*. In interpreting serum cystatin C values in a healthy adult population, age, gender, Body Mass Index, and cigarette smoking need to be considered, and determination of reference ranges among distinct subpopulations seem to be prudent.

1. Introduction

Cystatin C is a nonglycosylated, low molecular weight (13.250 Da), basic protein that is a member of the cystatin superfamily of cysteine protease inhibitors [1–3]. It consists of 120 amino acids, it is produced by all nucleated cells at a constant rate, and it is excreted by the kidneys by free glomerular filtration and complete tubular reabsorption and degradation [4–6]. Therefore, serum concentration levels of cystatin C are almost totally dependent on the glomerular filtration rate and—unlike serum creatinine levels which increase after glomerular filtration rate has fallen by approximately 50%—even a slight reduction in glomerular filtration rate causes a rise in serum cystatin C [7, 8]. Besides its usefulness as a marker of renal function, serum cystatin C appears to be a prognostic marker of cardiovascular events and death among elderly persons without chronic kidney disease [9, 10]. Therefore, it is important to establish reference values of cystatin C not only for nephrologists, but for cardiologists as well.

In this study, serum cystatin C concentrations were measured in a healthy Greek adult population, and reference intervals were derived after taking under consideration sources of variation for this population.

2. Materials and Methods

2.1. Participants. Between April 2009 and January 2010, a total of 490 consecutive adults (85% participation rate), who had visited the "Polykliniki" General Hospital for an annual health check, agreed to participate in the study. The retrieved data were confidential, and the study followed the ethical considerations provided by the World Medical Association (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). Moreover, the Institutional Review

Board approved the design, procedures, and aims of the study (GA 23/14.05.2009). All participants were informed about the procedures of the study and agreed to participate providing written informed consent.

Subjects who reported chronic diseases such as renal failure, diabetes mellitus, cardiovascular diseases, cancer, thyroid dysfunctions, or pregnancy were excluded as well as those treated with drugs that may influence renal function or cystatin C concentrations (i.e., antihypertensives, diuretics, antiinflammatory agents, hypoglycemic agents, anticonvulsants, and antibiotics). Other exclusion criteria were: (1) fasting serum glucose $\geq$ 126 mg/dL, (2) systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg, (3) Body Mass Index (BMI) $\leq$ 18.5 or $\geq$ 30, to avoid the extremes of body size, and (4) eGFR (glomerular filtration rate) < 60/ml/min/1.73 m^2, a threshold defining Chronic Kidney Disease (CKD) by the independent international Kidney Disease Improving Global Outcomes Organization (KDIGO) using the simplified Modification of Diet in Renal Disease Study (MDRD) equation [11, 12]. Therefore, 279 individuals (40 $\pm$ 13 yrs, 37% males) fulfilled the abovementioned criteria and were found eligible to participate in the study.

2.2. Other Characteristics. Participants were classified to the following age categories: 18–44 yrs, 45–64 yrs, and $\geq$65 yrs. Waist circumference and height (without shoes) were measured to the nearest 0.5 cm, and weight was measured with a lever balance, to the nearest 100 g, without shoes, in light undergarments. Body Mass Index (BMI) was then calculated as weight in kilograms divided by the square of standing height in meters. Participants were then classified in those with normal values of BMI (i.e., <25 kg/m^2) and to overweight/obese (BMI $\geq$ 25 kg/m^2). With respect to lifestyle characteristics, participants were asked to fill in a 10-grade scale range regarding their physical activity status (grade of scale used: 1–10, where 1 denotes sedentary lifestyle and 10 daily hard activity of at least 30 minutes). Participants with score $\leq$6 were classified as with low/moderate activity, while those with score >6 were considered as highly active. Alcohol consumption was assessed as the self-reported number of drinks per week and participants were categorized as never/rare (i.e., 0-1 drink/week) and current drinkers (i.e., >1 drink/week). Current cigarette smoking (yes, no) was also recorded.

2.3. Biochemical Characteristics. Systolic and diastolic blood pressures, together with fasting serum glucose, serum creatinine, and cystatin C, were measured in all participants. Blood pressure was measured by the same physician using a standard mercury sphygmomanometer on the right arm of the seated subject. Venipuncture was performed for each participant, early in the morning (between 07:00 am and 11:00 am), after a 12-hour fasting period by applying a natural latex rubber strap and using a 20 mL syringe. Blood was immediately transferred to two tubes without anticoagulant (Greiner Vacuette, Cat. no. 455071). Samples were left undisturbed for 20 minutes to clot and then centrifuged at 4000 Rotations per Minute (Relative Centrifugal Force: RCF 2.7) for 10 minutes so as to obtain serum.

2.4. Laboratory Analyses. Glucose was determined via an enzymatic colorimetric test (glucose oxidase PAP, Trinder endpoint reaction, GOD-PAP). Serum creatinine was determined via a kinetic colorimetric assay based on the reaction of creatinine with picric acid in alkaline solution and cystatin C via a particle-enhanced immunoturbidimetric assay. In the latter case, human cystatin C agglutinates with latex particles coated with anticystatin C antibodies, and the aggregate is determined turbidimetrically at 546 nm.

Reproducibility in the lab has been determined using human samples and controls in an internal protocol. For the above mentioned tests, within run and between day, coefficients of variation (CV) were less than 8%. Two levels of control sera were used for these assays (Precinorm U plus 12149435122 & Precipath U plus 12149443122 for glucose and serum creatinine, cystatin C control set 04975936190 for cystatin C). Control recovery for all tests was very close to the recommended target values (TV $\pm$ 5%). Accuracy of results is further supported by participation in suitable external quality assurance program for glucose and serum creatinine (ESEAP). All measurements were performed on a Roche/Modular *Analytics* analyzer. Reagents, calibrators, controls, and consumables were purchased from same supplier (Roche Diagnostics GmbH, Sandhofer Straße 116, D-68305 Mannheim, Germany).

2.5. Statistical Analysis. Continuous variables are presented as mean $\pm$ standard deviation and categorical variables as absolute (N) and relative frequencies (%). Comparisons of continuous variables between groups of study were performed using the independent samples t-test and the Analysis of Variance, after controlling for the normality of the distribution. Associations between categorical variables were tested using the chi-square test. Distribution of cystatin C levels was presented for the 2.5th, 5th, 10th, 25th, 50th (median), 75th, 90th, 95th, and 97.5th percentile. Subgroups analyses were performed by gender, age category (i.e., 18–44, 45–64, and $\geq$65 years old), obesity status (< or $\geq$25 kg/m^2), current smoking (yes versus no), alcohol drinking (yes versus no), and physical activity status (low/moderate versus high). All statistical analyses were performed using the SPSS version 14 (SPSS Inc., Chicago, Il, USA).

3. Results and Discussion

3.1. Descriptive Characteristics. Thirty-seven percent of participants were male, while the mean age between genders did not differ (40 $\pm$ 14 for males, 40 $\pm$ 13 for females, $P = .81$). Differences were not observed as well in physical activity status between genders (i.e., 5.8 $\pm$ 2.1 for males versus 5.9 $\pm$ 2.3 for females, $P = .91$). Percentage of current smokers was similar between males (34%) and females (36%) ($P = .79$). Approximately 2/3 of males and 27% of females were considered as overweight/obese ($P < .001$), while 85% of males and 73% of females were current drinkers ($P = .02$).

Table 1: The distribution of serum cystatin C levels according to gender (i.e., males and females) and age groups, of apparently healthy participants in the study.

	Males				Females			
	18–44	45–64	≥65	Total	18–44	45–64	≥ 65	Total
Percentiles of cystatin C								
Minimum	0.50	0.52	0.83	0.50	0.52	0.61	0.74	0.52
2.5	0.56	0.52	0.83	0.56	0.54	0.61	0.74	0.57
5	0.63	0.59	0.83	0.64	0.60	0.63	0.74	0.61
10	0.66	0.70	0.83	0.67	0.62	0.64	0.74	0.64
25	0.71	0.73	0.89	0.72	0.69	0.71	0.87	0.70
50	0.77	0.82	0.98	0.80	0.76	0.79	0.99	0.78
75	0.87	0.93	1.07	0.90	0.82	0.89	1.04	0.84
90	0.93	1.00	—	0.99	0.88	1.00	—	0.96
95	1.00	1.14	—	1.07	1.01	1.07	—	1.01
97.5	1.08	—	—	1.13	1.03	1.12	—	1.07
Maximum	1.10	1.21	1.18	1.21	1.05	1.12	1.14	1.14

Table 2: The distribution of cystatin C levels according to obesity and smoking status, of apparently healthy participants in the study.

	Overweight/obesity		Current smoking	
	No	Yes	No	Yes
Percentiles of cystatin C				
Minimum	0.52	0.50	0.50	0.52
2.5	0.57	0.60	0.56	0.59
5	0.61	0.63	0.61	0.64
10	0.64	0.68	0.64	0.68
25	0.70	0.72	0.70	0.74
50	0.77	0.80	0.76	0.81
75	0.84	0.90	0.84	0.92
90	0.95	0.99	0.94	1.01
95	1.02	1.04	1.00	1.06
97.5	1.07	1.15	1.08	1.11
Maximum	1.12	1.21	1.21	1.18

3.2. Distribution of Cystatin C Levels. Cystatin C levels varied from 0.50 to 1.21 mg/L among males and from 0.52 to 1.14 mg/L among females. In addition, cystatin C levels were normally distributed among the 176 healthy women and 103 healthy men that comprised the studied population (Figure 1).

The distribution of cystatin C levels among age groups between the two genders is presented in Table 1. In general, higher levels were observed for males as compared to females in all age groups. Specifically, cystatin C varied from 0.50 to 1.10 mg/L among males aged 18–44 yrs, from 0.52 to 1.21 mg/L among males aged 45–64 yrs, and from 0.83 to 1.18 mg/L among males over 65 yrs. Among females, the cystatin C levels varied from 0.52 to 1.05, 0.61 to 1.12, and 0.74 to 1.14 mg/L, respectively, for each age group (Table 1). The distribution of cystatin C levels was furthermore examined according to obesity and current smoking status. Levels of cystatin C varied from 0.52 to 1.12 mg/L for participants with BMI $< 25\,kg/m^2$ and from 0.50 to 1.21 mg/L for overweight/obese participants. Moreover, cystatin C levels varied from 0.50 to 1.21 mg/L for never or ex-smokers and from 0.52 to 1.18 mg/L for current smokers (Table 2). Regarding the distribution of cystatin C levels according to physical activity status, this varied from 0.50 to 1.18 mg/L among participants with low physical activity and from 0.52 to 1.21 mg/L among highly active participants. In addition, cystatin C levels varied from 0.52 to 1.10 mg/L among never/rare drinkers and from 0.50 to 1.21 mg/L among drinkers (data not shown here).

Differences in mean values of cystatin C levels were observed between genders, age group, smoking, and obesity status. In particular, higher values were noticed among males ($P = .04$), older participants aged over 65 yrs ($P < .001$), current smokers ($P < .001$), and overweight/obese participants ($P = .03$). In contrast, cystatin C levels did not seem to differ regarding alcohol drinking status and physical activity status ($P = .61$, $P = .95$, resp.) (Table 3).

Table 3: Mean values and standard deviation of serum cystatin C levels among subgroups of apparently healthy participants in the study.

	Cystatin C (mg/L)	*P*
Gender		.04
Male	0.82 ± 0.13	
Female	0.79 ± 0.12	
Age group		<.001
18–44	0.77 ± 0.11	
45–64	0.82 ± 0.13	
≥65	0.98 ± 0.12	
Overweight/obesity		.03
No	0.78 ± 0.12	
Yes	0.82 ± 0.13	
Current smoking		.001
No	0.78 ± 0.12	
Yes	0.82 ± 0.13	
Alcohol drinking		.61
0-1 drinks/week	0.80 ± 0.13	
>1 drinks/week	0.79 ± 0.13	
Physical activity		.95
Never/rare	0.80 ± 0.12	
High activity	0.80 ± 0.13	

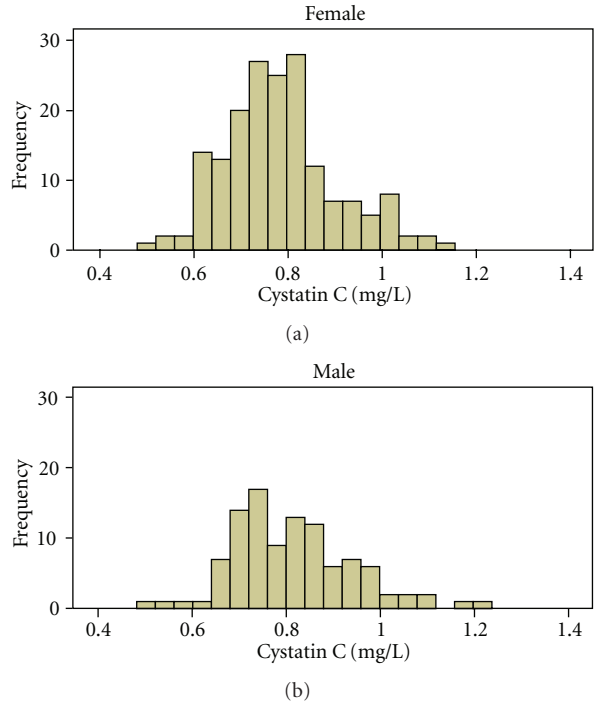

Figure 1: The gender-specific distribution of serum cystatin C levels among healthy participants of the study.

Various physiological sources of variation for serum cystatin C such as age, gender, BMI, cigarette smoking, and alcohol consumption have been reported based on analysis of healthy adult populations. Most studies have shown age-related differences in serum cystatin C, demonstrating that its levels increase with age [13–17]. Indeed, recent studies define reference values separately for adults and for older individuals. These studies have documented a variation in cystatin C levels as a function of age, probably due to the physiological aging of renal function [18–20]. In this study, higher values were noticed among older participants aged over 65 yrs ($P < .001$).

Gender differences in cystatin C levels have not been consistently observed. Such differences were significant in some studies, especially for adults below 60 years of age [20–22], but not significant in others [13, 23]. In this study, gender differences in cystatin C were revealed, with higher values of cystatin C among males as compared with females.

The findings of this study, regarding the influence of smoking in the levels of cystatin C, have been also confirmed by other studies [13, 24]. It seems likely that smoking is an independent source of variation for cystatin C, although the mechanism is not known.

Previous studies with respect to positive association of cystatin C levels with BMI support the above mentioned results of this study [25, 26]. Specifically, higher values of cystatin C levels among overweight/obese individuals in comparison with normal weight individuals were revealed. Laboratory studies have examined the expression of cathepsin S as a new biomarker of adiposity and have shown that human adipose tissue secretes and expresses cathepsin S, which is upregulated in obesity [27]. Cystatin C regulates cathepsin S activity by acting as an endogenous inhibitor. It has been found that cystatin C secretion increased and cathepsin S decreased during preadipocyte differentiation, suggesting a possible role of cystatin C in adipogenesis [28].

Alcohol consumption and physical activity did not seem to influence cystatin C levels in the studied population. This is in accordance with most studies that have been conducted until today [13, 29, 30].

As it is clearly mentioned on the package insert of the commercial assay for cystatin C "Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges."

4. Conclusions

This is—to the best of our knowledge—the first study for determination of cystatin C reference values in Greek population. In the era of newly discovered properties and clinical significance of cystatin C, factors such as age, gender, BMI, and cigarette smoking need to be considered when interpreting serum cystatin C values even in a carefully selected healthy adult population. Determination of reference ranges among distinct subpopulations must be taken into consideration.

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Research Article

Betel Nut Chewing and Subclinical Ischemic Heart Disease in Diabetic Patients

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Background. This study investigated the association between betel nut chewing and subclinical ischemic heart disease (IHD) in Taiwanese type 2 diabetic patients. *Methods*. A total of 394 male patients aging ≥45 years and without previous heart disease were studied. Among them 349 had no habit of chewing betel nut and 45 possessed the habit for ≥5 years. Subclinical IHD was diagnosed by a Minnesota-coded resting electrocardiogram and was present in 71 cases. Statistical analyses were performed considering confounding effects of age, diabetic duration, smoking, body mass index, blood pressure, dyslipidemia, and metabolic control status. *Results*. Betel nut chewers were younger and had higher prevalence of smoking (86.7% versus 60.5%), higher body mass index, poorer glycemic control, and higher prevalence of subclinical IHD (28.9% versus 16.6%). Patients with subclinical IHD were older and had higher prevalence of betel nut chewing (18.0% versus 9.9%). The multivariate-adjusted odds ratio for subclinical IHD for chewers versus nonchewers was 4.640 (1.958–10.999). The adjusted odds ratios in younger or older patients divided by the median age of 63 years were similar: 4.724 (1.346–16.581) and 4.666 (1.278–17.028), respectively. *Conclusions*. Betel nut chewing is significantly associated with increased risk of subclinical IHD.

1. Introduction

Areca nut is the seed of the palm tree *Areca catechu*, which is the fourth most commonly used psychoactive substance, after caffeine, nicotine, and alcohol [1]. Because areca nut is always consumed with the leaf of *Piper betle*, chewing of areca nut has always been referred to as "betel nut chewing" in the English literature [2]. There is an estimated 600 million people chewing betel nut worldwide [3]. It is a common habit and is a means of social interaction in Asia, particularly the South Pacific islands, Southeast Asia, Papua New Guinea, Bangladesh, Pakistan, and India [1–4]. Chewing of betel nut was forbidden in Taiwan during the Japanese reign more than 60 years ago [4]. But this habit has become popular in Taiwan during the past two to three decades, and it has been estimated that about 2.4 millions, or 11.4%, of the total population are chewing betel nut [5]. The chewing population in Taiwan keeps on increasing, especially in the male sex of the younger generation [6, 7]. In Taiwan, unripe areca nut is commonly chewed with a mixture of lime and the leaf or flower of the *Piper betle*, but without tobacco [4].

Betel nut chewing has been linked to a variety of health problems including oral lesions of leukoplakia, submucosal fibrosis, squamous cell carcinoma and periodontal disease [8, 9], albuminuria in diabetic patients [10], disruption of gastric mucosal barriers [11], aggravation of asthma [12], induction of extrapyramidal syndrome [13], milk-alkali syndrome (in a case report) [14], induction of uterine cervical dysplasia [15], cancers of the esophagus [16] and liver [17], and low birth weight of babies born to mothers chewing betel nut [18]. In more recent population-based studies in Taiwan, betel nut chewing is also associated with a higher risk of type 2 diabetes mellitus (T2DM) [19], hypertension [20], and total and cerebrovascular deaths [21].

Studies on the cardiovascular effects of betel nut chewing are rare. Hemodynamic changes have been observed during betel nut chewing [7]. However, whether the prolonged chewing of betel nut could exert an effect on the heart

has not been previously studied. Therefore, the purpose of this study was to evaluate whether betel nut chewing could be associated with the prevalence of subclinical IHD in a subgroup of patients with T2DM recruited as a long-term follow-up cohort in Taiwan.

2. Methods

2.1. Study Subjects. The study was approved by an ethics committee of the Department of Health, Taiwan, and the subjects voluntarily participated in the study. More than 96% of the population of Taiwan is covered by a compulsory National Health Insurance program. A total of 256,036 patients using this health insurance program were assembled from 1995 to 1998 [22–24]. Baseline data was collected by questionnaires on the onset symptoms and confirmation of diabetic diagnosis from 93,484 patients of the original cohort [22–24]. At random, 4,164 patients were selected from the main cluster of 93,484 patients and invited to participate in a health examination. A total of 1,441 patients participated in the health examination from March 1998 to September 2002. After excluding 21 patients with type 1 diabetes mellitus (T1DM), there were a total of 1420 patients diagnosed as T2DM. The patients with T2DM did not show a history of diabetic ketoacidosis at the onset of diabetes and were being treated with either oral antidiabetic drugs or insulin at the time of recruitment. For those under insulin treatment, none received such treatment within one year of diagnosis of diabetes mellitus.

Patients with T1DM were excluded because of the small number of cases who might also have different pathogenesis of IHD. Women with T2DM were further excluded because the habit of betel nut chewing is very uncommon in women in Taiwan [6, 7, 25]. Taking into account the possible requirement of prolonged chewing for the manifestations of clinical outcomes, this study recruited only adult male patients aging ≥45 years, and chewers must be current chewers and have retained the habit for ≥5 years at the time of recruitment. Patients with a clinical history of heart disease including angina pectoris, myocardial infarction, congestive heart failure or under treatment for such were also excluded because of the impossibility to clarify the correctness of temporality between cause and effects and because of the potential confounding effect caused by treatments. As a result, a total of 394 men with T2DM were included in this study. They were divided into two groups: one with no habit of chewing betel nut and the other should have persistently chewed betel nut for more than 5 years at the time of recruitment.

2.2. Diagnosis of Subclinical Ischemic Heart Disease. Resting electrocardiogram was performed in each subject, and the Minnesota codes were used to code the electrocardiograms. The coder was blind to the history or the biochemical data of the subjects. Subclinical IHD was defined by Minnesota codes of coronary probable (1.1, 1.2, 7.1) and coronary possible (1.3, 4.1–4.3, 5.1–5.3) [26].

2.3. Measurements of Blood Biochemistry and Other Covariates. Blood samples were collected in the early morning after fasting for at least 12 hours. Fasting plasma glucose (FPG), serum total cholesterol (TC), and triglyceride (TG) were measured by an automatic biochemistry analyzer (Cobas Mira S, Roche Diagnostica, Basel, Switzerland) with reagents obtained from Randox Laboratories Ltd. (Antrium, UK) [27].

The patients' age, duration of diabetes, body mass index (BMI), smoking status, and systolic (SBP) and diastolic blood pressure (DBP) were recorded or measured. Duration of diabetes was defined as the time period in years between the time being recruited into the study and the time diabetes was diagnosed. Blood pressure was measured on the right arm after 20 minutes rest in a sitting position with a mercury sphygmomanometer by the auscultatory method. Body height (in centimeters) was measured by having the subjects stand with their heals, buttocks, and heads against a wall. A flat object was placed on top of the subjects' head, and their height was marked on a tape measure affixed to the wall. Body weight was measured in kilograms with a standard portable scale. Body height and body weight were measured with the patient wearing light clothes and without socks and shoes. BMI was calculated as body weight in kilograms divided by the square of the body height in meters. Hypertension was defined by a positive history with the use of antihypertensive agents or by SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. Dyslipidemia was diagnosed by the use of lipid-lowering agents and/or a TC level ≥ 200 mg/dL and/or TG ≥ 150 mg/dL.

2.4. Statistical Analyses. Data were expressed as mean (SD) or percentage. A $P < .05$ was considered statistically significant, while $.05 < P < .1$ was borderline significant. Age was divided into two groups by the median and the prevalences of subclinical IHD between chewers and nonchewers were compared by Chi-square test in the respective age groups. The baseline characteristics between chewers and nonchewers and between patients with subclinical IHD and those without subclinical IHD were compared by Student's t-test for continuous variables and by Chi-square test for categorical variables. Logistic regression models estimating the odds ratios for subclinical IHD were created for all patients and for patients in the respective two age groups divided by the median of age. These regression models were generated in the following 3 ways: (1) unadjusted; (2) adjusted for variables found to be different between chewers and non-chewers, or between patients with and without subclinical IHD with P values < .1; (3) adjusted for all potential covariates (i.e., age, diabetic duration, body mass index, smoking, hypertension, dyslipidemia, FPG, SBP, DBP, TC, and TG).

3. Results

Figure 1 shows the prevalences of subclinical IHD in chewers and non-chewers in the respective age groups divided by the median of 63 years old. The prevalences of subclinical IHD differed significantly between chewers and non-chewers in either the younger or the older age groups ($P < .05$).

Table 1: Comparisons between patients chewing and not chewing betel nut and having and not having subclinical ischemic heart disease (IHD).

	Betel nut chewing		Subclinical IHD	
	No	Yes	No	Yes
n	349	45	323	71
Age, years	63.9 (9.3)	56.3 (8.6)**	62.0 (9.4)	67.6 (9.1)**
Diabetic duration, years	10.4 (7.6)	10.3 (8.8)	10.4 (7.6)	10.7 (8.5)
Body mass index, kg/m^2	24.5 (3.0)	25.9 (3.7)**	24.6 (3.2)	24.8 (2.9)
Smoking, %	60.5	86.7**	63.2	64.8
Fasting plasma glucose, mg/dL	159.4 (57.3)	178.6 (74.8)*	162.2 (56.5)	159.1 (72.9)
Hypertension, %	52.4	60.0	52.3	57.8
Systolic blood pressure, mmHg	132.8 (15.8)	131.9 (16.1)	132.1 (15.4)	135.2 (17.5)
Diastolic blood pressure, mmHg	83.2 (8.8)	84.8 (7.0)	83.4 (8.4)	83.1 (9.6)
Dyslipidemia, %	56.0	68.9	56.5	62.0
Total cholesterol, mg/dL	199.8 (45.9)	196.9 (38.2)	199.1 (45.1)	201.3 (44.9)
Triglyceride, mg/dL	168.7 (193.3)	180.0 (83.1)	168.9 (196.2)	174.9 (114.6)
Ischemic heart disease, %	16.6	28.9*	—	—
Betel nut chewing, %	—	—	9.9	18.0*

*$P < .05$; **$P < .01$.

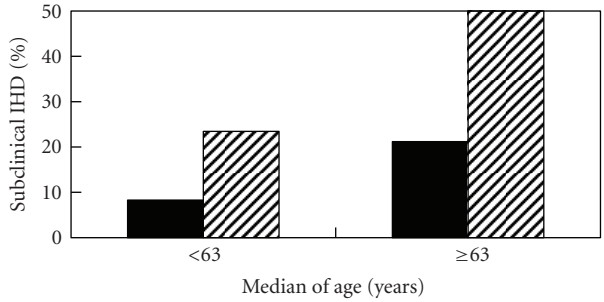

Figure 1: Prevalence of subclinical ischemic heart disease (IHD) between betel nut chewers (shaded column) and non-chewers (black column) by median of age ($P < .05$ for each subgroup of age).

Table 1 compares the baseline characteristics between chewers and nonchewers and between patients with and without subclinical IHD. Chewers were significantly younger in age, more prevalent in smoking and subclinical IHD, and had higher BMI and poorer glycemic control. Patients with subclinical IHD were significantly older and more prevalent in betel nut chewing.

Table 2 shows the odds ratios for subclinical IHD. Chewers consistently showed a significantly higher risk of subclinical IHD in either the older or the younger age group in all of the models.

4. Discussion

The findings of this study clearly demonstrated a higher risk of subclinical IHD in T2DM patients without a previous history of heart disease (Tables 1 and 2; Figure 1). This association was independent of traditional risk factors, and could be demonstrated in either the younger or the older patients (Figure 1; Table 2). To the best of our knowledge, this was the first study demonstrating a link between betel nut chewing and subclinical IHD. The association was consistent, and the magnitude of the odds ratios was large.

Although the real pathogenetic mechanism(s) remains unknown, some of the biological effects associated with the ingredients of areca nut or the compounds formed during chewing might explain some of the possibilities. The common preparations of the betel nut quid in Taiwan consist of three major components: the nut of *Areca catechu*, quicklime, and the leaf or the flower of *Piper betle* [4]. Areca nut contains arecoline which has a cholinergic action at the muscarinic and nicotinic receptors [28]. This cholinergic action on the central nervous system could possibly produce the cortical arousal and alertness which is always claimed as one of the merits experienced by the betel nut chewers. On the other hand, arecoline might stimulate the hypothalamic-pituitary-adrenal axis through a centrally mediated corticotrophin-releasing hormone-dependent mechanism in rats [29]. In the presence of lime, arecoline is hydrolyzed to arecaidine, which lacks the parasympathomimetic effects of arecoline [4] and exerts sympathetic effect by inhibition of γ-aminobutyric acid (GABA) uptake [30]. However, a later study suggested that arecaidine may not cross the blood-brain barrier and the central effects may involve transmitters other than GABA [31]. The aromatic substances (e.g., eugenol, isoeugenol, and hydroxychavicol) in the flower or leaf of *Piper betle* can stimulate the release of catecholamines from chromaffin cells *in vitro* [32], and circulating norepinephrine and epinephrine levels are elevated following betel nut chewing [33]. However, these sympathomimetic effects of arecoline might be mediated by central cholinergic mechanisms [34]. Therefore, both areca nut and *Piper betle* flower may exert sympathomimetic effects. Whether these sympathomimetic effects may be responsible for the subclinical IHD observed in the present study awaits further investigations. Reactive

Table 2: Odds ratios for subclinical ischemic heart disease comparing chewers versus nonchewers of betel nut.

	Odds ratio (95% confidence interval)		
	<63 years old	≥63 years old	All ages
Unadjusted	2.982 (1.087–8.182)*	3.267 (1.004–10.629)*	2.038 (1.008–4.118)*
Adjusted for age, BMI, smoking, and FPG	4.153 (1.280–13.471)*	4.183 (1.170–14.955)*	4.269 (1.837–9.920)**
Adjusted for all covariates (age, diabetic duration, BMI, smoking, hypertension, dyslipidemia, FPG, SBP, DBP, TC, and TG)	4.724 (1.346–16.581)*	4.666 (1.278–17.028)*	4.640 (1.958–10.999)**

*$P < .05$; **$P < .01$.

oxygen species and *N*-nitroso compounds can also be formed in the oral cavity during chewing of betel nut [35, 36]. *In vitro* studies also demonstrated that betel nut components increased the release of inflammatory mediators such as prostanoids, interleukin-6, and tumor necrosis factor-α [37, 38]. The production of these chemical agents has always been regarded as the mediators of carcinogenicity and diabetogenicity associated with betel nut chewing. Whether they can also be responsible for a hemodynamic or structural change in the coronary vascular system leading to subclinical IHD is an issue worthy of further investigation.

Some limitations deserve mentioning. This study was conducted in the diabetic patients, and it is not known whether similar effects can be extended to the general population without diabetes. Future studies should be aimed at a dose-response relationship and taking the duration of betel nut chewing into consideration. Longitudinal prospective studies are required to clarify the cause/effect relationship between betel nut chewing and subclinical IHD.

In conclusions, betel nut chewing in Taiwanese patients with T2DM is associated with subclinical IHD. While the chewing of betel nut is decreasing in some countries like Thailand [39], the prevalence keeps on increasing in Taiwan, especially in the younger generation. It is urgent for policy makers to implement programs of health education to the younger generation to curb the increasing prevalence of betel nut chewing and its associated health problems.

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Clinical Study

Association between Depression and C-Reactive Protein

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Objective. Depression has been associated with increased cardiovascular disease risk, and a depression-related elevation of high sensitivity C-reactive protein (hs-CRP) has been proposed as a possible mechanism. The objective of this paper is to examine association between depression and high sensitivity C-reactive protein (hs-CRP). *Methods*. Subjects consisted of 508 healthy adults (mean age 48.5 years; 49% women, 88% white) residing in central Massachusetts. Data were collected at baseline and at quarterly intervals over a one-year period per individual. Multivariable linear mixed models were used to assess the association for the entire sample and by gender. *Results*. The mean Beck Depression Inventory score was 5.8 (standard deviation (SD) 5.4; median 4.3), and average serum hs-CRP was 1.8 mg/L (SD 1.7; median 1.2). Results from the multivariable linear mixed models show that individuals with higher depression scores have higher levels of hs-CRP. Analyses by gender show persistence of an independent association among women, but not among men. Body mass index (BMI = weight(kg)/height(m)^2) appears to be a partial mediator of this relationship. *Conclusion*. Depression score was correlated to hs-CRP levels in women. Further studies are required to elucidate the biological mechanisms underlying these associations and their implications.

1. Introduction

Depression and inflammatory biomarkers have both been proposed as novel coronary heart disease (CHD) risk markers [1, 2]. Depression and CHD are common conditions that often occur together. Evidence suggests that their cooccurrence is not random, but is driven by depression as a risk factor for the occurrence and progression of CHD [3]. This link is thought to be due, in part, to the impact that depression has on neuroendocrine pathways that influence the pathogenesis and progression of coronary atherosclerosis and subsequent heart disease [4]. These include inflammatory markers, particularly high-sensitivity C-reactive protein (hs-CRP) [5]. Some studies suggest that the existence of a possible "psychoneuroimmune link" between negative affectivity (depression, anger and anxiety [6], poor subjective wellbeing [7]), inflammatory markers, and the development and progression of CHD [2]. Several behavioral and psychosocial factors, particularly depression, appear to increase the risk for acute coronary syndrome events independent of traditional risk factor status [8]. A meta-analysis of 11 cohort studies suggests that depression, assessed by self-reported symptoms or by formal psychiatric evaluation, significantly predicts risk for first CHD events independent of established CHD risk factors [1]. Similarly, elevated inflammatory biomarkers, hs-CRP in particular, have been established as risk markers for incident CHD events [2], and there are reports describing the underlying cellular and molecular mechanisms by which these biomarkers facilitate the development of atherosclerosis [9]. Although depression and hs-CRP are both associated with CHD events, less is known about their possible association with each other [1, 5, 10]. A review of NHANES III data indicated that a history of major depression was associated

with a 64% increase in the risk of having an elevated hs-CRP level. However, the association between depression and hs-CRP was much stronger among men than among women [10], an observation also reported in Europe [11] and Israel [12].

The goal of the present study was to analyze the relationship between hs-CRP and depression scores in healthy adults using longitudinal analysis, and to examine potential gender differences. This is important because, as pointed out by Shimbo and colleagues [5], cross-sectional data cannot determine the temporal nature of the relationship. We utilized available data from the Seasonal Variation in Blood cholesterol levels (SEASONS) study, which was designed to describe and prospectively delineate the nature and causes of seasonal variation in blood lipids, and is described in detail elsewhere [13, 14]. The SEASONS database provides a unique opportunity to examine the relationship of depression and hs-CRP in healthy adults by gender over a one-year time period, while controlling for a variety of socio-economic, anthropometric, physiologic, dietary, physical activity, and psychosocial factors.

2. Methods

2.1. Subject Recruitment and Study Design. The SEASONS study population consisted of 641 healthy adults, aged 20 to 70 years, enrolled at the Fallon Healthcare System, a health maintenance organization in central Massachusetts [13]. Eligible subjects, (1) were not taking cholesterol-lowering medications; (2) were not following a lipid-lowering or weight-control diet; (3) were not working night shifts; (4) were free from possible causes of secondary hypercholesterolemia (e.g., hypothyroidism, pregnancy); (5) did not have a chronic life-threatening illness (e.g., cancer, renal disease, or heart failure), and did not have evidence of clinical atherosclerotic disease such as coronary disease, stroke, or peripheral vascular disease. Subjects were followed prospectively for one year, during which time quarterly measurements were made of their serum lipids, hs-CRP, diet, physical activity, anthropometric measures, light exposure, and psychosocial factors. Subjects were recruited between December 1994 and February 1997 and enrollment occurred throughout the calendar year. The Institutional Review Boards of the Fallon Healthcare System and the University of Massachusetts Medical School approved all subject recruitment and data collection procedures.

2.2. Blood Sample Collection and Hs-CRP Assays. During each visit, a 12-hour-fasting blood sample was collected between 7 and 10 am. Serum was isolated and refrigerated at −70°C. Samples were transported to Dr. Nader Rifai's laboratory, in Boston, MA, and hs-CRP was measured using latex-enhanced immunonephelometric assays on a BN II analyzer described previously [15]. The measurement of hs-CRP was performed in batches. Inter-assay and intra-assay coefficients of variation for hs-CRP were in compliance with CDC-accepted ranges. In addition, we excluded 66 (3% of total) CRP values greater than 10 mg/L from this analysis because such elevated values are likely to be caused by acute infection or underlying medication problems [16].

2.3. Beck Depression Inventory. Depression symptoms were assessed using the Beck Depression Inventory (BDI) [17]. The BDI is a questionnaire developed to measure the intensity, severity, and depth of depressive symptoms. It is composed of 21 questions, each designed to assess a specific symptom common among people with depression. BDI items assess mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, body image, work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation, and loss of libido. Items 1 to 13 assess symptoms that are psychological in nature, while items 14 to 21 assess more physical symptoms [17]. Each of 21 questions or items has four possible responses. Each response is assigned a score ranging from zero to three, indicating the severity of the symptom and the overall score is calculated from the sum of responses to each item. A cut-off score of 21 or higher represents clinically-significant depressive symptomatology. The BDI was self-administered at baseline (upon study enrollment) and every 3 months thereafter for 12 months, for a total of five measurement points over one year of study participation.

2.4. Assessment of Diet and Physical Activity. Serial 24-hour dietary recall interviews (24HDR), three in each quarter of followup, were performed on randomly selected days (two weekdays and one weekend day) by trained registered dieticians in order to quantify dietary changes over the week. The 24HDR data were collected using the nutrition data System (NDS) data entry and nutrient database software developed and maintained by the Nutrition Coordinating Center at the University of Minnesota, Minneapolis [18]. Data collection for physical activity patterns also occurred at the time of the 24HDR. Subjects were asked to recall the amount of time they spent in light, moderate, vigorous, and very vigorous activities in household, occupational, and leisure-time activity domains. Estimates of physical activity energy expenditure in metabolic equivalent task hours (MET-hours) were calculated according to methods developed by Ainsworth and colleagues [19]. These data were validated against both accelerometers and standard questionnaires. Results obtained were comparable to published data from other short-term activity assessments employing the Beck Questionnaire and activity monitors as criterion measures [20].

2.5. Demographic, Anthropometric, and Blood Lipid Data. Detailed demographic, anthropometric, and blood lipid data collection methods are described elsewhere in our previous publications [13, 21, 22]. Briefly, demographic data including gender, age, race/ethnicity, educational level, occupational category, and so forth, were collected by a self-report questionnaire at baseline. Self-reported smoking status was ascertained at baseline and again at each quarter of followup by additional self-administered questionnaires. Height was measured at baseline, and body weight was measured at

each clinic visit, with the subject removing their shoes and extra layers of clothing. Relative mass was expressed as BMI (weight (kg)/height (m)^2). Subjects were classified as "overweight" if their BMI was equal or greater than 25 kg/m^2 and as "obese" if their BMI was equal or greater than 30 kg/m^2. Fasting (>12 hours) venous blood samples (10 mls) were obtained after sitting for 15 minutes at each clinic visit. Blood plasma was harvested by low-speed centrifugation at 4°C, aliquoted into individual tubes, and quickly frozen to −70°C. On a regular basis, plasma samples were packed in dry ice and shipped for analysis via overnight service to the Centers for Disease Control standardized laboratory at the University of Massachusetts at Lowell [23]. Assays for total cholesterol, HDL-C and triglycerides were done in this laboratory. LDL-C was calculated by the Friedewald formula (LDL-C = total cholesterol − {triglycerides/5 + HDL-C}) [24]. When triglycerides exceeded 400 mg/dl, the LDL-C was not calculated.

2.6. Statistical Analyses. Gender differences in demographic characteristics were assessed using two-group *t*-tests for continuous variables and Chi-square tests for categorical variables. Linear mixed models with a random intercept for each subject and unstructured within-subject correlation were used to assess the association between depression scores and hs-CRP levels. With this model, we examined both (1) the cross-sectional association (between-subject, i.e., the subject-specific average) between depression and hs-CRP and (2) the longitudinal association (within-subject, i.e., quarterly differences from the subject-specific average) between depression and hs-CRP. This method has been used in our previous analyses of the association between dietary carbohydrates and body weight and blood lipids, and the association between dietary fiber and hs-CRP [15, 21, 22]. The models were also adjusted for variables known to affect hs-CRP (e.g., BMI, smoking, and infection) and were repeated using either the raw values or logarithmic scales of both hs-CRP and Beck depression scores. Dietary and physical activity variables were considered in the multivariable linear mixed models, but they were not significantly related to hs-CRP when multiple variables were considered, and so they were not included in the final models. Gender-specific mixed model analyses were also conducted. All analyses were performed using Stata SE 9.2 (College Station, Texas).

3. Results

Of the 641 participants in the SEASONS study, 508 (79%) had at least two visits yielding both BDI score and hs-CRP values, and data derived from these individuals were included in the analyses. Of these 508 subjects, over 55% had paired BDI and hs-CRP data for 4 or more data points throughout the year, and 30% had all 5 measures.

Study participants were primarily middle-aged, white, well-educated, employed, nonsmoking, and generally overweight or obese (Table 1), and approximately half (49%) were women. Compared to women, men were more likely to be married or living with a partner, to have had a college education, to be employed full-time, and to be either overweight or obese (72% versus 53% for men and women, resp.). Men also reported significantly higher levels of caloric intake and physical activity as compared to women. Blood pressure was higher, and resting- heart rate was lower among men. Compared to men, women had significantly lower levels of triglycerides, higher levels of HDL-cholesterol, and a higher prevalence of minor inflammatory or infectious problems (Table 1).

Mean BDI score was 5.8 (standard deviation (SD) 5.4); median 4.3; range from 0 to 33 with only 2% of participants presenting scores above 21, suggestive of clinically significant depressive symptoms (1.2% of men and 2.8% of women, $P = .10$). Only 13 participants reported taking antidepressant medication, with 10 reporting taking antidepressants throughout the year. The limited number of participants taking antidepressant drugs precludes any meaningful subgroup-analyses for this characteristic. There were significant gender differences in average BDI scores: 5.2 (SD 4.8; median 4.0) among men and 6.5 (SD 6.0; median 4.6) among women, $P < .005$. Overall average serum hs-CRP was 1.8 mg/L (SD 1.7; median 1.2), with no statistically significant gender differences. Using the average values of five hs-CRP and depression measures from each individual, BDI scores and hs-CRP were positively correlated as depicted in Figure 1.

Results from the multivariable linear mixed models, controlling for age, BMI, resting heart rate, HDL-cholesterol, smoking status, and reports of minor infection or inflammation, suggest that individuals with higher depression scores tended to have higher hs-CRP levels ($\beta = 0.03$, $P < .05$) however, we failed to observe a significant longitudinal effect (Table 2). Analyses stratified by gender suggest that an independent association between depression score and hs-CRP is present among women ($\beta = 0.028$, $P < .05$), but not among men ($\beta = 0.024$, $P > .05$). Overall, other factors significantly and positively related to hs-CRP included BMI, age, resting-heart rate, and report of minor infection/inflammation process. Repeating multivariable analyses using log transformation for hs-CRP and BDI score, independently and together, showed similar results to that of the analyses using raw values (data not shown). However, they also suggested an inverse longitudinal relationship between BDI score and hs-CRP among women, that is, women, whose BDI score increased over the year showed a decline in levels of hs-CRP, and this was not related to weight loss.

4. Discussion

Findings from this longitudinal study are consistent with the results of prior cross-sectional studies suggesting that depression is cross-sectionally associated with higher hs-CRP levels in a population without evidence of a chronic life-threatening illness (e.g., cancer, or renal or heart failure). Among our sample of adults not reporting clinically significant depressive symptomatology, depression score appears to be independently and positively correlated to hs-CRP. After controlling for potentially confounding factors, analysis by

Table 1: Characteristics of study participants, overall and by gender, SEASONS study, Worcester, MA, 1994–1998.

Variables	Overall ($n = 508$) *N* (%)/Mean	Men ($n = 259$) *N* (%)/Mean	Women ($n = 249$) *N* (%)/Mean	*P* value for gender comparison
Age (years)	48.5	49.1	47.9	.28
Race				
White	436 (87.6%)	228 (87.2%)	208 (85.6%)	.19
Marital Status				
Married or Living with Partner	392 (77.3%)	214 (83.0%)	178 (71.5%)	.19
Education				<.001
Less than high school	125 (24.7%)	42 (16.3%)	83 (33.5%)	
Some college or Associates degree	181 (35.8%)	106 (41.1%)	75 (30.2%)	
College/graduate or more	200 (39.5%)	110 (42.6%)	90 (36.3%)	
Employment				.001
Full-time	336 (66.1%)	191 (73.8%)	145 (58.2%)	
Part-time	76 (15.0%)	27 (10.4%)	49 (19.7%)	
Unemployed/retired	96 (18.9%)	41 (15.8%)	55 (22.1%)	
Current smoking				
Yes	71 (15.0%)	35 (15.0%)	36 (15.1)	.97
Body Mass Index (BMI) classification				<.001
Normal (18.5–24.9 kg/m^2)	188 (37.0%)	72 (27.8%)	116 (46.6%)	
Overweight (25–29.9 kg/m^2)	206 (40.6%)	121 (46.7%)	85 (34.1%)	
Obese ($\geq$30 kg/m^2)	114 (22.4%)	66 (25.5%)	48 (19.3%)	
Mean BMI (kg/m^2)	27.2	27.8	26.6	.01
Blood Measurements				
High Sensitivity C-Reactive Protein mg/L (from natural log distribution)	1.05	1.09	1.01	.37
Total cholesterol (mg/dl)*	219.6	221.5	217.6	.28
LDL (mg/dl)*	143.6	146.2	140.8	.08
HDL (mg/dl)*	48.1	43.3	53.0	<.0001
Triglycerides (mg/dl)** (from natural log distribution)	118.8	136.4	102.8	<.0001
Dietary factors				
Total caloric intake (kcal per day)	1957	2263	1640	<.0001
% of calories from total fat	31.4	32.1	30.7	<.01
% of calories from saturated fat	11.2	11.5	10.9	.02
Total fiber intake (gram per day)	16.2	18.0	14.3	<.0001
Physical activity				
Total MET-h/d	30.17	31.58	28.71	<.0001
Leisure MET-h/d	1.87	2.07	1.67	.03
Occupational MET-h/d	4.32	5.74	2.85	<.0001
Household MET-h/d	4.8	4.6	5.0	.13
Psychosocial factors				
Beck Depression Inventory Score (from natural log distribution)	3.4	3.0	3.8	.11
Prevalence of depression (% with BDI scores $\geq$21)	10 (2.0%)	3 (1.2%)	7 (2.8%)	.18
Antidepressant Medication Use	11 (2.2%)	4 (1.5%)	7 (2.8%)	.3

Table 1: Continued.

Variables	Overall ($n = 508$) N (%)/Mean	Men ($n = 259$) N (%)/Mean	Women ($n = 249$) N (%)/Mean	P value for gender comparison
Physiologic measures and other				
Systolic blood pressure—mm Hg	119	124	113	<.0001
Diastolic blood pressure—mm Hg	75	77	73	<.0001
Heart rate—beats/min	69.7	67.1	72.3	<.0001
Prevalence of infection inflammation %	56 (30.0%)	19 (20.2%)	37 (39.8%)	.003

*To transform total cholesterol, LDL, and HDL units from mg/dL to mmol/L multiply value by 0.0259.
**To transform triglyceride units from mg/dL to mmol/L multiply value by 0.0113.
Due to missing values the total number of subjects differs.

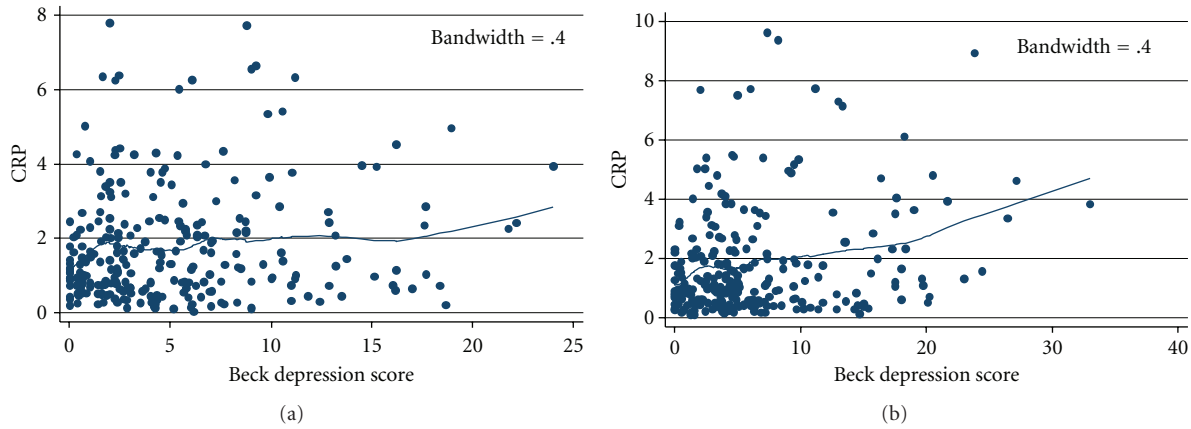

Figure 1: Association between Beck Depression Inventory score and high sensitivity C-reactive protein in men (a) and in women (b), SEASONS Study, Worcester MA, 1994–1998.

gender revealed that this association persisted only among women. The disappearance of this relationship among men after controlling for potential confounders, suggests that factors such as BMI, age, and resting heart rate (a marker of physical fitness) may confound this association among men. These factors also appear to mediate the relationship among women, but to a lesser extent.

Previous studies suggest that some types of depression are associated with weight gain which in turn may exacerbate inflammation by inducing leptin expression and increasing synthesis of inflammatory cytokines by adipose tissue [25]. Thus, the relationship between depression and hs-CRP may, at least partially, be mediated by weight gain. While our participants were, on average, not in the clinically depressed range, our findings suggest that the range of depressive symptomatology may be important, with low levels of depressive symptomatology having significance in these associations. The proposition that elevated depressive symptomatology leads to weight gain, and increase in body weight leads in turn to an increase in hs-CRP, would be a plausible explanation for our observation of the attenuation of the relationship between depression and inflammation among women, and the disappearance of the effect among men, after controlling for BMI.

The "psychoneuroimmune link" theory as an explanation of the relationship between the range of depressive symptomatology and hs-CRP can not be confirmed from the observations in this study; however, our findings support an independent association between depression scores and hs-CRP observed in women. On the other hand, among women, the observation of an independent and inverse relationship between depression scores and hs-CRP, over time, suggests that the relationship is complex and might be mediated mostly by behavior, since depression is related to changes in appetite and body weight, in either direction.

Our results are in contrast with reports from the NHANES III survey [10], which found that the relationship between hs-CRP and depression is stronger among men than in women. However, those reports used major depression diagnosis in contrast to depressive symptom scores as used in this analysis. The association between hs-CRP and depression was not observed in a recent study from adolescents aged 13–16 years old [26]. Differences in population characteristics and in the confounders controlled, also could account for some of the inconsistent results.

There are several strengths to our investigation. First, we collected detailed longitudinal data on a quarterly basis over the course of one year in various domains, including

Table 2: Multivariable Linear Mixed Model Predicting High Sensitivity C-Reactive Protein, SEASONS Study. Worcester MA, 1994–1998.

Overall	Coefficient	Standard Error	95% CI lower limit	95% CI upper limit
Beck Depression Inventory score—average	**0.030**	**0.011**	**0.009**	**0.051**
Beck Depression Inventory score—residual	−0.006	0.011	−0.027	0.016
Age in years	**0.018**	**0.005**	**0.008**	**0.027**
Body Mass Index kg/m^2—average	**0.162**	**0.012**	**0.139**	**0.186**
Body Mass Index kg/m^2—residual	**0.111**	**0.051**	**0.012**	**0.211**
Heart Rate beats per minute—average	**0.017**	**0.006**	**0.006**	**0.029**
Heart Rate beats per minute—residual	**0.014**	**0.004**	**0.005**	**0.023**
HDL Cholesterol mg/dl—average	−0.003	0.005	−0.013	0.007
HDL Cholesterol mg/dl—residual	−0.010	0.007	−0.023	0.003
Smoking	0.269	0.143	−0.012	0.549
Minor infection-inflammation	**0.280**	**0.069**	**0.145**	**0.414**
Constant	−4.894	0.646	−6.160	-3.628
Men				
Beck Depression Inventory score—average	0.024	0.017	−0.009	0.058
Beck Depression Inventory score—residual	0.003	0.016	−0.029	0.034
Age in years	**0.026**	**0.006**	**0.013**	**0.038**
Body Mass Index kg/m^2—average	**0.122**	**0.020**	**0.082**	**0.161**
Body Mass Index kg/m^2—residual	−0.059	0.078	−0.211	0.093
Heart Rate beats per minute—average	0.011	0.008	−0.006	0.027
Heart Rate beats per minute—residual	**0.013**	**0.007**	**0.000**	**0.026**
HDL Cholesterol mg/dl—average	−0.005	0.008	−0.022	0.012
HDL Cholesterol mg/dl—residual	−0.020	0.010	−0.040	0.000
Smoking	0.174	0.188	−0.194	0.542
Minor infection—inflammation	**0.375**	**0.097**	**0.185**	**0.565**
Constant	−3.699	1.008	−5.675	1.724
Women				
Beck Depression Inventory score—average	**0.028**	**0.014**	**0.001**	**0.055**
Beck Depression Inventory score—residual	−0.019	0.014	−0.046	0.008
Age in years	0.011	0.007	−0.003	0.025
Body Mass Index kg/m^2—average	**0.184**	**0.015**	**0.156**	**0.213**
Body Mass Index kg/m^2—residual	**0.222**	**0.063**	**0.099**	**0.345**
Heart Rate beats per minute—average	**0.023**	**0.009**	**0.005**	**0.041**
Heart Rate beats per minute—residual	**0.020**	**0.006**	**0.009**	**0.031**
HDL Cholesterol mg/dl—average	−0.006	0.007	−0.019	0.008
HDL Cholesterol mg/dl—residual	−0.007	0.008	−0.023	0.009
Smoking	0.370	0.216	−0.053	0.794
Minor infection—inflammation	0.172	0.092	−0.008	0.352
Constant	−5.323	0.954	−7.192	−3.453

demographic, psychosocial, dietary, and physical activity. Second, our study controlled for potential confounding factors for the depression and hs-CRP relationship, which previous studies had not included. Third, the study population is relatively healthy; subjects with diabetes and other chronic diseases were excluded as these conditions have been associated with both depressive symptoms and hs-CRP levels and may thus confound the BDI and hs-CRP relationship. Fourth, our data came from a study of seasonal variation in blood lipids, therefore patients planning to use or are using lipid medications and hormone therapy were excluded. Consequently, any effect of using statins and female hormones on hs-CRP concentrations was eliminated. Finally, use of a continuous measure of depressive symptomatology (BDI scores) allowed analyses across the continuum of depressive symptom severity.

Our study also has potential limitations. The study sample had a reduced range of depression scores, which limits our capacity to draw conclusions for individuals in the clinical-depression range. Although, the finding of a positive association between depressive symptom score and hs-CRP among adults who were on average not clinically depressed is also of interest, because it suggests that the entire range of depressive-symptomatology may be associated with health

risks. On the other hand, participants in this study were predominantly white, well-educated and employed therefore, caution should be taken when generalizing to populations that have different demographic characteristics or depression scores differing from the range found in this study. Finally, as with many studies that require a strong commitment on the part of the participants, selection bias is always possible.

In conclusion, multivariable longitudinal analyses suggest that an independent association between depression scores and hs-CRP is present among women, but not among men. It appears that obesity partially mediates this relationship. Other factors that were significantly and positively related to hs-CRP included body mass index, age, resting-heart rate, and concurrent minor infection/inflammation process. Further studies are required to elucidate the biological mechanisms of these associations and their implications.

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Review Article

Cardiovascular Prevention of Cognitive Decline

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Midlife cardiovascular risk factors, including diabetes, hypertension, dyslipemia, and an unhealthy lifestyle, have been linked to subsequent incidence, delay of onset, and progression rate of Alzheimer disease and vascular dementia. Conversely, optimal treatment of cardiovascular risk factors prevents and slows down age-related cognitive disorders. The impact of antihypertensive therapy on cognitive outcome in patients with hypertension was assessed in large trials which demonstrated a reduction in progression of MRI white matter hyperintensities, in cognitive decline and in incidence of dementia. Large-scale database correlated statin use and reduction in the incidence of dementia, mainly in patients with documented atherosclerosis, but clinical trials failed to reach similar conclusions. Whether a multitargeted intervention would substantially improve protection, quality of life, and reduce medical cost expenditures in patients with lower risk profile has not been ascertained. This would require appropriately designed trials targeting large populations and focusing on cognitive decline as a primary outcome endpoint.

1. Introduction

As a result of the increased life expectancy, the proportion of older people with cognitive impairment increases continuously. Alzheimer disease, which affects about 35 million people worldwide today, is estimated to afflict more than 100 million people by 2050 [1–3]. Amnestic mild cognitive impairment is found in about 20% of people older than 85 years with a conversion rate to Alzheimer disease of 10%–15% per year [4]. As a consequence, management of patients with cognitive disorders is quite common in daily cardiology practice. More recently, several studies have highlighted the deleterious role of cardiovascular risk factors on the incidence and progression of cognitive disorders in elderly people. This endorses the potential protection provided by therapeutic cardiovascular risk control.

2. Vascular Dementia and Alzheimer Disease

Besides Alzheimer disease, which account for about 60%–80% of cases of dementia in the elderly, vascular dementia has been increasingly recognized over the past decades as a late consequence of previous symptomatic [5] or clinically silent [6] stroke in patients with cerebrovascular disease, multifocal atherosclerosis, and cardiovascular risk factors. The spectrum of vascular dementia has subsequently expanded to include patients without stroke past history in whom brain magnetic resonance imaging (MRI) showed subcortical lesions such as white matter hyperintensities (Figure 1), lacunar infarctions and/or microhemorrhages [7]. Similar MRI lesions were also found in patients with cardiovascular risk factors only, especially hypertension [8, 9], and, paradoxically, in patients with Alzheimer disease. In addition, several studies showed that a past history of stroke or cerebral microinfarcts were associated with an increased risk of subsequent Alzheimer disease, its early onset and/or its accelerated clinical progression rate [10–14]. Consistent with these findings, pathological examinations revealed cerebral damages belonging to both forms of dementia in some instances, for example, coexisting senile plaques and neurofibrillary tangles with vascular lesions [15]. Furthermore, pathways common to progression of

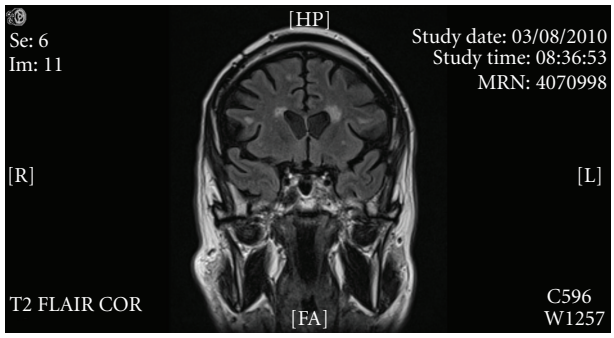

Figure 1: Periventricular and subcortical white matter hyperintensities. MRI, T2-weighted sequence, flair.

both diseases were also reported [16]. Finally, epidemiological studies demonstrated a correlation between late life occurrence of Alzheimer disease and the presence of midlife hypertension or cardiovascular risk factors [17, 18].

Accordingly, the diagnosis of vascular dementia, as defined using specifically selected clinical criteria only [23] has turned to a revisited framework in which vascular dementia and Alzheimer disease interplay with each other. Their incidence, the delay after which they appear, and their progression rate are promoted by cardiovascular risk factors [24]. As a result, control of cardiovascular risk factor may delay onset and slow down progression of cognitive disorders in elderly.

3. Diabetes

Cognitive disorders are observed with an increased prevalence among diabetics who suffered previous stroke [25]. In the *Honolulu-Asia Aging Study* (HAAS), a cardiovascular risk factor study initiated in 1965, cognitive function and brain MRI were assessed between 2004 and 2006 in 3734 survivors with regards to the presence of type 2 diabetes (38% of the population). Subjects with diabetes type 2 or impaired glucose tolerance have an increased risk of cerebral lacunes (odds ratio, OR: 1.6), hippocampal atrophy (OR: 1.7), and microinfarcts (OR: 1.9). The prevalence of either vascular dementia or Alzheimer disease with cardiovascular disease was 5.4% in diabetics and 2.9% and 2.5% in nondiabetics, respectively [26].

Although cognitive disorders are common in older diabetics, they develop slowly. They are limited to mild cognitive disorders in most patients for many years before more severe manifestations occur [35].

Several mechanisms have been advocate.

(i) Hyperinsulinemia: after crossing the blood brain barrier, insulin competes in the brain with amyloid β for insulin degradising enzyme, a pathway which is enhanced in patients with the apolipoprotein APOE-ε4 allele [36]. Conversely, rosiglitazone reduces progression of cognitive impairment and Alzheimer disease in diabetics by decreasing insulin blood levels and insulin resistance [37].

(ii) Advanced glycosylation end products (AGEs) resulting from glucose intolerance accumulate in senile plaque and neurofibrillary tangles. This pathway is enhanced by amyloid β binding to membrane AGEs receptors and further neuronal injury [36].

4. Hypertension

Large-scale epidemiological cohort studies initiated 4 decades ago correlated midlife hypertension to late life cognitive impairment. Among 392 aged survivors of the *NHLBI Twin study*, prevalence of dementia and white matter hyperintensities was higher in subjects whose blood pressure was increased at the follow-up visit in 1970, 1980, and 1985 [38]. Similar correlations between midlife hypertension and late life prevalence of dementia and/or extent of white matter hyperintensities were found in several other longitudinal follow-up studies [39–41].

Among 226 participants of *PROGRESS* (Perindopril Protection against Recurrent Stroke Study) in whom brain MRI was performed, the extent of white matter hyperintensities predicted development of dementia during followup: the relative risk increased from 1.6 (0.4–6) in patients with mild to moderate lesions to 7.7 (2.1–28.6) in patients with severe lesions [41]. Progression of white matter hyperintensities over time is increased in patients with either systolic or diastolic elevated blood pressure [40–42]. A similar relationship between midlife systolic or diastolic blood pressure levels and subsequent hippocampal volume reduction was observed in the *Honolulu-Asia Aging Study* [43].

The impact of antihypertensive therapy on cognitive impairment in patients with high blood pressure (HBP) was assessed in several trials. *SCOPE* (Study on Cognition and Prognosis in the Elderly) included 4964 patients with mild hypertension ($160 < \text{SBP} < 179$ mmHg; $90 < \text{DBP} < 99$ mmHg), aged 70 to 89 years and Mini Mental State Examination (MMSE) score ≥ 24. Double-blind treatment consisted of candesartan or placebo. Open label therapy was added to control blood pressure. Blood pressure reduction was significantly higher in patients receiving candesartan (21.7/10.8 mmHg) than in controls (18.5/9.2 mmHg), resulting in a decreased stroke incidence after a 3.7 years followup (-23.6%). There were no significant differences in MMSE scores between intervention and control group [44]. However, when patients were stratified according to baseline MMSE score, the incidence of dementia was higher among those with a low cognitive function ($24 < \text{MMSE} < 28$) when compared with those with a preserved cognitive function ($\text{MMSE} > 28$). Among patients with a low baseline cognitive function, the MMSE score declined less in the candesartan group (mean difference 0.49, $P = .04$). Of note, patients with a low baseline cognitive function were older and had more cardiovascular risk factors [45].

Although designed to include cognitive function in the assessment of benefits of antihypertensive therapy in elderly, *HYVET* (Hypertension in the Very elderly Trial) failed to reach definite conclusions about this specific issue. Indeed, the trial was stopped early after 2.2 years because

treatment resulted in a reduction in stroke and total mortality. This double-blind, placebo-controlled trial enrolled 3336 patients aged 80 years or more with hypertension (160 < SBP < 200 mmHg; DBP < 110 mmHg). Patients received inda-pamide (1.5 mg daily) ± perindopril (2–4 mg daily) or placebo. Although blood pressure was lower in the intervention group, the difference in dementia incidence rate was not statistically different between patients receiving therapy and controls (33 versus 38 per 1000 patients-years). However, when the authors combined their data in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, results reached statistical significance [46].

Two other trials, PROGRESS and SYST-EUR, provided convincing data on the protection of cognitive decline in older patients treated with antihypertensive agents.

PROGRESS (Perindopril Protection against recurrent Stroke Study) included 6105 patients (mean age: 64 years) with previous stroke or transient cerebral ischemic attack and assessed incidence of (vascular) dementia and cognitive decline (MMSE score reduction >2) with regards to therapy consisting of either perindopril/indapamide or placebo. After a 3.9-year mean followup, treatment reduced the incidence of dementia by 12%, of cognitive decline by 19% and of a combination of cognitive decline or recurrent stroke by 34% [47]. A substudy compared baseline and followup brain MRIs in 192 patients to assess progression of white matter hyperintensities in patients receiving therapy and in controls. Whereas the extent of baseline white matter hyperintensities was similar in both groups, new hyperintensities appeared in 16% of controls and 9% of patients receiving therapy. Although these changes were not statistically significant, the mean total volume of new white matter hyperintensities was reduced in the treatment group (0.4 versus 2 mm^3, $P = .012$) [48].

Whereas *PROGRESS* by selecting patients with cerebrovascular disease targeted the impact of antihypertensive therapy on vascular dementia mainly, *SYST-EUR* (Systolic Hypertension in Europe) was intended to include a broad population, consisting of patients > 60 years with systolic hypertension (160 < SBP < 219 mmHg; DBP < 95 mmHg). The initial double-blind trial randomized 579 patients with either nitrendipine (10–40 mg daily), completed by enalapril (5–20 mg daily) and hydrochlorothiazide (12.5–25 mg daily) if required to control BP or placebo [49]. After a 2-year followup, the trial was continued on the basis of an open-label active treatment study in which a total of 2902 patients received therapy. After a mean follow up of 3.9 years, blood pressure control, though improved, remained suboptimal in the control group ($156 \pm 12/82.5 \pm 6$ versus $149 \pm 9.7/79 \pm 6$ mmHg at the last follow up visit), in connection with fewer patients receiving antihypertensive drugs (nitrendipine: 48.1% versus 70.2%; enalapril: 26.4% versus 35.4%; hydrochlorothiazide: 11.4% versus 18.4%). This was associated with a decreased incidence of dementia in the intervention group when compared with the control group (dementia all causes: 3.3 versus 7.4 per 1000 patient-year; Alzheimer disease: 1.9 versus 5 per 1000 patient-year; mixed or vascular dementia: 1.1 versus 2.1 per 1000 patient-year) [50].

5. Hyperlipemia

Although increased levels of total and LDL-cholesterol are associated with cardiovascular risk, atherosclerosis, and vascular dementia, similar correlations failed to be demonstrated with the incidence of Alzheimer disease [51]. However, Helzner et al. showed that both parameters are correlated with Alzheimer disease progression, each 10 mG/dL decrease in either being associated with a 0.10-SD decrease in cognitive score per year of followup [52].

Large-scale database correlated statin use and reduction in the incidence of dementia. Using the US Veteran Affairs database which collected information on approximately 4.5 million subjects and 110 million prescription annually, Wolozin et al. showed a strong reduction in the incidence of dementia in patients receiving simvastatin (HR = 0.46), a moderate reduction in those receiving atorvastatin (HR = 0.91), whereas no change was observed among patients treated with lovastatin [53]. Similar results were obtained using a nested case-control study on 309 patients with Alzheimer disease at the US Veteran Affairs Medical Center of Birmingham between 1997 and 2002. Patients treated with statins had a 39% lower risk of Alzheimer disease related to nonstatin users. Of note, this association was observed in patients with ischemic heart disease, cerebrovascular disease, or hypertension but not among those without any of these conditions [54]. Conversely, data from the specialized register of the Cochrane dementia and cognitive improvement group, which analyzed the 2 double-blind, randomized, placebo-controlled trials *HPS* and *PROSPER*, failed to reach similar conclusions. Indeed, among the 5804 patients aged 70 to 82 years included in *PROSPER*, there was no difference in cognitive performance nor in incidence of dementia between pravastatin treated and placebo group. Also, no difference in incidence of dementia or in cognitive performance tests decline was noted in *HPS*, in which 5806 patients over 70 years received simvastatin or placebo [55].

Thus, although several epidemiological and clinical trials provided evidence and a rationale basis for a preventive role of statins in Alzheimer disease [56], one should also argue that many others showed that this benefit was limited to patients with cerebrovascular, coronary artery disease, or hypertension.

6. Diet and Physical Activity

A lower level of physical performance in ageing adults is associated with an increased risk of dementia. In a prospective cohort study of 2288 people 65 years and older with a 6-years followup, Wang et al. observed an age-specific incidence rate of dementia, reaching 53.1 per 1000 person-year for participants who scored lower on a performance-based physical function test at baseline compared with 17.4 per 1000 person-years for those who scored higher. These impairments in physical function, which are interconnected with onset of cognitive decline, occur during the early, subclinical, stage of the disease. Conversely, a higher level of physical function is associated with a delayed onset of Alzheimer disease [57].

Table 1: Age-dependent prevalence of dementia (%) in selected populations.

	Population	Criteria	Disease	65–69 yrs	70–74 yrs	75–79 yrs	80–85 yrs	>85 yrs
Hofmanet al. [19]	12 European surveys	clinical		1.4	4.1	5.7	13	21.6
Ritchie and Kildea [20]	9 US and European surveys	clinical		1.5	3.5	6.8	13.6	22.3
Anstey et al. [21]	Australia	MMSE		3.78	5.16	10.6	16.3	22.3
Dong et al. [22]	China	clinical	AD (w/m)	0.5/0.3	1.8/0.9	4.4/2.3	11/3.8	23.4/10.6
Dong et al. [22]	China	clinical	VD (w/m)	2/0.9	2/0.4	1.9/0.6	1.1/1.8	0.4/0

AD: Alzheimer disease. VD: vascular dementia w/m: women/men.

Table 2: Prevalence of dementia (clinical criteria) in people aged > 65 years.

	Country	Prevalence rate (%)
Fitzpatrick et al. [27]	USA	6.3
Graham et al. [28], Hébert et al. [29]	Canada	5.3
Berr et al. [30], Riedel-Heller et al. [31]	15 European countries (EURODEM)	5.9
Lobo et al. [32]	Spain	5.2
Nitriniet al. [33]	6 countries, South America	7.1
Kalaria et al. [34]	India	3.4
Dong et al. [22], Kalaria et al. [34]	China	3.1

Several studies have shown that a healthy lifestyle, including diet and exercise training, may prevent cognitive decline in the elderly. Their results migh however have been biased by confounding factors such as educational and socioeconomic status and the impact of diet and exercise on cardiovascular risk factors. These drawbacks were not supported by recent studies suggesting that diet and exercise prevent and slow down dementia independently of such confounding factors.

The *WHICAP* (Washington Heights-Inwood Columbia Aging Project) cohort study enrolled 1880 Medicare beneficiaries in Northern Manhattan in 1991. Food consumption, a Mediterranean-type diet adherence score and a physical activity score were documented. Neuropsychological tests were repeated every 18 months from inclusion through 2006. Dementia developed in 282 subjects. Patients adhering to the Mediterranean-type diet and participating to physical activities with the highest scores have a lower risk of subsequent Alzheimer disease in a model adjusted for age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, body mass index, smoking status, leisure activities, and a comorbid index [58].

Similar results were obtained among 1410 participants included in the Bordeaux cohort study. After a 5-year followup, higher adherence to the Mediterranean-type diet was associated with a slower MMSE cognitive decline [59].

7. Risk Profiles for Dementia

7.1. Multifactorial Prevention. Although numerous studies have linked cardiovascular risk factors profile to subsequent incidence of dementia, most interventions to prevent cognitive decline were performed on a single risk factor control basis. Whether multifactorial prevention will provide substantially improved protection has not been ascertained, especially in patients with a lower risk profile.

Targeting high-risk patients for cardiovascular prevention of vascular dementia and Alzheimer disease requires assessment of aggregation of cardiovascular risk factors and detection of subclinical atherosclerosis in individuals.

In a cohort-study of 1270 dementia-free subjects aged 75 years or more, Qiu et al. scored cardiovascular risk factors at baseline and tracked incident dementia during a 9-year followup. A twofold increased risk for dementia (428 subjects including 328 with Alzheimer disease) was observed in subjects with an atherosclerotic profile (systolic BP > 160 mmHg or diabetes or previous stroke) and cerebral hypoperfusion (diastolic BP < 70 mmHg or pulse pressure <70 mmHg, or heart failure) [60]. Similarly, de la Torre suggested that detection of subclinical atherosclerosis and carotid plaques using carotid artery ultrasound may identify patients at increased risk for subsequent cognitive impairment, thereby allowing reinforced preventive control of cardiovascular risk factors, a strategy which may ultimately reduce the incidence of dementia [61]. Whether translating such an approach to lower risk patients would be clinically relevant remains to be ascertained using appropriately designed trials targeting large populations and focusing on cognitive decline as primary outcome endpoints [62].

7.2. Age-Related Risk. Although prevalence and incidence of Alzheimer disease increase with age, further increase after the age 90 has been questioned, as approximately half of the centenarians (43%) did not experience dementia [63]. In addition, pathological studies also showed that the distribution pattern of neurofibrillary tangles, senile plaque, microvascular impairment, and neuronal loss changes in extreme aging relative to the younger old [64]. As a result, the benefits expected from cardiovascular prevention of cognitive disorders in the oldest-old and centenarians may be more limited than in younger old.

7.3. Risk Control Across Populations. The benefit of cardiovascular risk factors control in preventing cognitive disorders

among elderly may also largely vary across populations living in different geographical areas.

Dementia prevalence rates among people over 65 years ranges from 3% to 11%, depending on diagnosis criteria (clinical, mostly DSM III, or MMSE-guided), age (Table 1), and countries (Tables 1 and 2). However, age-related increases in prevalence are observed independently of the population studied (Table 1), with limited differences in prevalence across populations and geographical areas (Table 2).

The burden of cardiovascular risk factors and its impact on vascular dementia have also been reported to increase with age in patients in western countries [29, 65–67]. Concomitantly, population-based surveys complemented by data from *MONICA* and *INTERSALT* showed a linear association of systolic blood pressure with age in men and women aged 30 to 70 years. This program, which encompassed 230 surveys and over 660 000 participants worldwide showed that age-related increase in blood pressure is observed in all WHO subregions populations [68].

Although this may argue for some rationale for expecting similar results from cardiovascular prevention of cognitive decline among different populations, including in developing countries, trials to support such hypotheses remain to be performed.

8. Conclusion

Optimal treatment of cardiovascular risk factors prevents and decreases progression of vascular dementia and Alzheimer disease. As a 5-year delay in the onset of Alzheimer disease could reduce the prevalence of Alzheimer disease by 50%, epidemiological forecasting estimate about 25% of the 5-fold increases in prevalence of dementia expected to occur until 2050 could effectively be prevented by optimal cardiovascular risk factors control [3, 61].

Thus, facing the worldwide burden of cardiovascular risk factors in a population growing in weight and in age continuously, slowing the incidence and progression of dementia may be a valuable challenge for cardiovascular prevention and cardiology practice. As life expectancy is expected to increase further in the decades to follow, limiting its age-related counterparts such as Alzheimer disease may also be relevant in an individual perspective as well as in a community opportunity to reduce medical cost-expenditures.

Conflicts of Interest

The authors declare that there is no conflicts of interest.

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Review Article

Efficacy of Dietary Behavior Modification for Preserving Cardiovascular Health and Longevity

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Cardiovascular disease (CVD) and its predisposing risk factors are major lifestyle and behavioral determinants of longevity. Dietary lifestyle choices such as a heart healthy diet, regular exercise, a lean weight, moderate alcohol consumption, and smoking cessation have been shown to substantially reduce CVD and increase longevity. Recent research has shown that men and women who adhere to this lifestyle can substantially reduce their risk of coronary heart disease (CHD). The preventive benefits of maintaining a healthy lifestyle exceed those reported for using medication and procedures. Among the modifiable preventive measures, diet is of paramount importance, and recent data suggest some misconceptions and uncertainties that require reconsideration. These include commonly accepted recommendations about polyunsaturated fat intake, processed meat consumption, fish choices and preparation, transfatty acids, low carbohydrate diets, egg consumption, coffee, added sugar, soft drink beverages, glycemic load, chocolate, orange juice, nut consumption, vitamin D supplements, food portion size, and alcohol.

1. Introduction

Healthy choices and behaviors influence CVD incidence and mortality. However, changing our dietary lifestyle in order to avoid cardiovascular disease is not easy. To succeed in reducing CVD, dietary alterations have to be maintained long term, which is a much more difficult task than taking pills. As a result, both patients and physicians gravitate toward medication for lowering CVD risk and prolonging life with only cursory attempts at changing lifestyle behaviors such as eating habits. There is the unfortunate perception that even with intensive counseling, risk factor modification by dietary means is trivial. Recent research indicates that this is not the case and that the necessary behavior modification regarding the diet can be achieved and confers a substantial benefit when implemented in conjunction with other behavior modification [1].

2. Methods

We performed a systematic review focused mainly on large trials with about 1900 subjects and meta-analyses of evidence for relationships of dietary factors with incident CHD, CVD, stroke, and diabetes mellitus. We searched for any cohort study, case-control study, or randomized trial that assessed these exposures and outcomes in generally healthy adults or subjects with overt CVD. We completed a Google search using keywords such as healthy lifestyle, healthy behaviors, CVD, CHD, stroke, and diabetes. Thus, this paper is based mainly on a 2000–2010 Internet search for well-designed relevant trials and data that confirm and quantify established dietary recommendations and novel nutritional data, shown or alleged to be alterable by changes in behavior and to be beneficial for CVD risk factor control.

3. Results

Despite decades of efforts to control them, half of USA adults still have unacceptable CVD risk factors. The latest NHANES survey (1999–2006) shows that 45% had one of the three major risk factors: 30.5% had hypertension, 26% high blood cholesterol, and 9.9% diabetes. About 13% had two of the conditions and 3% had all three. The risk factor rates were higher in blacks and 15% were unaware of having these

conditions. The fraction of persons with one or more of these conditions and unaware of it was consistent across all ethnic groups. With 60% of adults and 30% of younger Americans obese, the CVD risk burden threatens to worsen. We appear to be headed for a generation with poorer health than the preceding one, which is unique [2].

Lifestyle, in general, and the diet we choose to eat, in particular, affects each of the major risk factors. A number of nutritional behaviors are recommended for avoiding cardiovascular risk factors and thereby prolonging our lifespan. In addition to recommendations for medicating hypertension, HDL-C, LDL-C, and diabetes, strong behavioral measures are now available for control of these major risk factors. In the Nurses' Health Study 82% of CHD incidence occurred in those who failed to adhere to a sustained regimen that incorporates healthy dietary choices along with moderate exercise, maintaining a normal body weight, smoking abstinence, and moderate alcohol intake. Also, in the Health Professionals Follow-Up Study adherence to this healthy lifestyle reduced the lifetime risk of heart failure [3, 4].

3.1. Established Nutritional Factors. Evidence has now accumulated that quantifies and substantiates accepted recommendations for consumption of cholesterol, saturated, polyunsaturated, and transfats in the diet. In addition, new data suggest that some foods we were told to avoid may be acceptable if consumed in moderation.

3.1.1. Replacing Saturated Fat with Polyunsaturated Fat. People have been advised to avoid eating saturated fats to preserve CVD health for 60 years or more. However, there has been little evidence from research to substantiate this recommendation. The food industry and the general public have reduced saturated fat over the years, but have often replaced them with harmful trans fats and refined carbohydrates. A recent study by the Harvard School of Public Health has produced the first conclusive evidence that reducing saturated fat with polyunsaturated fat substitution reduces CHD risk by 19%. The meta-analyses of 8 randomized trials revealed that for every 5% increase in polyunsaturated fat consumed, the risk of CVD decreased by 10%. The Institute of Medicine recommends that 5%–10% of energy intake should come from polyunsaturated fats. Other trials have advised an intake of 15% [5].

3.1.2. Processed versus Unprocessed Red Meats. Probing of the influence of saturated fat and cholesterol in the diet has now been examined from the real-world perspective of the marketplace. For example, a unique meta-analysis of globally obtained data reported an examination of the relationship between eating processed as opposed to unprocessed red meats and the risk of CHD and diabetes. The analyses indicated a direct relationship between consumption of processed meats and the risk of CHD and diabetes. After adjustment for CHD risk factors, the risk of CHD increased by 42% and the risk of diabetes increased by 19% for every 50 gm of processed meat consumed daily. Processed meats, for example, bacon, sausages, or luncheon meats are preserved by adding salt, smoking, curing, or by adding preservatives. A 50 gm serving would be equivalent to a hot dog or 1-2 slices of processed meat. The amount of cholesterol and saturated fat contained in both processed and unprocessed meat is comparable. However, the amount of sodium in processed meats is four times greater than that of unprocessed and it has 50% more nitrate preservatives. The results of this study suggest that it is the sodium and preservatives in processed red meats, and not the fats that increase its risk of CVD and diabetes. Dietary salt does increase blood pressure, and studies of animals suggest that nitrate preservatives contribute to atherosclerosis and decrease glucose intolerance; conditions that are known to raise CHD and diabetes risk [6]. However, it is not established that processed meat confers a higher CHD risk than unprocessed meat.

3.1.3. Hazards of Red, White, and Processed Meats. A study of the relationship between white, red, and processed meat with mortality in half a million middle-aged participants of the NIH-AARP Diet & Health Study was recently reported by Sinha et al. Consumption of processed and red meats was found to increase total deaths, cancer, and CVD deaths, whereas white meat protected against total mortality and cancer mortality. Red meat appeared to increase all the specified mortalities more than the processed meats. Red meat increased overall mortality 31% in men and 35% in women, whilst processed meat increased it 15% and 25% in men and women, respectively. For cancer mortality there was a 27% increase for red meat for men and 50% increase for women, whereas processed meat conferred a lesser 12% increase in men and 11% in women. For CVD, red meat imposed a 27% increase in men and 50% in women, while for processed meat the increases were 9% in men and 38% in women [7].

Unlike meat products that are high in fat, fish is low in saturated fats and is a good source of protein and omega-3 fatty acids. Omega-3 fatty acid has been linked to a reduction in the development of atherosclerotic plaque, triglyceride levels, blood pressure, and the risk of arrhythmias. Consumption of fatty fish high in omega-3 fatty acids such as salmon, sardines, and tuna at least twice per week is recommended for preserving cardiovascular health. Furthermore, Omega-3 fatty acid intake from food rather than from supplements is advisable. However, for persons with established coronary disease it may be advisable to also prescribe a supplement of omega-3 [8].

Consideration of the type of fish to be consumed as well as the means of preparation is also necessary. Due to the high levels of contaminants and mercury contained in some larger fish, such as swordfish and king mackerel, the USA Food and Drug Administration recommend that children, expectant women, and nursing mothers avoid consumption of these fish and opt for fish that are lower in mercury such as, salmon, catfish, and canned light tuna. For the middle-aged and the elderly, eating an assortment of fish to help diminish the detrimental effects of potential impurities is recommended [8]. The cardioprotective benefits of eating fish are dependent not only on the quantity and the type

of fish consumed, but also the way that it is prepared. Meng et al. found that men who ate the most fish had a 23% decrease in coronary heart disease and those who ate adequate amounts of baked or boiled fish had a lower coronary disease death rate than those who ate little fish. On the other hand, those who ate deep fried, salted, and dried fish daily had an *increase* in CHD mortality of 12%–15% [9].

Hu et al. provide evidence supporting recommendations to eat fish for cardioprotection. They found that 84,000 women nurses enrolled in the Nurses' Health study who consumed higher amounts of fish and omega-3 fatty acid supplements have a reduced risk of *CHD.* Within a 16 year observational period, 1,513 cases of incident CHD occurred, 484 CHD mortalities and 1,029 nonfatal myocardial infarctions. Women who consumed a higher amount of fish had a lower risk of coronary disease compared to those who ate fish less than once per month. A comparable result was found for those who consumed higher amounts of omega -3 fatty acids. The protective relationship appeared to be more powerful for coronary mortality than for nonfatal myocardial infarction [10].

Contrary to the aforementioned research studies and recommendations, Nair and Connolly did not find convincing evidence to support the recommendation for routine consumption of omega-3 fatty acids. They reported that Jenkins and colleagues failed to demonstrate a convincing beneficial effect for prevention of arrhythmia and concluded that cited meta-analyses had provided weak evidence that omega-3 fatty acid intake can prevent either ventricular arrhythmia or cardiovascular mortality [11].

3.1.4. Egg Consumption. As early as 1982 Dawber et al. of the Framingham study reported on the nutrient intake of a subsample of Framingham study participants that allowed an estimate of egg consumption on 912 subjects. It was concluded that within the range of egg intake of this general population sample egg consumption is unrelated to serum cholesterol or to CHD incidence [12].

In 1999 Hu et al. reported findings from the Health Professionals Study and Nurses' Health Study that prospectively examined consumption of eggs as a risk for initial CVD events in subjects free of high cholesterol, diabetes, or cancer. There were 1805 initial CHD and 821 first strokes in 8 years. Adjusting for age, smoking, and other risk factors, they found no significant link between 1–6 eggs weekly and coronary heart disease or stroke risk in either sex. However, egg use was associated with a statistically significant 1.5-2-fold increased coronary disease risk in diabetic men and women on comparison of consumption of more than 1 egg daily versus less than 1 egg per week. They concluded that eating one or fewer eggs per day has little impact on risk of coronary disease or stroke in healthy persons but that egg consumption in diabetics warrants further study [13].

A later study of egg consumption in the Physicians' Health Study by Djoussé et al. in 2008 examined the relationship between egg intake and the risk of CVD events and mortality prospectively in 21,327 participants. Over the 20 year period, there were 8061 new events; 19% of which were new myocardial infarctions, 17% initial strokes, and 64% deaths. After adjustment for other risk factors multivariable analysis showed that consumption of eggs was unrelated to incident myocardial infarction or stroke, however with respect to mortality there is a modest relationship particularly in diabetics where the risk was increased twofold (P for interaction = 0.09). It does not appear that physicians need to restrict moderate egg consumption in patients, unless they are diabetic [14].

3.2. Novel Dietary Factors. Recent research of modifiable elements of behavior has reported findings that are contradictory *to* some common perceptions about nutrition. Many lifestyle elements that were once believed to be detrimental to health do not appear to be damaging and in some cases are beneficial. Among the novel factors reported in recent studies are consumption of coffee, dark chocolate, nuts, orange juice and vitamin D.

3.2.1. Coffee Consumption. There has been a long standing controversy about the effect of coffee on CVD risk with early studies finding it harmful and recent ones judging it helpful or harmless. Until recently, studies have reported that coffee lovers risk having excess cardiac rhythm disturbances as well as myocardial infarctions and coronary heart disease in general. In a review of coffee consumption and cardiovascular disease in 1989 Wilson et al. called attention to a prospective study of 45,589 subjects that reported only a trivial increase in CVD risk for persons who consume more than 4 cups of coffee per day, whereas there was a strong positive correlation between *decaffeinated* coffee and the risk of CHD [15].

More recent large studies have reported that coffee actually does not increase CVD risk and may even decrease the rate of CVD events. These include the Nurses' Health Study that reported no association between coffee consumption and CVD occurrence in a study of 85,747 women who were followed for 10 years, a Swedish study found no association between coffee and post-MI death and an inverse relationship between coffee consumption and CHD and a 6-year study of 2,975 men cited by Wilson et al. that reported, that the risk of a first cardiovascular event was decreased by 67% for those who drank more, rather than less, than 8 cups of coffee per day [15]. In addition, Ahmed et al. opposed the claim that coffee consumption increases the risk of heart failure [16].

Further studies have also indicated a beneficial effect of coffee. A recent *NHANES* prospective study found a strong protective association of coffee in elders without HBP. This finding was tested in the Framingham Study on 1,354 subjects aged 65–97 years. There were 210 CVD deaths and 118 CHD deaths during 10 years of surveillance. A significant 43% inverse relation between *caffeinated* coffee use and CHD mortality was observed for subjects with BP < 160/100 mm Hg. This lowered risk appears to be primarily attributable to a protective relationship between *caffeinated coffee* use and the onset of heart valve disease [17].

Most physicians and their patients believe that "palpitations" can result from drinking caffeinated coffee. However, after adjustment of cholesterol, BMI, BP, and other risk factors Kaiser Permanente investigators found that drinking

more than 4 cups of coffee daily resulted in an *18% reduction* in hospitalizations for cardiac rhythm disturbances in men and women, in different ethnic groups, and in smokers. An analysis of the risk reduction of *decaffeinated* coffee resulted in no protection, indicating that *caffeine* may actually be protective [18].

3.2.2. Sugar Consumption. USA sugar consumption has increased greatly in recent decades, largely due to added sugars in foods processed to increase their desirability. In an analysis of nutritional US data, Welsh et al. found a correlation between the consumption of sweeteners and blood lipid levels. This Emory University study analyzed the data of more than 6,000 men and women from 1999–2006. They found that people who add more sugar to their diet are more likely to have higher triglycerides and triglyceride/high-density lipoprotein cholesterol ratios. Highest consumers ate 46 teaspoons of added sugars daily, the lowest 3 teaspoons daily [19]. This study, the first to examine the relation between added sugars and lipids, did not evaluate natural sugars in fruits and juices.

National surveys show that adding dietary sugar is contributing to overconsumption of calories. Johnson et al. postulate that the detrimental effect of elevated sugar consumption during a pandemic of obesity and CVD is cause for alarm. Between 1970 and 2005, dietary sugar intake increased by 19% to the current level of 22.2 teaspoons per day. The additional sugar appears to come chiefly from excessive intake of beverages. This high consumption of soft drinks replaces some essential nutrients and predisposes its association with adiposity and the "metabolic syndrome." As a consequence the American Heart Association advises limiting daily intake of sugar to less than 100 calories for women and less than 150 calories for men [20].

3.2.3. Glycemic Diet. Prospective studies of the relationship between glycemic load (GL) and glycemic index (GI) with CVD have yielded inconsistent results, especially for men. Sieri et al. investigated this issue in a 7.9 year follow-up study of 47,749 EPICOR study volunteers who had completed a nutritional survey. Over the follow-up period, 158 women and 305 men developed CHD. Women in the highest quartile of carbohydrate consumption experienced a doubling of CHD risk compared to those in the lowest quartile. However, the same analysis in men yielded no association. Excess intake of carbohydrate foods with a high-glycemic index raises the blood sugar level and increases insulin resistance. This imposes a significant 1.7-fold excess of CHD for women only. For those in the highest quartile as opposed to those in the lowest quartile CHD risk was increased more than 2-fold. It is postulated that the adverse effects of a high glycemic diet in women may be attributable to sex differences in lipoprotein and glucose metabolism [21].

Switching to a low glycemic diet can be relatively easy. As recommended by the Glycemic Index Foundation Sydney Australia, the basic premise is to substitute high glycemic index carbohydrates for low glycemic carbohydrates. This entails use of oats, barley and bran in breakfast cereals; eating wholegrain breads and cutting down on the amounts of potatoes consumed. All other types of fruits and vegetables can be savored along with basmati rice, pasta, noodles, quinoa and salad vegetables with a vinaigrette dressing [22].

3.2.4. Chocolate. Recent data suggest that eating chocolate may actually *lower* blood pressure and risk of CVD. In a large European study of more than 19,000 volunteers, Buijsse et al. found that participants eating 7.5 grams of chocolate daily had a lower risk of myocardial infarction and stroke than those who consumed only 1.7 g of chocolate per day. During the 8 years of the study, there were 166 myocardial infarctions and 136 strokes. The top quartile of chocolate consumers had a 27% reduced risk of myocardial infarction and 48% lower risk of stroke than the lowest quartile chocolate consumers. The combined outcome of myocardial infarction and stroke was reduced 39% ($P = .01$). Chocolate and cocoa have a marked effect on blood pressure and in this study the lower blood pressure induced accounted for 12% of the reduction in CVD risk. However, even after adjusting for blood pressure, those in the top chocolate consumption quartile still had a 32% decreased risk of CVD compared to those in the bottom quartile [23].

To date, there is no established recommendation for healthful chocolate consumption for the purpose of preserving cardiovascular health. Flavonoids in cocoa oppose free radical injury because of their antioxidant effect. They also decrease cholesterol, lower blood pressure, inhibit sticky platelets, and improve blood flow to vital organs. During the processing of cocoa into chocolate some of its beneficial flavonoids are lost. Adding dark chocolate to the diet appears preferential to eating milk chocolate. However, despite the potential health benefits, one must recognize that 100 g of dark chocolate has 500 calories, which must be taken into account if weight gain is to be avoided. Presently, it appears prudent to enjoy moderate one ounce portions of chocolate several times a week. Other options for supplementing the diet with flavinoid-rich foods are apples, cranberries, grapes, onions, peanuts, orange juice, red wine, and tea [24].

3.2.5. Nut Consumption. It appears that eating nuts as part of a balanced diet may favorably affect blood lipids and potentially lower the risk of CHD. Epidemiological studies indicate that the risk of CHD is 40% lower in persons who eat more than 4 servings of nuts per week as opposed to those who do not eat any. A meta-analysis of 25 studies undertaken by Sabaté et al. examined whether the effects of eating nuts on blood lipids vary by population, type of nuts consumed, diet, or BMI in untreated subjects with normal lipids and blood pressure. The results of this analysis indicate that consuming 67 g of nuts daily reduced total cholesterol by 10.9 mg/dL and LDL-C 10.2 mg/dL. It also significantly improved the ratios of LDL/ HDL cholesterol and total/HDL cholesterol. However, there was no significant effect on HDL-C or triglycerides per se. The risk effect was similar in both sexes and all age groups, and it was observed regardless of the specific nut consumed. Lipid lowering was greater for persons with higher LDL-C (18.4 mg/dL) than lower LDL-C (3.5 mg/dL) and a BMI < 25 [25].

3.2.6. Orange Juice. A new study claims that drinking orange juice with meals can counter the proinflammatory effects of high-carbohydrate, high-fat meals. High carbohydrate, high fat meals induce a protein, suppressor of cytokine signaling 3 (SOCS-3), that interferes with the action of insulin promoting insulin resistance. These adverse changes can be avoided when orange juice is consumed with a meal. This implies that drinking orange juice could potentially help prevent insulin resistance, diabetes, CHD and strokes. This benefit may be attributable to the flavinoids in orange juice, which suppress reactive oxygen metabolites [26].

3.2.7. Vitamin D. New studies support the link between vitamin D deficiency and CVD [27–35]. Bair et al. observed 9.491 persons with low-level vitamin D and those who normalized D levels after one year comparing outcomes in CHD, MI and heart failure, stroke, renal failure, and death. They found that those who normalized vitamin D levels were less likely to develop heart failure or CVD, and they were less likely to die [27]. The effect of vitamin D was quantified in a study by May et al. who divided 31289 patients into 3 levels and linked them with several adverse outcomes, mostly CVD. An inverse relationship was found between increasing vitamin D levels and adverse events. Optimal vitamin D was defined as greater than 43 nanograms per milliliter (ng/mL) [28]. Penckofer et al. indicate a further benefit showing that adequate intake of vitamin D may impede diabetes. They postulate that vitamin D may aid in the regulation of metabolic factors via beta-cell operation [29].

Vitamin D deficiency also appears to lead to high blood pressure. In a study of premenopausal women with deficient vitamin D levels, Griffin et al. found that after 15 years, women whose vitamin D levels remained deficient, (less than 80 nmol/L), had a three times greater risk of developing hypertension than those women whose vitamin D levels were normal [30]. In the Framingham Study, Wang et al. found that persons with >15 ng/mL versus <15 ng/mL vitamin D had a multivariable adjusted hazard ratio of 1.62 ($P < .01$) for new CVD, but only in hypertensive subjects (HR 2.13) [31]. Evidently the health benefits of vitamin D go beyond strong bones, protecting against CVD and even boosting the immune system [32].

However data reported on utility of vitamin D supplements for the treatment, prevention, and reversal of many health conditions such as hypertension, diabetes, obesity, and CVD are inconsistent. In a systematic review of 5 prospective studies of dialysis patients and one general population study of subjects receiving vitamin D supplements, Wang et al. found a decrease in CVD deaths [33]. However, Pittas et al. found the association between vitamin D status and cardiometabolic outcomes to be uncertain. Trials they reviewed showed no clinically significant effect of vitamin D supplementation [34]. Further studies may be necessary to determine an optimum dosage of vitamin D.

Meanwhile, increasing vitamin D levels appears to be necessary. Small amounts of vitamin D can be obtained from foods such as fish and mushrooms as well as from vitamin supplements. However, obtaining vitamin D from sun exposure has a greater duration of effect. Although, physicians usually advise patients to avoid unprotected sun exposure, its beneficial effects are essential, albeit in moderation. On exposure to the sun, the skin produces vitamin D and preserves it in adipose tissue. Vitamin D is then released when sunlight is limited such as in winter months in the Northern Hemisphere. Ten minutes of sun exposure daily is not only safe, but necessary for optimal health. In person over 65 years of age and for residents living in areas where sun exposure is limited, a dietary supplement is recommended [29, 35].

3.3. Portion Control for Weight Management. Portion control is essential for weight loss and for maintaining a healthy weight. In 2007, Pederson et al. completed a randomized trial of weight control in 130 participants with type 2 diabetes. The group using a portion-control plate decreased their body weight by 1.75% versus a 0.05% weight loss in the group who did not. The group using the portion-control plate also decreased use of medication for the management of diabetes, suggesting that portion-control plates are as effective as costly diet medication [36]. The diet plate is a commercially available plate with recommended foods and serving sizes for a healthful diet depicted on it.

When presented with greater portion sizes, people tend to eat more but report the same level of satiation. In a study by Rolls et al. participants were given four different portion sizes of macaroni and cheese on different days. Although, consumption increased with the portion size served, participants reported similar levels of satiation and less than half noticed that portion sizes had changed. Consumption of the largest portion as opposed to the smallest portion of macaroni amounted to 30% more energy (162 cal) [37]. In a similar study, the same participants were given different sizes of subsandwiches on 4 different days. The participants ate significantly more as the sandwich size increased [38] Rolls et al. also examined how energy intake increases in both men and women as the portion size of a snack increases. On 5 different occasions, they gave men and women bags of potato crisps that appeared to be similar in size but the quantity varied from 28 g to 170 g. As the package size increased the amount of consumption also increased [39]. A study by Diliberti et al. showed similar effect in that participants who were served different quantities on different days in a restaurant, increased consumption as portion sizes increased [40]. Increased portion size appears to make it difficult for people to determine how much is being consumed and leads to excess calorie consumption. Therefore, public awareness of the effect portion size can have on weight control efforts is essential [41].

3.4. Alcohol and Cardiovascular Disease. Meta-analyses of experimental and observational studies indicate that moderate consumption of alcohol is beneficial for decreasing the risk of CHD. Published research *has for many years* suggested a link between alcohol consumption and reduced CVD mortality. Alcohol is associated with a modest increase in HDL cholesterol and may play a role in reduction of thrombus formation which reduces risk of stroke and CHD. A study examining the effects of alcohol on cholesterol and

haemostatic factors by Rimm et al. showed that consumption of 30 g of alcohol per day can reduce risk of CHD by 24.7% [42]. Some speculate that the benefits may derive from the beneficial antioxidants and flavonoids contained in red wine. However, it is unclear if the type of alcohol consumed, or other healthy behaviors of those who consume alcohol in moderation, is responsible for the reduced risk [43]. Nonetheless, Mukamal et al. found that moderate alcohol consumption appears to confer a lower risk of myocardial infarction even in men who were already determined to be at low risk of MI based on their healthy lifestyle choices and BMI [44]. Likewise, Sesso et al. found a significant reduction in risk of CHD in men who increased consumption of alcohol from very low to moderate levels. The study included 18,455 men who were tracked over a period of 7 years [45].

The AHA reluctantly recommends moderate consumption of no more than two drinks per day for men and one drink per day for women. A drink is one 12 oz. beer, 4 oz. of wine, 1.5 oz. of 80-proof spirits, or 1 oz. of 100-proof spirits. It reminds us that drinking more alcohol than recommended is associated with alcoholism, accidents, suicide, cirrhosis of the liver, and breast cancer. With consideration of the detrimental effects, the AHA does not recommend that abstainers start drinking alcohol [46].

4. Discussion

4.1. Magnitude of the Cardiovascular Threat. The Framingham study has determined the actual lifetime risk of developing atherosclerotic cardiovascular disease from a general population sample examined biennially since 1950. In the 60 years of surveillance by routine examination of the population, the lifetime risk of developing a cardiovascular event for a 50-year-old was 52% for men and more than 39% for women with little or suboptimal treatment [47–50]. Ford et al. estimate that half the reduction in USA CHD mortality since 1980 is attributable to cardiovascular risk factor reduction in the population [51] Thus, correction of risk factors discovered by the Framingham study has resulted in a major reduction in CHD deaths in the US population; 64% for non-CHD deaths and 49% for sudden deaths [52]. A faulty diet is in part responsible for many of the major CVD risk factors including dyslipidemia, hypertension, obesity, impaired glucose tolerance, and diabetes.

4.2. Lifestyle and Behavior. The USA allocates more funds for its medical system than any other country but performs poorly on all measures for the quality of health care. In comparison with 30 developed nations of the world, the US trails behind on most standard measures of quality health care. Reports based on 2004 data from 192 nations, placed the USA at 46th in average life expectancy and 42nd in infant mortality. Whereas a mere 10% of the population's mortality is attributable to the quality of health care and 40% is attributable to detrimental behaviors, the best means for improving health and reducing premature death may lie in the modification of personal behavior [53, 54]. Physicians need to place greater emphasis on modifying patient's CVD-promoting behavior and among these, a more healthy diet warrants a high priority.

5. Conclusion

A healthy lifestyle for avoiding CVD and its predisposing risk factors and thus prolonging lifespan must include a healthy diet that has many features of a Mediterranean or Oriental cuisine. Recent trials and data suggest that certain nutrients formerly indicted as harmful need not be avoided including moderate consumption of eggs, chocolate, nuts, and caffeinated coffee, among others. Recommendations for prevention of CVD have much in common regarding CVD risk factors. Nutritional risk factors appear to apply for more than dyslipidemia. For *hypertension* recommendations include a lean body mass, restricted sodium intake, and a diet that emphasizes fruits and vegetables, and low-fat dairy products. For *Diabetes* recommendations include curbing weight gain, control of blood pressure and lipids by eating a balanced diet. For a reduced *HDL-C* one should also control weight and eat fatty fish (e.g., salmon, sardines, and tuna). For *Obesity* requirements include control of food portion size. For a healthy *LDL-C* one must eat less saturated fat, trans fatty acids, fewer calories and cram up on whole grains (at least 3 servings a day) eat 6 ounces of fattier fish and gorge on fruits, vegetables, and legumes (6 servings a day). Dietary lifestyle and behavior modification can play a major role in avoiding and correcting risk factors for CVD a major determinant of longevity.

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Research Article

Sociodemographic and Lifestyle Statistics of Oldest Old People (>80 Years) Living in Ikaria Island: The Ikaria Study

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Background. There are places around the world where people live longer and they are active past the age of 100 years, sharing common behavioral characteristics; these places (i.e., Sardinia in Italy, Okinawa in Japan, Loma Linda in California and Nicoya Peninsula in Costa Rica) have been named the "Blue Zones". Recently it was reported that people in Ikaria Island, Greece, have also one of the highest life expectancies in the world, and joined the "Blue Zones". The aim of this work work was to evaluate various demographic, lifestyle and psychological characteristics of very old (>80 years) people participated in Ikaria Study. *Methods*. During 2009, 1420 people (aged 30+) men and women from Ikaria Island, Greece, were voluntarily enrolled in the study. For this work, 89 males and 98 females over the age of 80 yrs were studied (13% of the sample). Socio-demographic, clinical, psychological and lifestyle characteristics were assessed using standard questionnaires and procedures. *Results*. A large proportion of the Ikaria Study's sample was over the age of 80; moreover, the percent of people over 90 were much higher than the European population average. The majority of the oldest old participants reported daily physical activities, healthy eating habits, avoidance of smoking, frequent socializing, mid-day naps and extremely low rates of depression. *Conclusion*. Modifiable risk factors, such as physical activity, diet, smoking cessation and mid-day naps, might depict the "secrets" of the long-livers; these findings suggest that the interaction of environmental, behavioral together with clinical characteristics may determine longevity. This concept must be further explored in order to understand how these factors relate and which are the most important in shaping prolonged life.

1. Introduction

Demographic analyses throughout the world suggest that the oldest old (i.e., people of age 80 years and older) are the fastest growing portion of the population [1]. Due to these changes, the United Nations' Global Population Pyramid is undertaking a shift, from the classical shape of a pyramid to a cube [2]. The resultant change in the age distribution of the world's population has been, partially attributed to the medical advancements of the recent years, a reduction in maternal and infant mortality, as well as in improved nutrition [3]. Beyond these global considerations it is of interest that there are places around the world where people live longer and, most importantly, they are physically active even after the age of 100 years. Specifically, in the past years anthropologists observed that people living in Sardinia (Italy), Okinawa (Japan), Loma Linda (California), and Nicoya Peninsula (Costa Rica) have very high life expectancy, with the percent of people over the age of 90 being at amazing rates as compared with the developed world average rate. These places have been defined as the "Blue Zones" and are a part of a large anthropologic and demographic project [4]. It has been observed that people living in these areas share common behavioral and lifestyle characteristics, despite the different race, nationality, and regional characteristics they have. Particularly, the investigators of the Blue Zones reported that "*some lifestyle characteristics, like family coherence, avoidance of smoking, plant-based diet, moderate and daily physical activity, social engagement, where people of all ages are socially active and integrated into the community, are common in all people enrolled in the surveys*" [4]. Clearly, longevity is a complex attribute, determined by

factors such as, exposure to disease, variability in sleeping patterns, smoking, physical activity, and dietary habits, in addition to the indirect emotional and cognitive influence on physiological pathways.

Recently it was reported that people in Ikaria Island (in Greece) have also one of the highest life expectancies in the world [4]. The Ikaria Island is located in the central-eastern part of Aegean Sea (Figure 1). The first name of Ikaria was *Dolichi,* but through Greek mythology it became connected to *Ikarus*, the first man who succeeded to fly and commemorates his fall [5]. Total population of the Island is about 8,000 people, and the vast majority of them follow a traditional way of living (i.e., traditional dietary habits that included plant foods, daily physical activities, daily naps, mountain living, low stress). Moreover, Ikaria has eight super-hot, radioactive, saline springs, which flow at various points on the Island's shores. The history of the mineral springs is linked with that of the country. *Herodotous* (484–425 BC) was the first observer of curative waters. Indeed, he preceded *Hippocrates* (460–370 BC) and described a good number of health springs [5]. Thus, the aim of this work was to evaluate various sociodemographic, lifestyle and psychological characteristics of oldest old (>80 years) people participated in the Ikaria Study.

2. Methods

2.1. Participants of the Study. The "Ikaria epidemiological study" is a cross-sectional survey that took place in the summer of 2009. In brief, the goals of the study were to evaluate various biological, clinical, lifestyle and behavioral characteristics of the adult population of Ikaria Island. A volunteering-based, multistage sampling method was used to enroll 631 men (65 ± 13 yrs) and 699 women (64 ± 13 yrs), from all areas of the island. Individuals residing in assisted-living centers were not included in the survey. The participation rate was 94%. Specifically for this work, 89 men and 98 women over the age of 80 (average 84 ± 4 yrs) and one individual per household were studied.

A group of health scientists (physicians and nurses) with experience in field investigation collected all the required information, using a structured, quantitative questionnaire and standard procedures.

2.2. Bioethics. The study was approved by the Medical Ethics Committee of our Institution and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All individuals were informed about the aims of the study, agreed to participate, and provided an informed consent.

2.3. Sociodemographic and Lifestyle Measurements. Mean annual income during the past three years was assessed into four categories: low (inability of earnings to cover vital needs), moderate (6,000–9,600€ per year), good (9,601–18,000€ per year), and very good (>18,000€ per year). The educational level of the participants was recorded in years of school. Moreover, number of cars owned by the participant, square meters of house or apartment, members of family living together with the individual and marital status were also recorded.

Regarding lifestyle characteristics, current smokers were defined as those who smoked at least one cigarette per day, and former smokers were defined as those who had stopped smoking at least during the past year. Occasional smokers (less than 7 cigarettes per week) were recorded and combined with current smokers due to their small sample size. The rest were defined as nonsmokers. Physical activity was evaluated using the shortened version of the self-reported International Physical Activity Questionnaire (IPAQ) [6]. Frequency (times per week), duration (minutes per time), and intensity of physical activity during sports, occupation and/or free-time activities were assessed. Participants who did not report any physical activity were defined as sedentary. In accordance with the standard IPAQ scoring procedures, physically active participants were classified into one of the following groups: upper tertile: "vigorous" physical activity (<2500 MET/min/week), middle tertile: "moderate" physical activity (500–2500 MET/min/week), or lower tertile: "low" physical activity (<500 MET/min/week). Dietary assessment was based on a semiquantitative, food frequency questionnaire (FFQ) that has been validated in a previous study [7]. Specifically, consumption (in times per week or month) of the main 15 food groups and beverages (i.e., meat and its products, poultry, fish and fisheries, milk and other dairy products, fruits, vegetables, greens and salads, legumes, refined and nonrefined cereals, as well as coffee, tea, and soft-drinks) was measured on weekly or monthly consumption basis. Alcohol consumption was recorded in 100 mL wineglasses (1 wineglass = 12% ethanol concentration). Furthermore, overall assessment of dietary habits was evaluated through a special diet score (MedDietScore, range 0–55), which assesses adherence to the Mediterranean dietary pattern [8]. Higher values on the score indicate greater adherence to this pattern and, consequently, healthier dietary habits.

2.4. Psychological Evaluation. Symptoms of depression during the past month were assessed using the self-report Geriatric Depression Scale (GDS) that has been validated for the Greek population [9, 10]. The following "yes or no" items were included in the GDS questionnaire: "*Are you basically satisfied with your life? Have you dropped many of your activities and interests? Do you feel that your life is empty? Do you often get bored? Are you in good spirits most of the time? Are you afraid that something bad is going to happen to you? Do you feel happy most of the time? Do you often feel helpless? Do you prefer to stay at home, rather than going out and doing new things? Do you feel you have more problems with memory than most? Do you think it is wonderful to be alive now? Do you feel pretty worthless the way you are now? Do you feel full of energy? Do you feel that your situation is hopeless? Do you think that most people are better off than you are?*" Responses were coded with 1s (for positive answers) and 0s (for negative answers) yielding a total possible score between 0 and 15. For clinical purposes, GDS scores have been used to indicate no depression (0–4), mild depression (5–10), or severe depression (11–15).

Figure 1: The Ikaria Island (Ikaria lies in the east Aegean, within the complex of the East Sporades, between Samos and Mykonos. Area: 255.32 km^2, location: 37° 35′41.42″ N-26° 09′30.88″ E, distance from Piraeus 140 nm, coastline length: 160 km, population: 8,312. Administratively Ikaria is divided into three municipalities, the Municipality of St. Kirykos which is the capital and the south port of the island, the Municipality of Evdilos where is the north port, and the municipality of Rahes which is in the central-west part of the island. Ikaria is exclusively comprised of crystalloid schist metamorphic rocks. Ikaria's wider area has been incorporated in NATURA 2000 network for the protection of natural environments, due to its biophysical variety).

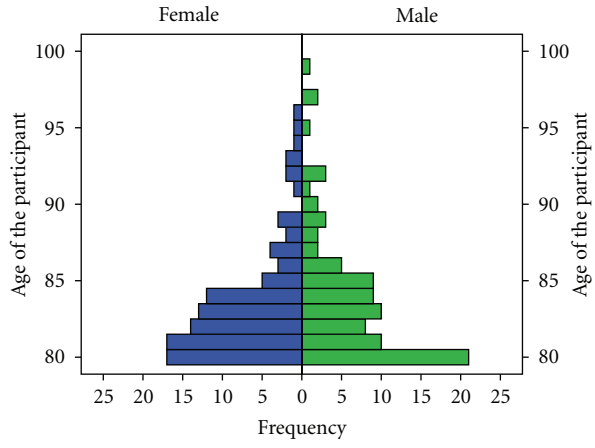

Figure 2: Age pyramid of oldest old (i.e., >80 years) people who participated in the Ikaria Study (n = 187).

2.5. Statistical Analysis. Prevalence was defined as the ratio of cases with the specific characteristic by the total sample size. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequencies. Gender-specific comparisons of continuous variables were performed using the t-test (for normally distributed) or the Mann-Whitney U-test (for skewed variables). Associations between categorical variables were tested using the Pearson's chi-square test. All tested hypotheses were two-sided. A P value <.05 was considered to be statistically significant. SPSS version 18 software was used for all calculations (SPSS Inc., Chicago, Il, USA).

3. Results and Discussion

3.1. Sociodemographic Statistics. In Figure 2 the age pyramid of the studied sample is presented. Taking into account that the life expectancy in Greece is 79.78 yrs and the percent of people over 80 years is less than 5% [11], the Ikaria study's sample consisted of 187 people (13% of the total study's sample) who were over the life expectancy (i.e., >80 years) of the Greek population. Globally, those 80 years old or over are now only slightly more than 1% of the total human population; moreover, the oldest old people constitute 3% of the population of Northern America, almost 3% of the population of Europe (where only one country, Sweden, has

more than 5% in this age group), less than 0.9% of the population in Asia, Latin America, and the Caribbean, and less than 0.4% of the population in Africa [12]. In addition, 1.6% of the men and 1.1% of women participants in the Ikaria study were over the age of 90. Finally, the parental age of death of the participants' was 76 years for their father and 80 years for their mother. These figures are of major importance since they suggest that the life expectancy of these people that were born in the late of the 19th century was similar with the current life expectancy of the Greek population (e.g., the life expectancy at the beginning of the 20th century in Greece was roughly 50–55 yrs). At this point it could be argued that the applied sampling procedure did not follow strict demographic methodologies, and therefore the age distribution of the study's sample is not representative of the total population of the island. However, the call for participating was for all people aged 30+ years that they were permanently living in the island, so people from all age groups had equal probability to participate; moreover, taking into account that the proportion of people over 65 years old in Ikaria island is 26% [11], as well as that older people tend not to participate in surveys like the present, the proportion of oldest old people enrolled in the study could be considered at least close to the actual population rate.

Furthermore, based on demographic data from the United Nations in 2000, the woman to men ratio among people over the age of 80 was roughly 2 to 1. In our survey this ratio was much lower (i.e., 100 women to 90 men or 1.1 to 1); a fact that may lead to the conclusion that men from Ikaria live longer than other men around the world. However, this can also be attributed to limitations in the sampling procedures followed in the study (e.g., volunteering call, women in islands like Ikaria tend not to participate in such surveys).

The gender-specific distribution of various sociodemographic characteristics is presented in Table 1. The majority of men were married, whereas the majority of women were widowed, a fact that could be explained by an old Greek tradition for men to marry much younger women (i.e., usually 5–15 years younger). It is of interest that almost the one half of the oldest old participants of the Ikaria study reported low income (i.e., below their annual average "needs"). It was also reported that a large proportion of people, especially women, were without any pension. Moreover, people were living together with other members of their families (i.e., children, relatives etc.), in relatively small, but own houses.

In addition, 3.3% of men and 4.1% of women of these oldest old participants were still working (mainly in their own works), whereas 3.4% of men and 27.6% of women were doing works in their houses (i.e., gardening, housekeeping).

The education status of these people was very low, that is, 7.4 ± 3.4 years of school, where 20.3% of them did not complete the primary school, and the illiteracy rate was 10.1%.

3.2. Lifestyle Characteristics. Regarding lifestyle characteristics, the frequency of physical activity varied with gender (Table 2). Men compared with women were more physically active; almost 9 out of 10 men versus 7 out of 10 women reported daily activities (mainly occupational). This proportion of people is much higher than the one reported by the investigators of the MEDIS Study where roughly 1500 elderly (65+ years) people from eight Greek Islands and Cyprus Republic were enrolled [13, 14]. In particular, in MEDIS Study approximately half of men and one out of four women participants were physically active. Although it is expected that walking and other activities decline with age, nearly 6 out of 10 participants of the Ikaria Study over the age of 90 were still physically active; a proportion which is also very much higher than the one reported by the MEDIS Study investigators (i.e., 20%) [14]. Very few men and women were current smokers. However, almost all men (i.e., 99%) and 32% of women reported ever smoking. These extremely high rates, especially in men, are in discordance with the reported low rates of cancer and cardiovascular disease in Ikaria Island [5].

Dietary characteristics of the MEDIS study sample display a favorable adherence to the Mediterranean diet (with slight differences from the traditional recommendations, especially regarding the increased potatoes consumption) (Table 2). The overall adherence to the Mediterranean diet was good (i.e., average score was 38/55 or 69% adherence to the traditional dietary pattern), with no differences between genders. Compared with the level of adherence reported by the elderly participants of the MEDIS Study (i.e., 33/55 ± 4), the level observed in the Ikaria Study elders was much higher, suggesting greater dedication to the traditional dietary habits. It seems that westernization and modern food traditions did not affect the lifelong habits of Ikaria people. Moreover, the energy intake was adequate for this specific age-group (Table 2). The observed differences between genders and intake of various foods were of limited nutritional information.

Similar findings as regards dietary habits and prolonged life have already been reported by other studies, too. For example, Knoops and colleagues in the multinational HALE study observed that lower mortality rates from all causes were associated with higher adherence to the Mediterranean diet, moderate alcohol consumption, moderate to high physical activity levels, and nonsmoking [15]. Other studies have also found that regular activity and healthy eating were associated with reduced overall mortality [16–18]. High fruit and vegetable consumption, often exceeding dietary recommendations, was a characteristic of the studied sample. This finding reflects a typical feature of the Mediterranean food culture, since green vegetables eaten not only as a salad dish, but also as the main meal, are usually cooked in olive oil. Moreover, wild plants that are frequently collected and utilized as source of food are widely accepted means of daily living on the Greek islands.

3.3. Psychological Evaluation. Depressive symptomatology as assessed by the GDS was much higher in women as compared with men (Table 3), a fact that confirms many previous reports in other populations. Nevertheless, the average scores were very low (i.e., <5), suggesting absence of depressive symptomatology in this age-group. Comparing these figures

Table 1: Socio- demographic characteristics of the $n = 187$ oldest old (>80 yrs) people who participated in the Ikaria Study.

	Men	Women	*P*
N	89	98	
% of people between 85–90 yrs	23.6	17.3	.28
% of people over >90 yrs	11.2	8.2	.49
Marital status, %			<.001
Never married	1.1	2.0	
Married	87.7	40.9	
Widowed	9.0	46.9	
Divorced	2.2	10.2	
Financial status, %			.39
Low	41.4	49.5	
Moderate	35.6	36.1	
Good	17.2	12.4	
Very good	5.7	2.1	
No. of own cars	0.8 ± 0.7	0.3 ± 0.5	.001
Members living within family (children, relatives)	3.1 ± 1.6	2.6 ± 1.9	.04
Sq meters of house or apartment	79 ± 24	76 ± 27	.53
% of people with own house or apartment	97	96	.81

Data are presented as mean ± SD or relative frequencies. *P*-values derived using the *t*-test or the chi-square test (for the categorical variables).

Table 2: Lifestyle and dietary characteristics of the $n = 187$ oldest old (>80 yrs) people participated in the Ikaria Study.

	Men	Women	*P*
N	89	98	
Physical activity status, %			<.001
Low	16.3	29.8	
Moderate	66.6	68.1	
High	22.1	2.1	
Current smoking, %	17.0	7.0	.04
Former smoking, %	82.0	25.0	<.001
MedDietScore (0–55)	38 ± 2.7	38 ± 3.0	.97
Energy intake (kcal/day)	1425 ± 532	1087 ± 460	<.001
Alcohol drinking (mL/day)	186 ± 181	117 ± 114	.04
Coffee drinking (mL/day)	339 ± 260	293 ± 228	.25
Tea drinking (mL/day)	109 ± 84	97 ± 90	.53
Consumption of food groups in times/week			
Olive oil	6.8 ± 2.7	5.3 ± 2.5	<.001
Cereals	1.7 ± 2.5	0.9 ± 1.7	.02
Fruits	5.5 ± 3.1	3.9 ± 2.7	.001
Vegetables and salads	4.8 ± 2.8	3.5 ± 2.8	.004
Legumes	2.0 ± 1.5	1.3 ± 1.1	.001
Fish	2.1 ± 1.6	1.5 ± 1.2	.001
Potatoes	3.3 ± 0.9	3.1 ± 0.8	.20
Sweets	1.2 ± 2.4	1.3 ± 2.1	.88
Red meat and products	1.8 ± 1.9	1.2 ± 1.4	.02

Data are presented as mean ± SD or relative frequencies. *P*-values derived using the *t*-test, the Mann-Whitney test (for food groups), or the chi-square test (for the categorical variables).

with the ones presented by the MEDIS Study that also investigated depressive symptomatology among elders living in Greek islands using the same instrument [19, 20], it could be suggested that elders in Ikaria have much lower rates as compared with their peers from the other Greek islands or Cyprus (25% of elderly men and 35% of elderly women participated in the MEDIS study were classified in the highest GDS category, that is, GDS score > 10, indicating intense depressive symptoms, while 54% of men and 70% of women scored above the depression cut-off, that is, GDS

Table 3: Behavioural characteristics (depression and mental health) of the $n = 187$ oldest old (>80 yrs) people who participated in the Ikaria Study.

	Men	Women	P
N	89	98	
Participating in social events, %			.09
Never	13.3	27.7	
Rare	44.6	44.7	
Sometimes during a month	27.7	16.0	
Weekly	8.4	8.5	
Daily	6.0	3.2	
Siesta on daily basis, %	84.0	67.0	.006
Geriatric Depression Scale (0–15)	3.1 ± 3.3	4.9 ± 3.5	.002

Data are presented as mean ± SD or relative frequencies. P-values derived using the t-test or the chi-square test (for the categorical variables).

score > 5, indicating mild-to-severe depressive symptoms). Moreover, almost all participants of the Ikaria Study reported napping regularly. Slightly more men than women napped; ultimately, all participants over 90 reported sleeping at noon. Recently, in a sample of 23, 681 residents from Greece with no history of chronic disease, the investigators suggested that a midday siesta may reduce a person's risk of death from heart disease, possibly by lowering stress levels [21]. In the present study we had the opportunity to test this hypothesis, too. It was observed that people taking regularly a midday nap had lower GDS scores as compared with those that did not follow this habit (3.4 ± 3.0 versus 5.8 ± 4.2, $P < .001$). Also, a large present of the studied sample was living together with another person (mostly husband/wife or relative), which may minimize feelings of loneliness. *Heather Arthur*, studying older adult populations in a secondary prevention setting, reported a consistent relationship between social support, social isolation, and chronic diseases, especially cardiovascular disease [22].

4. Conclusive Remarks

The present work investigated "healthy ageing secrets" of long-lived individuals from the Ikaria Island, Greece. It is of major interest nowadays to study characteristics of people living over the expected life span. It is of interest that in 1995, 13% of the European population was over the age of 65, while the projection for 2015 is expected to rise to 16% [2]. Impressively, the present study included roughly 13% of men and women who were over the age of 80. Although sampling limitations may exist and do not allow for direct comparisons, the inclusion of the Ikaria Island in the Blue Zones seems to be more rational than ever. Data analysis of the Ikaria Study also revealed that modifiable risk factors, such as physical activity, dietary habits, smoking cessation, and midday naps, might depict the "secrets" of the long livers. The discussed findings are in accordance with previous reports [23] and suggest that the interaction of environmental, behavioral, and clinical characteristics may determine how long an individual lives. This is a widely adopted concept and must be further explored in order to understand how these factors relate and which are most important in shaping longevity.

Conflict of Interests

No conflict of interests was declared.

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Review Article

Lessons from Studies in Middle-Aged and Older Adults Living in Mediterranean Islands: The Role of Dietary Habits and Nutrition Services

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Background. Islands in the Mediterranean basin share particular habits and traditions and greater life expectancy than other European regions. In this paper, particular interest has been given to the effect of the Mediterranean diet, as well as nutritional services on CVD risk, on Mediterranean islands. *Methods*. Published results from observational studies were retrieved from electronic databases (Pubmed and Scopus) and summarized. *Results*. Prevalence of CVD risk factors is increased. Adherence to the Mediterranean diet was moderate, even among the elderly participants. Furthermore, the presence of a dietician was associated with higher adherence to the Mediterranean dietary pattern and consequently lowers CVD risk. *Conclusion*. Adherence to the Mediterranean diet is reduced, while the prevalence of CVD risk factors is increasing at alarming rates. Public health nutrition policy has the opportunity to improve the health and quality of life of people living in isolated insular areas of the Mediterranean basin.

1. Introduction

According to the World Health Organization (WHO), the proportion of people over the age of 60 is growing faster than any other age group [1]. In many countries, the older population, over 80 years of age, is the fastest growing portion of the population [2]. Due to these changes, the global population pyramid (Figure 1) is undertaking a shift—from pyramid to cube—as the proportion of young adults' declines and the proportion of older people increases [3]. Prevention programs to reduce chronic disease risks have traditionally focused on younger adults. However, a variety of researchers have started to focus their attention on elders. This change in outlook has come about since people are now living longer, and consequently the older population is rapidly increasing and medical expenditure is rising with the onset of several major chronic diseases [4].

The role of healthy diet in the prevention and control of morbidity and premature mortality due to noncommunicable diseases, like CVD and cancer, has well been established by the vast population-based epidemiological research carried out during the last two-three decades [5, 6]. Older adults represent a group of population with special needs. Many of them lose their interest in food have chewing difficulties, difficulties in meal preparation, and more financial restraints [7]. A lot of them can show deficiencies in macromicronutrients, which may be the main cause for many cardiovascular diseases [8]. For those reasons, a Modified Pyramid for the older adults has been designed [8], that recommend to the elders emphasizing in whole grains, vegetables and fruits, also, in low-fat and nonfat forms of dairy products, including reduced lactose while they have to avoid high saturated and trans fatty acid types of oils and high saturated fat animal.

Improving diet and nutrition represent key public health targets. Mediterranean diet is a healthy dietary pattern which refers to specific food consumption patterns typical of some Mediterranean regions in the early 1960s, such as Crete, other parts of Greece, Spain, south France, and south Italy [9]. The Mediterranean dietary pattern emphasizes a consumption of fat primarily from foods high in monounsaturated fatty acids, and mainly olive oil, and encourages

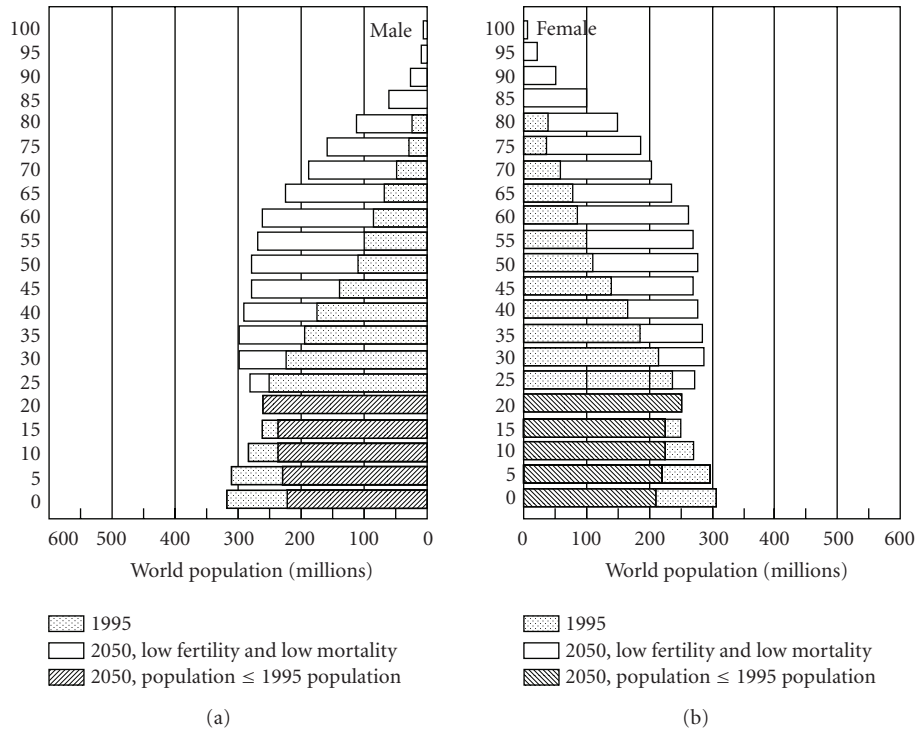

Figure 1: Global population pyramid (adopted from International Institute for Applied Systems Analysis)

the consumption of fruits, vegetables, tree nuts, legumes, whole grains, fish and poultry in low to moderate amounts, a relatively low consumption of red meat, as well as a moderate consumption of alcohol normally with meals, but the proportions of macronutrients may vary. This traditional dietary pattern, however, is not a homogeneous nutritional model. Instead, food and nutritional aspects vary between Mediterranean regions [10]. Adherence to the Mediterranean pattern has been associated with lower risk of cancer and CVD and consequently higher life expectancy [9, 11, 12]. Unfortunately, observational studies have reported strong evidence that this traditional dietary pattern, has changed to a more "westernized" type of diet in nowadays, at all ages [13–15]. This change was mainly attributed due to the rapid urbanization, economic development, and other related factors [13].

All the previously mentioned underline the importance of targeted public health services on prevention. Global planning on nutrition policies has provided by the 1992 world declaration on nutrition and plan of action on nutrition. Most countries around the world are still facing nutrition-related problems [16]. However, the role of nutritional services on population's health status has not been well evaluated and documented, yet. Public health nutrition, even in the elderly should emphasize on planning special programs that provide food assistance, nutrition screening and education, nutrition therapy, and care management [17]. Furthermore, according to international dietetic organisations, the promotion of a healthy aging requires rectifies in the lack of nutritional services and increment in the nutritional capacity such as adequate number of staff and infrastructure [17]. Furthermore, nutritional education could be, from the public health practitioners, the way to improve health and quality of life of middle-aged and older populations [18].

This paper focuses on studies that investigated food habits on CVD risk factors, in middle-aged, and elderly populations living at the Mediterranean islands. The Mediterranean islands were selected because in a manner of speaking are more isolated than other continental areas. Moreover people living in these islands, have various habits that are quite different from those of people living on the mainland. Furthermore, the Mediterranean diet, which has been the basic nutritional model in these insular areas for many years and has been associated with lower risks of cancer and CVD mortality [9] and higher life expectancy [6].

2. Methodology

Table 1 summarizes the studies that will be discussed in this paper. Original research studies published in English between 1975 and 2009 were selected through a computer-assisted literature search (i.e., Pubmed http://www.ihm.nlm.nih.gov/ and Scopus http://www.scopus.com/). Computer searches used combinations of keywords related to the cardiovascular disease, middle-aged and elderly populations, islands of the Mediterranean area (middle-aged population, elderly population, cardiovascular disease, coronary heart disease, cardiovascular risk factors, Mediterranean islands) and diet, nutrition or lifestyle habits. Additionally, the reference lists of the retrieved articles, which assisted in

finding relevant-to-the-present articles that did not allocate through the searching procedure. The following information was abstracted according to a fixed protocol: design of study (cross-sectional or prospective cohort), sample size, mean age and sex of participants, followup duration, assay methods, and degree of adjustment for potential confounders. Thus, 7 studies were selected and discussed out of which 2 were prospective and 5 were cross-sectional.

3. A Summary of the Main Findings

3.1. The Seven Countries Study. This was the first study that included Mediterranean islands and investigated among other factors, the relationship between eating habits and long-term incidence and mortality (25 year followup) from cancer, CHD, and stroke in different populations [19, 20]. Large variations, about a 10-fold difference, in age-adjusted 25-year death rates were reported between cohorts [19]. Death rates varied greatly from east Finland exhibiting 268 per 1000, compared to 25 per 1000 observed in Crete [21]. The investigators attributed the differences in mortality rates between the 16 cohorts to the nutritional habits of the participants and, in particular, to the intake of saturated fatty acids and flavonoids. The effects of saturated and unsaturated fats on CHD mortality surfaced subsequent to this study. Dairy fat (saturated fat) was consumed in Northern Europe, whereas, in Southern Europe (the lowest risk area) fat was predominated by olive oil (unsaturated fat). Furthermore, Menotti and colleagues [20] examined the association of simple foodgroups and their combinations with 25-year mortality from CHD. Similar findings were discovered. Overall, combined vegetable foods (excluding alcohol) were inversely correlated with CHD death rates, whereas combined animal foods were directly correlated. Greek islands and Japan experienced the fewest death rates caused by CHD. These findings suggest that healthy dietary patterns are an important determinant of CHD risk, and reveal the Mediterranean diet has a major effect in the protection against CVDs.

3.2. The Mediterranean Islands Study (MEDIS). The MEDIS (MEDiterranean ISlands) study is a health and nutrition survey which aimed to evaluate bioclinical, lifestyle, behavioral and dietary characteristics of elderly people living in Greek Mediterranean islands and Cyprus Republic. According to the MEDIS study, the level of adherence to the Mediterranean diet was 61% in both men and women. Level of adherence to the Mediterranean diet (i.e., at what percent individuals' adopted the Mediterranean diet pyramid) was 55% in Aegean islands and Cyprus Republic, 58% in Crete and 60% in the Ionian Islands ($p<0.001$). Especially, level of adherence to the Mediterranean diet was 61% in Samothrace, 54% in Lesvos, 64% in Lemnos, 64% Zakynthos, 59% in Corfu and Cephalonia, 58% in Crete, and 55% in Cyprus Republic. The level of adherence to the traditional Mediterranean diet was moderate and people living in rural areas seem to hold onto traditional dietary habits in a better way [22]. Moreover, the researchers noticed that a healthy diet, close to the Mediterranean model, high in carbohydrates and vegetable protein is associated with a lower likelihood of being obese and may help better elderly people to preserve a normal weight [23]. Furthermore, higher adherence to the Mediterranean diet seems to be associated with lower likelihood of being an elder obese and having diabetes [24]. Also, this study evaluated the association between the consumption of various patterns and the prevalence of CVD risk factors among elderly participants. Healthier patterns, like the Mediterranean, were correlated with lower likelihood of having an elder a CVD risk factor [25].

Furthermore, the MEDIS study, revealed the association between long-term fish intake (a basic component of the Mediterranean diet) and health status [26]. Particularly, fish intake was inversely associated with systolic blood pressure ($P = 0.026$), fasting glucose ($p<0.001$), total serum cholesterol ($P = 0.012$), and triglyceride levels ($P = 0.024$). Additionally, multinomial logistic regression revealed that a reduction of 100 g per week in fish intake was associated with a 19% higher likelihood of having one additional cardiovascular risk factor such as hypertension, hypercholesterolemia, diabetes, and obesity. The MEDIS study also evaluated whether alcohol consumption is associated to blood pressure [27]. The major finding was that when adjusting for confounding factors (age, sex, years of school, physical activity level, body mass index, medication use, dietary and smoking habits) a J-shaped association of alcohol intake with systolic ($P = 0.001$), diastolic ($P = 0.02$), mean ($P = 0.001$), and pulse pressure ($P = 0.07$) was observed. Therefore, long-term moderate alcohol consumption in elders may improve blood pressure levels and thus, CVD prognosis. Moreover, recently published findings from this epidemiological study revealed a positive association between coffee consumption and Body Mass Index (BMI). Specifically, coffee drinking was positively related to BMI levels, after adjustment for various confounding factors. However, when the analysis was performed separately for active and inactive participants, it has been found that only in those who were inactive, coffee drinking was significantly associated with BMI [28]. Furthermore, the MEDIS study, reported the prevalence of hypertension, hypercholesterolemia, diabetes and obesity, depressive symptomatology, smoking, and physical inactivity in the elderly; by the exception of smoking, all other rates were high, suggesting increased cardio-metabolic risk in these people [29].

Recent data related to nutritional services on the islands studied in MEDIS [30], revealed deficits on dieticians'/nutritionists' supply in the public and private sector on the studied islands. Furthermore, in some areas there was no dietician to offer nutritional services and there were no legislated job positions for dieticians (in hospital or health centres) or no one covered the job positions. It seems that the dietician's job positions (in public health services), in these insular areas, presented under availability [30]. Finally, further analysis after various adjustments made revealed that the longer the presence of a dietician on an island the greater the level of adherence to the "healthy" Mediterranean dietary pattern of the older population (i.e., higher MedDietScore) ($P = 0.03$) [31].

Table 1: A summary of studies that evaluated the role of diet on CVD risk in populations living on Mediterranean islands.

Study	Design	Sample	Main findings
The Seven Countries Study [17–19].	Cohort.	Of the total Study's sample, 1,200 middle-aged men (40–59 years old) were living in Crete and Corfu islands.	Saturated fat associated with increased CHD mortality rates. Mediterranean diet appeared a cardio-protective effect.
MEDIS Study [20–29].	Cross-sectional.	553 men and 637 women (>65 years) living in Cyprus republic, and in 7 Greek islands (Mitilini, Samothraki, Cephalonia, Crete, Corfu, Lemnos and Zakynthos).	The level of adherence to the traditional Mediterranean diet was moderate in the elderly inhabitants of these insular areas. Adherence to this dietary pattern was associated with lower likelihood of diabetes and obesity, as well as overall CVD risk.
'Ventimiglia di Sicilia' project [30–33].	Prospective.	363 males and 472 females (20–70 years) living in Sicilia island.	Lower CVD mortality in persons of ages 40 to 64 years old. Increase of total and complex carbohydrates intake and significant decrease of the consumption of total, saturated and polyunsaturated fats with increment of age.
'Spili' study [30].	Cross-sectional.	445 males and females (15–79 years) living in rural area of Crete island.	Appeared high prevalence in many CVD risk factors. However there were no signs of postmyocardial infarction in men aged 63 and under.
"Messara" study [31].	Cross-sectional.	502 (15–79 years) male farmers living in rural area of Crete island.	The level of adherence to the traditional Mediterranean diet was moderate in the inhabitants of these insular areas. The lack of adherence to this traditional dietary pattern have led to the fact that the rural inhabitants from Crete are likely to be at a higher risk for developing CVD in comparison with earlier generations.
"Balearic Islands" study [34, 35].	Cross-sectional.	498 males and 702 females (16–70 years) living in Balearic islands.	The elders seem to better hold the traditional Balearic Mediterranean dietary habits, than younger ones. However, Mediterranean diet appeared to being lost in the Balearic Islands, mainly in the younger generations.
"Sardinia and Malta Islands" study [36].	Cross-sectional.	30 mother-daughter pairs were interviewed in Sardinia and Malta islands.	The Sardo-Mediterranean dietary model is evolving under the impact of modernization - globalisation, but it is not disappearing. In Malta, the western modernity has led to a more sudden shift where the local nutrition identity is no longer Mediterranean.

3.3. The "Spili" Study and the "Messara" Study at the Greek Island of Crete. The "Spili Study" has taken place in the rural village of Spili at the island of Crete. The aim of this study was to survey the cardiovascular risk profile of a defined 'low-risk' population [32]. The studied population comprised of men and women aged 15–79 years in the village of Spili ($n = 445$). In this cross-sectional study the researchers found a high (44%) prevalence of smoking in men aged 45–64 years as well as a high alcohol intake (48% drank greater than or equal to 210 g of pure alcohol every week). Also, there was a high cholesterol level and a high prevalence of hypertension and diabetes. Furthermore, the investigators did not find any signs of postmyocardial infarction in Spili men aged 63 and under. According to the researchers this effect could be due to positive factors such as the closely knit social networks, the low unemployment rate, the hard water, and some of the dietary habits, for example the high consumption of olive oil, that may counter-balance the negative factors mentioned above. They also support that the low-risk factors in the past in the area of Crete could explain the low incidence of myocardial infarction today, and that this will change in the years to come.

The "Messara Study" has taken place in the rural valley of Messara on Crete Island [33]. The aim was to evaluate the changes in CVD risk factors among farmers in Crete and compare the findings with data from the 1960s (Crete island-Seven countries study). Study's population was comprised of 502 male farmers aged 15–79 years from the rural valley of Messara. According to the study, the male farmers were found to have a 30% higher BMI, a 16% higher total

cholesterol level, and also a not so favourable daily dietary intake compared with the Cretan farmers 45 years ago. The main finding of this study was the population's lack of adherence to the Mediterranean diet, which has led to the fact that currently farmers from Crete are likely to be at a higher risk for developing CVD compared to earlier generations.

3.4. The "Ventimiglia di Sicilia" Project. In Sicily, the greater Italic island, the "Ventimiglia di Sicilia" project began in 1989 aiming to evaluate the cardiovascular risk factors and dietary habits in a low-risk population [34]. According to this study, after the third decade of life more than 80% of this population was out of the normal weight range with a peak at 60 years and over of life for females, where the researchers found only 9.9% of subjects with a normal weight. Moreover, in this area the researchers found low mean total and LDL-cholesterol plasma concentrations and a rate of early cardiovascular mortality of 0.6 deaths/year/1000 inhabitants in subjects of ages 40–64 years in the period 1988–1997, a rate lower than that in the rest of Italy [35]. Furthermore, among the increment of age, researchers observed a significant increase of total and complex carbohydrates intake and a significant decrease of the consumption of total, saturated and polyunsaturated fats compared older with younger participants. They also observed a nonsignificant trend to decrease the daily cholesterol intake, whereas monounsaturated fat and fibre intake was not different. Calories intake strongly decreased in the people after the 6th decade of life compared with middle-aged groups [35].

3.5. The "Balearic Islands" Study. Another observational study that focused on Balearic Islands made an effort to evaluate dietary habits in the local Spanish insular population. Adherence to the Mediterranean diet among the population of the Balearic islands was found to be 43,1%, and was similar in all sociodemographic and lifestyle groups, with some differences according to age, sex and physical status. The main finding was that there was an increase in the percentage of adherence with age, which was greater in males than in females. According to the researchers, the Mediterranean diet appeared to have been lost in the Balearic Islands, mainly in the younger generations [36]. Furthermore, the researchers showed from multivariate analysis that younger age groups (26–45 years) were at higher risk of being low-antioxidant consumers when compared to the 46–65 year age group. The researchers mark that this finding appeared due to the loss of the traditional Balearic Mediterranean diet towards a more western dietary pattern [37].

3.6. The "Sardinia and Malta Islands" Study. This study was developed between 2001 and 2002 in Sardinia and Malta islands and examined dietary habits of thirty mother-daughter pairs in each insular area [38]. The design of the study allowed the researchers to show the contrast in the evolution of dietary habits over time not only between Sardinia and Malta, but also within each island. According to the study there was a trend revealing a shift away from cereals, pulses, and potatoes to the benefit of meat products, fats, and sugar. Furthermore, fruit and vegetables, olive oil, and fish, which are part of the main components of the Mediterranean diet, were among the top foods for which consumption frequency has increased in Sardinia. On the other hand, in Malta, besides an increase in olive oil and vegetable consumption, cheeses and desserts showed the highest increase. Along with modernity and improved living conditions, enhanced commercial availability and increased diversity of food preparation were also identified as factors contributing to changes in dietary habits. Finally, according to the investigators, the Sardo-Mediterranean dietary model is evolving under the impact of modernisation, but it is not disappearing. In Malta, the western modernity has led to a more sudden shift where the local nutrition identity is no longer Mediterranean but Anglo-Saxon.

4. Conclusive Results

The conclusion of this paper is that high adherence to a Mediterranean type of diet or a "healthy dietary" pattern was associated with reduced risk of CVD in middle-aged and even in the older people of the Mediterranean islands. Furthermore, it seems that the inhabitants of the Mediterranean islands have changed the traditional Mediterranean diet towards a more western dietary pattern. However, the elderly people living in these insular areas seem to better hold the traditional healthy dietary habits than the younger ones. The beneficial effects on blood pressure and lipids levels, body fat, and other surrogate markers of CVD risk, add biological plausibility to the epidemiologic evidence that supports a protective effect of the Mediterranean diet. Therefore, public health policy makers (physicians, dieticians, nurses, public health practitioners) should emphasize the promotion of healthy dietary patterns, like the Mediterranean diet in order to reduce the burden of CVD and improve population's quality of life. Enhancing nutritional services may contribute to holding a healthy dietary pattern and consequently improving the quality of life even in older population. Community-based, targeted nutritional policy could be one mean to this effort.

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Research Article

Fish Consumption Moderates Depressive Symptomatology in Elderly Men and Women from the IKARIA Study

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Background. The aim was to examine the association of depressive symptoms with fish eating habits, in elderly individuals. *Methods*. From June to October of 2009, we studied 330 men and 343 women, aged 65 to 100 years, permanent inhabitants of Ikaria Island. Among several characteristics, depression was assessed with the Geriatric Depression scale (GDS range 0–15), while dietary habits through a valid semiquantitative food frequency questionnaire. *Results*. Women had significantly higher values of the GDS compared to men (4.8 ± 3.5 versus 3.3 ± 3.1, $P = .001$). Participants in the upper tertile of depression scale ate less frequent fish and consumed higher quantities of alcohol, compared to those in the lowest tertile (all $P < .05$). Regarding fish consumption, 50% of the individuals reported consuming 1-2 times weekly, 32% 3 to 5 times weekly, 11% 2-3 times monthly, while the rest reported rare (4.5%) and everyday (1.2%) consumption. Logistic regression showed that increased fish consumption (>3 times/week versus never/rare) was inversely associated with the odds of having GDS greater the median value (i.e., 4) (odds ratio = 0.34, 95% CI: 0.19, 0.61), after controlling for several cofounders. *Conclusion*. Frequent fish consumption in elderly seems to moderate depression mood.

1. Introduction

Depression is a frequent mental disorder that in our age is characterized by a high level of morbidity which is expected to increase over the next 20 years. The World Health Organization has appreciated that major depression disorder will follow ischemic cardiomyopathy as the second more frequent reason of disability world widely and will become the first cause in the developing countries up to 2020 [1]. Especially elderly individuals show increased vulnerability for expressing depressive symptomatology, which is often related with other pathological conditions [2]. As the social and economic cost of depression continues to increase, it is essential to find alternative therapeutic solutions [3]. Among other therapeutic modalities, lifestyle habits have been related to a significant reduction of cardiovascular morbidity and mortality, especially among elderly individuals [4, 5]. Especially n-3 polyunsaturated fatty acids (PUFAs) provide a promising approach in the treatment of depression [5, 6]. Furthermore, it has been observed that populations with high consumption of fish appear to have a lower frequency of major depressive disorders [7, 8]. Clinical studies have found that people with depression n-3 PUFA administration had additive therapeutic effects [9, 10]. Moreover several randomized clinical studies have reported that treatment with n-3 PUFAs improves depression [11].

Recently, Ikaria island inhabitants have been recognised as having one of the higher longevity rates universally with high percentage of healthy aging. While in Europe only the 0,1% of population lives long (over 90 years old), in Ikaria island the percentage of longevity rises 10-fold in the 1% [12]. As Ikaria elderly population consist of an isolated rural group with established lifestyle conditions, the research of risk factors related to cardiovascular morbidity and behavioural habits that may influence this relationship seems stimulating.

The aim of this study was to investigate the impact of a diet rich in n-3 PUFAs, through high consumption of fish, on depression symptomatology in a long-lived population of elderly people.

2. Methods

2.1. Population of the Study. The "IKARIA" epidemiological study has been carried out in the Province of Ikaria Island. From June 2009 to October 2009, 673 elderly above the age of 65 years old, permanent inhabitants from the above area were, enrolled into the study. Of them, 343 were females and 330 males. All participants were interviewed by trained personnel (cardiologists, general practitioners, and nurses) who used a standard questionnaire.

The study was approved by the Medical Research Ethics Committee of our Institution and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All subjects were informed about the aims of the study, agreed to participate, and signed an informed consent.

2.2. Dietary Assessment. Dietary assessment was based on a validated food frequency questionnaire (FFQ) [15]. Regarding dietary habits, consumption of 15 food groups and beverages (i.e., meat and meat products, fish and fish products, poultry, milk and other dairy products, fruits, vegetables, greens, legumes, refined and nonrefined cereals, coffee, tea, and soft-drinks) was measured through a semi-quantitative food-frequency questionnaire, in terms of weekly consumption. Based on the FFQ, all participants were asked about their usual average frequency of fish consumption. Particularly for fish intake, we coded it as follows: 0 for none or very rare, 1 for rare (i.e., <150 g/week), 2 for moderate (i.e., 150–300 g/week), and 3 for frequent (i.e., >300 g/week). Alcohol consumption was recorded in 100 mL wineglasses (1 wineglass = 12% ethanol concentration). All participants were asked about their usual frequency of coffee consumption (i.e., never, <1 cup per week, 1-2 cups/day, 3–5 cups/day, and >5 cups/day) over the previous year. Because the number of participants in the last 2 categories was small, we decided to combine them in all analyses. Consumption of various alcoholic beverages (wine, beer, etc.) was measured in terms of wine glasses adjusted for ethanol intake (e.g., one 100 mL glass of wine was considered to be 12% ethanol). Furthermore, overall assessment of dietary habits was evaluated through a special diet score (MedDietScore, range 0–55), which assesses adherence to the Mediterranean dietary pattern [4]. Higher values on the score indicate greater adherence to this pattern and, consequently, healthier dietary habits.

2.3. Sociodemographic and Lifestyle Variables. As proxies of social status we recorded mean annual income during the past three years and the educational level of the participants in years of school. Current smokers were defined as those who smoked at least one cigarette per day; never smokers were those who have never tried a cigarette in their life, and former smokers were defined as those who had stopped smoking for at least one year. Occasional smokers (less than 7 cigarettes per week) were recorded and combined with current smokers due to their small sample size. For a more accurate evaluation of smoking habits we calculated the pack-years (cigarette packs per day $\times$ years of smoking), adjusted for a nicotine content of 0.8 mg/cigarette. Exposure to environmental tobacco smoke (at workplace, home, or restaurants, etc.) for more than 30 minutes per day assisted us to define people as passive smokers. Physical activity was evaluated using the shortened version of the self-reported International Physical Activity Questionnaire (IPAQ) for the elderly [16]. Frequency (times per week), duration (minutes per time) and intensity of physical activity during sports, occupation, and/or free-time activities were assessed. Participants who did not report any physical activity were defined as sedentary. In accordance with the standard IPAQ scoring procedures, physically active participants were classified into one of the following groups: upper tertile: "vigorous" physical activity (>2500 MET/min/week), middle tertile: "moderate" physical activity (500–2500 MET/min/week), or lower tertile: "low" physical activity (<500 MET/min/week). The latter category consist of the group of physically inactive participants.

The survey also included basic demographic characteristics, such as age, gender, financial status (average annual income during the past three years), educational level (years of school), and various clinical characteristics. Weight and height were measured to give body mass index (BMI) scores (kg/m^2). Obesity was defined as a BMI >29.9 kg/m^2.

2.4. Clinical and Biochemical Characteristics. Resting arterial blood pressure was measured three times in the right arm, at the end of the physical examination with subject in sitting position. People, who had blood pressure levels $\geq$140/90 mmHg or used antihypertensive medications, were classified as hypertensive. Fasting blood samples were collected from 08.00 to 10:00 hours. All the biochemical evaluation was carried out in the same laboratory that followed the criteria of the World Health Organization Reference Laboratories. Serum creatinine and urea were measured in serum using a colorimetric method (BioAssay Systems, Hayward, CA, USA). Renal function is evaluated by the glomerular filtration rate (GFR) which describes the flow rate of filtered fluid through the kidney. However, GFR was not available in this study, and therefore the creatinine clearance rate (C_{cr}) was calculated, which is the volume of blood plasma that is cleared of creatinine per unit time.

Table 1: Characteristics of the study's participants.

	Men $n = 330$	Women $N = 343$	P
Age (years)	75.36 ± 7	75.5 ± 6	.72
Current smokers (%)	23	11	.001
Education level (years of school)	8.6 ± 3.6	7.3 ± 3	.001
Body mass index (Kg/m^2)	28.0 ± 4.0	28.5 ± 5	.146
Physical inactivity (%)	12	20	.007
Hypertension (%)	69	75	.08
Hypercholesterolemia (%)	62	69	.08
Diabetes mellitus (n, %)	32	25	.05
Waist circumference (cm)	105 ± 11	102 ± 13	.007
Obesity (%)	29	30	.72
Metabolic syndrome (%)	52	63	.007
Cardiovascular disease	23	19	.17
GDS score (0–15)	3.26 ± 3	4.8 ± 3.5	.001
MedDietScore (0–55)	37.9 ± 2.8	38 ± 3.6	.77
Fish consumption (times per week)	2.7 ± 2.2	1.87 ± 1.5	.001
Alcohol consumption (%)	74	46	.001
Alcohol intake (wine glasses per week)	13 ± 11	6.4 ± 6	.001
Total Cholesterol levels (mg/dL)	192 ± 42	203 ± 39	.001
Glucose levels (mg/dL)	110.2 ± 33	106 ± 34	.11
Triglycerides (mg/dL)	147.6 ± 87	132.8 ± 56.2	.01
HDL-C (mg/dL)	44 ± 10	49.7 ± 11	.001
LDL-C (mg/dL)	120.7 ± 33.4	126.7 ± 32.7	.019
Creatinine Clearance (mL)	72.2 ± 22	64.7 ± 20.6	.001
Systolic Blood Pressure (mm Hg)	144.3 ± 19.4	142.8 ± 20.4	.34
Diastolic Blood Pressure (mm Hg)	80.3 ± 11.2	78.9 ± 11.6	.14

In particular, based on serum creatinine measurements, the C_{cr} was calculated using the Cockcroft-Gault formula [17] $C_{cr} = (((140 - \text{age}) \times \text{weight})/(72 \times \text{serum creatinine}))$ for men, while for female gender, the result of the above equation was multiplied by 0.85 [18].

Blood lipid examinations (serum total cholesterol, high density lipoprotein cholesterol, and triglycerides) were measured using chromatographic enzymatic method in an automatic analyzer RA-1000. Low-density lipoprotein cholesterol calculated using the following Friedewald formula: {total cholesterol} − {HDL cholesterol} − 1/5 (triglycerides). The intra- and interassay coefficients of variation of cholesterol levels did not exceed 3%, triglycerides 4%, and HDL-cholesterol 4%. Hypercholesterolemia was defined as total serum cholesterol levels higher than 200 mg/dL or the use of lipid lowering agents. Diabetes mellitus type 2 was determined by fasting plasma glucose tests and was analyzed in accordance with the American Diabetes Association diagnostic criteria (fasting blood glucose levels greater than 125 mg/dL (7 mmol/L) or use of special medication indicated the presence of diabetes) [17].

2.5. Assessment of Depressive Symptoms. Symptoms of depression during the past month were assessed using the validated Greek translation of the shortened, self-report, Geriatric Depression Scale (GDS) [13, 14]. The following "yes or no" items were included in the GDS questionnaire. "*Are you basically satisfied with your life? Have you dropped many of your activities and interests? Do you feel that your life is empty? Do you often get bored? Are you in good spirits most of the time? Are you afraid that something bad is going to happen to you? Do you feel happy most of the time? Do you often feel helpless? Do you prefer to stay at home, rather than going out and doing new things? Do you feel you have more problems with memory than most? Do you think it is wonderful to be alive now? Do you feel pretty worthless the way you are now? Do you feel full of energy? Do you feel that your situation is hopeless? Do you think that most people are better off than you are?*" Responses were coded with 1 s (for positive answers) and 0 s (for negative answers) yielding a total possible score between 0 and 15. For clinical purposes, GDS scores have been used to indicate no depression (0–4), mild depression (5–10), or severe depression (10–15) [14].

2.6. Statistical Analysis. Continuous variables are presented as mean values ± standard deviation or standard error, while categorical variables are presented as absolute and relative frequencies. Associations between categorical variables were tested by use of contingency tables and chi-squared test. Correlations were evaluated by calculation of the Pearson correlation coefficient for the normally distributed variables and by the Spearman correlation coefficient for skewed variables. Comparisons of continuous variables between fish-consuming groups were performed by the use of ANOVA, using post hoc analysis, after correcting the probability (P) value for multiple comparisons using the Bonferroni correction rule. Moreover, logistic regression analysis estimated the odds of having GDS > 4.0 (median value) by fish intake group (i.e., never/rare, <3 times per week, and >=3 times/week), and controlling for various potential confounders. Results are presented as odds ratios and 95% confidence intervals. Hosmer-Lemeshow test evaluated goodness-of-fit. All reported P values were based on two-sided tests. Statistical Package for Social Sciences software, version 14.0 (SPSS Inc., Chicago, IL, USA), was used for all the statistical calculations.

3. Results

3.1. Demographic and Clinical Characteristics. During the survey 96% of the participants reported that they consume at least one unit of fish per week (more than 80% of them reported that they consume small lean fishes, like

Table 2: Demographic, behavioral, and clinical characteristics, by fish consumption frequency.

	Fish consumption				
	Never/rare	2-3 times per month	2-3 times per week	>=3 times per week	*P*
Number of participants	26	76	326	222	
Age (years)	75.5 ± 7.5	75.5 ± 6	76 ± 6.5	75 ± 6.5	.408
Body mass index (kg/m^2)	27.3 ± 4.6	27.9 ± 4.5	28 ± 4.2	28.5 ± 4.5	.330
Current Smoking habits (%)	18	26	15	16	.460
Education status (years)	6.8 ± 3.6	7.5 ± 3.6	8 ± 3.6	8 ± 3.5	.701
IPAQ	1.96 ± 0.6	1.96 ± 0.6	2 ± 0.6	2.2 ± 0.6	.249
Male gender (%)	40	46	47	55	.056
Hypertension (%)	51	45	45	45	.347
Hypercholesterolemia (%)	46	47	48	46	.550
Diabetes (%)	22	25	29	29	.747
Creatinine Clearance (mL/min)	70.3 ± 18	70 ± 22	66 ± 20	71 ± 22	.088
History of Cardiovascular disease (%)	30	20	21	16	.526
Total Cholesterol (mg/dL)	195 ± 35	195 ± 40	198 ± 40	195 ± 40	.911
HDL-C (mg/dL)	45 ± 8	47 ± 13	46 ± 10	46 ± 10	.596
LDL-C (mg/dL)	126.5 ± 31.5	121 ± 33	123 ± 34	124 ± 33	.870
Triglycerides (mg/dL)	150 ± 70	134 ± 63	137 ± 70	147 ± 65	.731
GDS score (0–15)	5.6 ± 3.5	5 ± 3.3	4.1 ± 3.5	3.2 ± 2.8	.0001
MedDietScore (0–55)	32 ± 4.2	35.6 ± 3.6	37.6 ± 2.6	39.4 ± 2.2	.0001

Data are expressed as mean ± standard deviation.

sardines, goatfish, giltheads, tope etc.). Additionally, the majority of them (i.e., 80%) reported that they have the same dietary habits for at least a decade. Table 1 presents several demographic, clinical, and behavioural characteristics of the participants among sexes. In particular, males showed higher education level, higher levels of physical activity, higher prevalence of diabetes mellitus, lower prevalence of metabolic syndrome, and higher fish and alcohol consumption, compared to females.

Several demographic, clinical, behavioral, and biochemical characteristics of the participants among levels of fish consumption are presented in Table 2. In particular those who had high rates of fish consumption were more frequent males, showed closer adherence to Mediterranean type of diet, and had lower depression rates.

The distribution of clinical, biochemical, and anthropometric characteristics of the participants according to their depression status is presented in Table 3. Those with the high rates of depression, according to the GDS scale, showed lower levels of physical activity, were less frequent males, had higher levels of hypertension and diabetes mellitus, and consumed less often fish, compared to those in the lower levels of depression.

In order to evaluate the impact of fish consumption on depression status, we performed a multivariate logistic regression analysis, after adjustment for several cofounders, like age in years, sex, smoking status, physical activity status, hypertension status, hypercholesterolemia status, obesity, diabetes mellitus, MedDietScore, and history of cardiovascular disease. The analysis revealed that compared to never or rare fish consumers people who ate 3 or more times per week fish (i.e., >300 g) had 66% lower likelihood of having GDS levels above the median value (Table 4).

When the analysis was stratified by gender, the association between fish consumption and depressive symptomatology remained similar in both sexes.

4. Discussion

In this study is observed a relationship between fish consumption and depression in an elderly population, as frequent fish consumption seems to have beneficial effect on depression mood in elderly individuals. This association remained significant even after various adjustments were made, including obesity, diabetes, lipidaemia, smoking habits, hypertension, physical activity, sex, age, Mediterranean diet score, and cardiovascular disease. In particular, consumption of 300 g of fish on weekly basis was associated with about 66% lower likelihood of having depression levels above the median value of the GDS score for this population.

Fish consumption has been associated with lower prevalence of depression. A recent meta-analysis confirms that depression is related with lower levels of total n-3 PUFAs and both members of n-3 PUFAs, EPA, and DHA [19]. The findings of this survey extend the results from a number of studies that n-3 PUFAs are of a great significance in depression. In fact, a large cohort study, the Rotterdam study, that involved 3884 elderly adults, showed relation between the type of fatty acid composition and depressive disorders in elderly [20]. Moreover, Féart et al., in a cross-sectional study that consisted of 1390 elderly subjects, observed significantly lower plasma EPA in the elderly group with depression than in control subjects [21].

The mechanism of n-3 PUFAs effect on depression is still unknown. PUFAs are mainly separated in n-3 and n-6

Table 3: Demographic, behavioral, and clinical characteristics, by depression status.

	GDS score; depression status			
	<5; normal	5–10; moderate	11–15; severe	*P*
Number of participants	381	243	26	
Age (years)	74 ± 9	74 ± 7	77 ± 7	.256
Body mass index (kg/m^2)	28.3 ± 4	28.4 ± 4	28.1 ± 4	.967
Current Smoking habits (*n*, %)	18%	18%	15%	.948
Education status (years)	8 ± 4	8 ± 4	6 ± 3	.038
Physical inactivity (%)	89	86	75	.001
Male gender (%)	57%	42%	19%	.001
Hypertension (%)	68	74	71	.199
Hypercholesterolemia (%)	66	69	54	.253
Diabetes mellitus (%)	26	32	42	.062
Creatinine Clearance (mL/min)	72 ± 24	69 ± 24	64 ± 21	.201
Systolic Blood pressure (mm Hg)	143 ± 19	144 ± 22	140 ± 20	.467
Diastolic Blood Pressure (mm Hg)	79 ± 12	80 ± 12	75 ± 10	.177
History of Cardiovascular disease (%)	19	21	42	.031
Total Cholesterol (mg/dL)	196.6 ± 42	199 ± 40	199 ± 45	.557
HDL-C (mg/dL)	46 ± 11	47 ± 12	45 ± 13	.582
LDL-C (mg/dL)	123 ± 34	125 ± 33	115 ± 33	.341
Triglycerides (mg/dL)	139 ± 79	142 ± 67	148 ± 74	.781
Fish (times/week)	2.64 ± 2.1	2.28 ± 1.84	1.95 ± 1.5	.001
MedDietScore (0–55)	34.81 ± 3.5	34.9 ± 3.2	35 ± 3.3	.736

Data are expressed as mean ± standard deviation.

Table 4: Logistic regression analysis of fish consumption on depression status (GDS > 4).

	Odds ratio	95% confidence interval
Fish consumption		
Never/rare (ref. category)	1	
<3 times/week	0.64	0.37–1.1
>=3 times week	0.34	0.19–0.61
Age (years)	0.99	0.96–1.02
Sex (male)	0.44	0.3–0.65
Current smoking habits (yes/no)	1.031	0.61–1.72
History of CVD (yes/no)	1.07	0.67–1.7
Physical activity (yes/no)	0.39	0.22–0.7
Body mass index (per 1 kg/m^2)	0.99	0.95–1.46
Hypertension (yes/no)	1.24	0.8–1.93
Hyperlipidaemia (yes/no)	0.21	0.86–1.98

groups. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the most important bioactive components of n-3 PUFAs; they are not effectively synthesized in human body and must be obtained mainly from the diet not synthesized in the human organism and can be obtained only from the diet, mainly with the consumption of fatty fish [8]. DHA is the main n-3 PUFA in the brain [9] and is correlated with the stability of membrane of the nervous cell and the functions of serotonin and dopamine transmission, which might explain some of the clinical manifestations of depression [5–11]. In fact, one of the most promising hypothesis is that n-3 PUFAs have a positive impact in the altered membrane microstructure and also improve neurotransmission in patients with depression [22]. Moreover, Delion et al. support that altered brain fatty acid concentration, due to prolonged dietary n-3 PUFAs deficiency, modifies serotonergic and dopaminergic neurotransmission and causes an increase in 5-HT$_2$ and decrease in D$_2$ frontal cortex receptor density in rat brain [23]. This upregulation of 5-HT$_2$ receptors is thought to play a role in the pathophysiology of depression.

Furthermore, depression symptomatology has been linked with increased inflammation process, as cytokines synthesis and release activate the inflammatory response system and provoke neuroendocrine changes that are interpreted by the brain as being stressors, leading to a hyperactivity of the hypothalamic-pituitary-adrenal axis and contributing to the development of depression [24, 25]. Previous population studies have illustrated the association between and heightened expression of inflammation and coagulation markers implicated in the pathogenesis of atherosclerosis [26]. Additionally, fish consumption has been linked with decreased expression of circulating inflammatory markers, indicating a possible cardioprotective effect [27].

Depression symptomatology has been also linked with physical inactivity and unhealthy lifestyle habits, like smoking and diet [28]. In our study, those elderly participants with the higher rates of depression were more females, had lower

education status, higher prevalence of diabetes mellitus, inactivity status and known history of cardiovascular disease, and lower weekly fish consumption, while there was no difference in adherence to Mediterranean type of diet, and smoking habits, compared to those in the lower tertile of depression score. On the other hand, high fish consumption was related with the lower rates of depression, male gender, greater adherence to Mediterranean diet, and improved renal function. The role of physical inactivity and poor dietary intake has been illustrated in recent studies in elderly population, where they have been related with depressive symptomatology and mortality [29, 30]. In our study late-life depression showed an independent reverse association with fish intake, irrespective of total dietary habits, physical activity, and smoking status. This may be attributed to the observed lower prevalence of smoking and the higher prevalence of physical activity and adherence to healthy dietary patterns, in this elderly population, compared to urban population from previous studies [26, 27]. This finding strengthens the beneficial role of at least moderate fish consumption on mood disturbances in elderly population.

5. Limitations

Some limitations in our study may exist. For example, the design of the study is cross-sectional, and therefore we cannot make assumption for causal relationships. Fish intake was evaluated by self-reports through food frequency questionnaires, and therefore, information about the amount of fish consumed could be over- or underestimated. Another limitation is the small number of individuals who consumed >300 g/week of fish. There was a lack of exact quantification of type of fish consumed (i.e., small or fat, fresh or freeze), but in this country we mainly consume small lean fish, which is also inexpensive. There was lack of measurements of n-3 and n-6 fatty acids.

6. Conclusion

This study revealed that long-term intake of fish was associated with significant lower likelihood of having depression symptomatology above the median values, in elderly general population. As elderly individuals show increased vulnerability for expressing depressive symptomatology, which is often related with other pathological condition and the social and economic cost of depression continues to increase, it is essential to find alternative therapeutic solutions. Dietary intervention enriched with fish consumption may be proved useful in lowering the burden of morbidity related to depression in elderly population.

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Research Article

Mediterranean Diet Mediates the Adverse Effect of Depressive Symptomatology on Short-Term Outcome in Elderly Survivors from an Acute Coronary Event

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Aims. We evaluated the interaction effect between depressive symptoms and dietary habits on 30-day development of cardiovascular disease (CVD) (death or rehospitalization) in elderly, acute coronary syndrome (ACS) survivors. *Methods*. During 2006–2008, we recorded 277 nonfatal, consecutive ACS admissions (75 ± 6 years, 70% males, 70% had diagnosis of myocardial infarction) with complete 30-day follow-up. Assessment of recent depressive symptoms was based on the CES-D scale. Among sociodemographic, bioclinical, lifestyle characteristics, the MedDietScore that assesses the inherent characteristics of the Mediterranean diet was applied. *Results*. 22% of the ACS pts developed a CVD event during the first 30 days (14.8% rehospitalization and 9.4% death). Patients in the upper tertile of the CES-D scale (i.e., >18) had higher incidence of CVD events as compared with those in the lowest tertile (21% versus 8%, $P = .01$). Multiple logistic regression analysis revealed that 1-unit increase in CES-D was associated with 4% higher odds (95% CI 1.008–1.076, $P = .01$) of CVD events; however, when MedDietScore was entered in the model, CES-D lost its significance ($P = .20$). *Conclusion*. Short-term depressive symptoms are related to a worsen 30-day prognosis of ACS patients; however, this relationship was mediated by Mediterranean diet adherence.

1. Introduction

Depression has been recognized as an independent predictor for the development of coronary heart disease (CHD) among healthy and, especially, elderly individuals. Rugulies [1], in a recent meta-analysis, reported that depression increases the risk of myocardial infarction (MI) and coronary death, while that risk is not limited to patients with clinical depression. Similarly, in patients recovering from an acute coronary syndrome (ACS), even the presence of mildly elevated depressive symptoms is associated with a worse prognosis [2]. Additionally, a linear association seems to exist between the occurrence of depressive symptomatology at the time of an MI and the risk of subsequent cardiac morbidity and mortality [3, 4].

During the past 30 years, several observational studies and clinical trials have provided scientific evidence that the Mediterranean diet is associated with decreased all-cause mortality and improvements in cardiovascular risk factors levels [5, 6]. From the late 1960s, Keys and his colleagues from the Seven Countries study underlined the effect of the dietary habits observed in Mediterranean populations on cardiovascular disease risk [7]. De Lorgeril et al., from the Lyon Heart Study, that was a randomized secondary prevention clinical trial of CHD patients, revealed the protective effect of this traditional dietary pattern on cardiac

complications of the patients within the first 27 months of followup after an acute coronary event [8]. A more recent study in ACS patients illustrated that greater adherence to the Mediterranean diet seems to preserve left ventricular systolic function and is associated with better long-term prognosis of [9].

Although it is generally accepted that depression is independently associated with a worse cardiac prognosis, controversy persists whether this association is a reflection of cardiac disease severity, as some studies have reported significant univariate associations, but have failed to find a significant relationship after adjustment for markers of cardiac disease severity [10, 11]. Furthermore, other protective lifestyle factors may play a mediator role in the effect of depressive symptomatology on clinical outcome. Among those lifestyle factors, healthy dietary habits due to their anti-inflammatory and antioxidative properties have revealed cardioprotective effect [8, 9]. Finally, it is well known that the elderly represent the fastest growing segment of the population. In addition, although it is widely adopted that the risk for CVD is an exponential function of age, because of various functional changes observed, the rate of these changes varies greatly among elderly individuals. The relationship between depression and cardiovascular health may also be attributed to lifelong behavioral and lifestyle.

The purpose of this work was to evaluate the role of short-term depressive symptoms in relation to dietary habits on the short-term (i.e., 30-day) clinical outcome of elderly patients who survived ACS.

2. Methods

2.1. Study's Sample. From May 2006 to March 2009, 1000 of the 1257 consecutive patients who were hospitalised in our Institution for an ACS (first or recurrent) were enrolled in the study (participation rate 80%); nonparticipants were patients who denied to provide the requested information or died during the first 48 hours of hospitalization. For the present analysis, 277 elderly (i.e., >65 years) patients (75 ± 6 years, 70% males, 70% had a diagnosis of myocardial infarction) that gave the requested information regarding psychological evaluation were studied.

2.2. Bioethics. The study was approved by the Medical Research Ethics Committee of our Institution and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All patients were informed about the aims and procedures of the Study and gave their consent to participate.

2.3. Diagnosis of ACS. At entry, a 12-lead electrocardiogram was performed and clinical symptoms were evaluated in all patients by a cardiologist. Moreover, blood tests were performed to detect evidence of myocardial cell death (i.e., Troponin I and the MB fraction of total creatinine phosphokinase (CPK)). As mentioned above, the study's sample included only cases with diagnoses of ACS (i.e., acute myocardial infarction (MI) or unstable angina (UA)). Acute MI was defined according to the latest guidelines [12] based on ECG findings and the aforementioned blood tests. Additionally, unstable angina was defined by the occurrence of one or more angina episodes, at rest, within the preceding 48-hours, corresponding to class III of the Braunwald classification [13].

2.4. Clinical and Biochemical Measurements. A detailed medical history was recorded, including (i) previous hospitalization for CVD (coronary heart disease or stroke), (ii) history and management of hypertension (defined as systolic or/and diastolic blood pressure >140/90 mmHg or use of antihypertensive medication), (iii) hypercholesterolemia (defined as fasting serum total cholesterol >200 mg/dL or use of lipid lowering agents), and (iv) diabetes mellitus (defined as fasting glucose >125 mg/dL or use of special treatment), as well as patients' medical family history of CVD. Furthermore the clinical course of all patients during hospitalization was recorded, including coronary angiography results and number of coronary vessels involved, thrombolysis, type of revascularization (primary angioplasty, coronary artery bypass grafting), and time delay from the onset of symptoms to the arrival at the hospital.

In addition to the clinical information, white blood cell counts, uric acid, and brain natriuretic peptide (BNP) were measured at the time of hospital admission. BNP was determined by an enzyme-linked immunosorbent assay (Biomedica, Vienna, Austria), with inter- and intra-assay coefficients of variation being <5% and with normal range of 0–100 pg/mL. Total cholesterol, high-density lipoprotein cholesterol, blood glucose, and triglycerides were also measured in all participants at the time of hospital admission using colorimetric enzymic method in a Technicon automatic analyzer RA-1000 (Dade-Behring Marburg GmbH, Marburg, Germany). Low-density lipoprotein cholesterol was calculated using the Friedewald formula: total cholesterol—HDL cholesterol—1/5 X (triglycerides). An internal quality control was in place for assessing the validity of cholesterol and triglycerides methods. The intra- and interassay coefficients of variation of cholesterol and triglycerides levels did not exceed 4%. Renal function was evaluated using the baseline creatinine clearance rate (CrCl) that was calculated using the Cockcroft-Gault formula: CrCl = [[(140 − age) × weight]/(72 × serum creatinine)] for men, while for women, the result of the above equation was multiplied by 0.85. A Roche/Hitachi Modular analyzer was used (Roche Diagnostics, Manheim, Germany) for all biochemical measurements. The biochemical evaluation was carried out in the same laboratory that followed the criteria of the World Health Organization Lipid Reference Laboratories. Samples were immediately processed for the determination of all biochemical parameters.

2.5. Demographic, Anthropometric, and Lifestyle Characteristics. Sociodemographic characteristics included age and sex. Height and weight were measured to the nearest 0.5 cm and 100 g, respectively. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Obesity was defined as BMI greater than or equal to 30 kg/m^2. To evaluate physical activity status of the patients

during the past year, a modified version of a self-reported questionnaire provided by the American College of Sports Medicine was used [14]. Based on this questionnaire, the frequency (times per week), duration (in minutes per time) and intensity of sports or occupation-related physical activity were evaluated. Patients who did not report any physical activities were defined as sedentary. Current smokers were defined as those who smoked at least one cigarette per day or have stopped cigarette smoking during the past 12 months. Former smokers were defined as those who had stopped smoking more than one year previously. The rest of the patients were defined as never smokers or rare smokers.

2.6. Dietary Assessment and Evaluation of Adherence to the Mediterranean Diet. The dietary evaluation took place after the third day of hospitalization. Usual dietary intake over the year preceding hospitalization was assessed in all patients by a validated, semiquantitative food frequency questionnaire [15]. The questionnaire included 75 items (i.e., foods and beverages commonly consumed in Greece, as well as dietary habits). Portion sizes were included in the food frequency questionnaire to assist patients to report accurate information and to quantify dietary habits. Alcohol consumption was measured in wineglasses (100 mL) and quantified by ethanol intake (grams per drink). One wineglass was equal to 12 g ethanol concentration. The MedDietScore was calculated for each participant in order to evaluate the level of adherence to the Mediterranean diet. In particular, intake of 10 food groups was evaluated (i.e., nonrefined cereals and products, fruits and nuts, vegetables, olive oil, dairy, fish, poultry, potatoes, pulses, red meat or meat products, and eggs), as well as alcohol drinking. The diet score was calculated as follows: for the consumption of items presumed to be close to the Mediterranean pattern (i.e., nonrefined cereals and products, fruits and nuts, vegetables, olive oil, nonfat or low fat dairy, fish, potatoes and pulses), score 0 was assigned when a patient reported no consumption, 1 when reported consumption of 1 to 4 times/month, 2 for 5 to 8 times/month, 3 for 9 to 12 times/month, 4 for 13 to 18 times/month, and 5 for more than 18 times per month. For the consumption of foods presumed to be away from this diet (like meat or meat products, eggs, poultry, and dairy), reverse scores were assigned (i.e., 0 when a patient reported almost daily consumption to 5 for rare or no consumption). Regarding alcohol intake, score 5 was assigned for consumption of less than 3 wineglasses per day, 0 for none or consumption of more than 7 wineglasses per day, and scores of 4, 3, 2, and 1 for the consumption of 3, 4-5, 6, and 7 wineglasses, respectively. This nonmonotonic scoring follows the rationale of the Mediterranean dietary pattern that suggests an intake of 15–30 g of ethanol per day. Higher values of this diet score indicate greater adherence to the Mediterranean diet (theoretical range 0–55), and have already been associated with CVD risk and markers [16].

2.7. Assessment of Depressive Symptoms. Clinical symptomatology of depression during the past month was determined by a specialised, confidential and weighted questionnaire, which was based on a self-reported depression scale (range 0–60) developed by Radloff, known as the Center of Epidemiological Studies-Depression scale (CES-D) and validated for the Greek population, by Fountoulakis et al. [17]. The aforementioned scale has been found a reliable and valid measure of depressive symptomatology [18]. Since no accurate cut-offs have been proposed for the Greek population the tertiles of the CES-D score were used to classify the patients. Thus, the participants were divided in three equal size categories (tertiles): (a) 1st tertile (CES-D < 6), that represents rare symptoms, (b) 2nd tertile (18 < CES-D < 26), that represents moderate symptoms, and (c) 3rd tertile (CES-D > 26), that represents more severe symptoms. The questions used for the evaluation of the investigated emotions are listed below: "How often during the past month you…" were bothering by things that usually do not bother you; had poor appetite; feeling that you could not shake off the blues even with help from your family; feeling of being just as good as other people; trouble keeping your mind on what you were doing; feeling that everything you did was an effort; feeling hopeful about your future; thought that your life had been a failure; feeling fearful; having restless sleep; being happy; talking less than usual; feeling lonely; considering people being unfriendly to you; enjoying your life; having crying spells; feeling sad; feeling that people disliked you; could not get "going".

2.8. Follow-Up of the Patients. The lost to follow up rate was 10% for the 30-days, re-evaluations. Patients lost to follow-up were considered as missing cases. The follow up of the patients included evaluation for vital status (death from CVD or other cause) and rehospitalization due to acute coronary syndrome (i.e., acute MI or unstable angina as defined above) or other cardiac symptoms (i.e., arrhythmias, stable angina).

2.9. Statistical Analysis. Power analysis (GPower 3.1.1, Germany) showed that the number of enrolled participants ($n = 277$) is adequate to evaluate a 0.05 change in the odds ratio of developing a 30-day adverse CVD event per 1-unit change in the CES-D score used, achieving statistical power equal to 98% at 5% significance level. Normally distributed continuous variables are presented as mean values ± standard deviation, skewed variables are presented as median and quartiles, while categorical variables are presented as relative (%) frequencies. Associations between normally distributed continuous variables and group of patients were evaluated through the Student's t-test, after controlling for equality of variances (homoscedacity) using the Levene test. The associations between skewed variables (i.e., Troponin I, BNP, glucose, triglycerides) and group of patients were evaluated through the Mann-Whitney test. Associations between categorical variables were evaluated by the use of the chi-squared test, without the correction of continuity. Correlations between continuous variables were evaluated by the use of Pearson's correlation coefficient for the normally distributed and by the Spearman's rho coefficient for the ordinal or skewed variables. Normality was evaluated through the Shapiro-Wilktest.

The association between the MedDietScore and CES-D score with the occurrence of a CVD event was evaluated using multiple logistic regression analyses, after controlling for socio-demographic, clinical, and biochemical characteristics of the patients. Appropriate tests for goodness-of-fit (i.e., Hosmer-Lemeshow and deviance residuals) were applied in all models. Results are presented as odds ratios and their corresponding 95% confidence intervals. All statistical calculations will be performed on the SPSS version 18 software (SPSS Inc, Chicago, Il, USA).

3. Results

The follow-up evaluation of the patients showed that 22% had a CVD event during the first 30-days following hospitalization (14.8% were re-hospitalised and 9.4% died). Regarding in-hospital mortality, 6% of the ACS patients died while hospitalized. There were no gender differences between those who developed an adverse cardiac event compared to the rest. In Table 1 clinical, biochemical and lifestyle characteristics of the patients who developed or not an adverse CVD during the 30-day followup are presented.

Moreover, patients in the upper tertile of the CES-D scale (i.e., >18) had higher incidence of 30-day CVD events as compared with those in the lowest tertile (21% versus 8%, $P = .01$); in addition they were more likely to be females (48% versus 10%, $P = .001$), they had higher prevalence of hypertension (88% versus 63%, $P = .05$) and lower current smoking habits (27% versus 20%, $P = .05$), while no difference was observed according to diabetes mellitus history, physical activity status, dietary habits, BMI, left ventricular ejection fraction, and previous history of CVD.

In Table 2, clinical, biochemical, and lifestyle characteristics of the patients who developed or not an adverse CVD during the 30-day followup by the tertile of the MedDietScore (<16, 16–19, >19) are presented. Among all tertiles of MedDietScore, those patients who presented an adverse cardiac event had lower prevalence of smoking habits, higher plasma BNP levels, higher prevalence of myocardial infarction than unstable angina, lower creatinine clearance levels, more advance age, higher CES-D score, higher diabetes mellitus prevalence, and lower left ventricular ejection fraction.

From the abovementioned results, it seems that a positive relationship between depression status and short-term prognosis of ACS patients exists. However, residual confounding may be present, since several clinical, lifestyle, and behavioural characteristics were associated with adherence to the depression status, as well as the prognosis of the patients. In addition, a significant interaction was observed between CES-D score and MedDietScore ($P = .03$); thus, the following analysis was stratified by dietary habits class (i.e., away, close, and very close to the Mediterranean diet). Multiadjusted analyses revealed that one-unit increase (1/60) in the Depression scale was associated with 4% higher odds of developing 30-day adverse cardiac event after discharge, controlling physical activity status, age, gender, BMI, smoking habits, history of hypertension, hypercholesterolemia, diabetes, first event of CVD, and left ventricular ejection fraction. When in the model the MedDietScore was entered, CES-D variable lost its significance, suggesting a strong mediating effect (Table 3).

4. Discussion

This study demonstrated that the relationship between depression and CVD development following an ACS in elderly patients is mediated by dietary habits. In particular, previous depression status was initially associated with the development of CVD events; however, when dietary habits were taken into account this relationship was lost. The findings were independent of several potential cofounders such as sex, age, ejection fraction of the left ventricle, body mass index, smoking habits, history of CVD, diabetes mellitus, hypercholesterolemia, hypertension, number of vessel disease, revascularization, and physical activity status.

Previous studies have shown that even minor elevations in depressive symptoms (subthreshold depression, defined to include mood, somatic, and interpersonal symptoms of depression, but not necessarily a diagnosable depressive disorder) significantly increase the risk of incidence of CHD among previously healthy participants or worsen the cardiac prognosis in patients with established CHD [19–21]. The scientific evidence is strongest for patients who have been hospitalized for an ACS, that is, MI or unstable angina [22]. Similarly, according to the GREECS study, which included 2172 patients with ACS, the short-term depressive symptoms are related to more severe disease and a worsen 30-day prognosis of patients hospitalized for ACS [23].

Despite the consistency of the findings in these reviews, it remains unclear why a number of individual studies with robust methodologies have failed to show an adverse effect of depression on mortality especially among the elderly [24, 25]. Furthermore, psychological interventions have failed to show a reduction in mortality, which would be expected if depression caused an increase in mortality [26]. The conflicting results of previous studies may be attributable to the way depression is measured, because different measures may be sensitive to different dimensions of depression, or duration of followup [19]. Furthermore, variation in timing of the assessments and variable attempts to control for the confounding effect of severity of heart disease may be also responsible for the heterogeneity [27]. However, what are less established are the mechanisms responsible for the effect of depression on cardiovascular risk [28]. It has been reported that depression might increase CHD incidence and mortality by promoting factors associated with coronary atherosclerosis. The effect of depressive symptoms may be direct, inducing cardiac ischemia, increasing the risk for cardiac arrhythmias and sudden death, increasing the levels of blood lipids, platelets, and inflammatory factors, as well as indirect by promoting unhealthy behaviours, like cigarette smoking, decreased adherence to medications, physical inactivity, poor, unhealthy diet, and other lifestyle characteristics [29]. Especially for the prognosis of CHD patients, van Melle et al. [30] reported that among myocardial infarction survivors, the rate of depression and the severity of depressive symptoms were significantly related

Table 1: Clinical, biochemical, and lifestyle characteristics of ACS elderly patients ($n = 277$), according to the development of 30-day CVD events.

	30-day CVD event	Free of 30-day CVD event	*P*-value
N, (%)	61 (22)	216 (78)	
Age (yrs)	76 ± 6	74 ± 6	.036
Gender (%male)	69	70	.82
Body mass index (kg/m^2)	26.7 ± 5.2	28 ± 5	.197
Hospital admission variables			
MI (%)	85	67	.001
First CVD event (%)	52%	56%	.672
Ejection Fraction (%)	33	44	.001
Revascularization (%)	33%	27%	.347
Creatinine Clearance (mL)	49.22 ± 23	60.2 ± 22	.003
Troponin I (ng·mL)	10.22 ± 22	8.3 ± 2.1	.56
Glucose levels (mg/dL)	189.5 ± 118.7	161 ± 79.4	.034
BNP (pg/mL)	943 ± 148	475 ± 66	.005
Medical history variables			
CES- scale (0–60)	34.20 ± 18.44	22.68 ± 12.5	.007
Physical active (%)	51%	59%	.376
Smoking current (%)	31%	30%	.865
Hypercholesterolaemia (%)	71%	53%	.013
Hypertension (%)	71%	72%	.901
Diabetes mellitus (%)	45%	41%	.551
MedDietScore	17.5 ± 4	18.1 ± 4	.05
Systolic blood pressure	125 ± 29	134 ± 24	.064

Table 2: Clinical, biochemical, and lifestyle characteristics of ACS elderly patients ($n = 277$), according to the development of 30-day CVD events and their dietary habits.

	MedDietScore (0–55)								
	Lowest tertile (<16)			Middle tertile (16–19)			Upper tertile (>19)		
	30-day CVD event			30-day CVD event			30 day event		
	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
N, %	31	78		8	75		22	63	
Age (yrs)	77 ± 6	76 ± 6	.731	76 ± 6	75 ± 6	.707	75 ± 6	75 ± 5	.767
Gender (%male)	57	59	.918	35	38.5	.632	34.5	46	.003
Hospital admission variables									
MI (%)	95	74	.001	50	61	.745	60	74	.458
First CVD event (%)	43	50	.664	50	39	.745	40	56	.425
Ejection Fraction (%)	34.5	35	.822	57.53.6	56.6 ± 23	.859	65 ± 25	63 ± 19	.817
Revascularization (%)	42	23	.229	25	18	.807	50	52	.925
Creatinine Clearance (mL)	41.37 ± 24.94	58.36 ± 24.74	.044	50	76	.444	80	81	.924
Troponin I (ng·mL)	6.71 ± 9.77	10.57 ± 21.6	.415	9.5 ± 13	6.67 ± 17	.751	12.4 ± 27	9.9 ± 28	.819
BNP (pg/mL)	1089 ± 1043	642 ± 714	.241	1460 ± 1045	629 ± 870	.453	744 ± 440	375 ± 490	.09
Medical history variables									
CES- scale (0–60)	21 ± 24	19 ± 9	.947	34 ± 19	25 ± 15	.924	41 ± 20	31 ± 13	.467
BMI (kg/m^2)	25.4 ± 3.2	27.5 ± 3.7	.057	33 ± 7.5	26.9 ± 4	.295	27 ± 4	28.5 ± 9	.487
Physical active (%)	36	47	.482	67	61	.875	70	70	.984
Smoking current (%)	14	32	.164	67	33	.424	30	30	.984
Hypercholesterolaemia (%)	57	53	.808	67	55	.755	80	65	.384
Hypertension (%)	64	62	.238	100	69	.001	70	70	.984
Diabetes mellitus (%)	43	53	.541	67	48	.645	60	33	.176

Table 3: Results from additive logistic regression models that evaluated the association of CES-D score on the likelihood of developing 30-day CVD events among $n = 277$ elderly ACS survivors.

	OR (95% CI)	OR (95% CI)	OR (95% CI)
CES-D (per 1/60 units)	1.011 (0.98–1.046)	1.042 (1.008–1.076)	1.025 (0.987–1.065)
First coronary event (Y/N)	0.909 (0.43–1.889)	0.505 (0.210–1.217)	0.63 (0.234–1.693)
Age (per 1 year)	1.015 (0.985–1.045)	1.018 (0.946–1.096)	0.987 (0.908–1.072)
Male versus female gender	1.118 (0.495–2.524)	0.568 (0.224–1.438)	0.731 (0.258–2.067)
Revascularization (Y/N)	—	2.453 (0.97–6.305)	2.477 (0.866–7.086)
Physical activity (Y/N)	—	1.138 (0.476–2.723)	0.868 (0.325–2.318)
Current smoking habits (Y/N)	—	0.668 (0.23–1.941)	0.688 (0.215–2.202)
Body Mass Index (per 1 kg/m^2)	—	0.946 (0.853–1.048)	0.961 (0.866–1.067)
Hypercholesterolemia (Y/N)	—	1.869 (0.762–4.586)	1.246 (0.46–3.37)
Hypertension (Y/N)	—	0.983 (0.378–2.551)	0.876 (0.294–2.604)
Diabetes mellitus (Y/N)	—	1.009 (0.432–2.354)	1.139 (0.428–3.033)
Ejection fraction (per 1%)	—	0.935 (0.897–0.975)	0.951 (0.903–1.001)
MedDietScore (per 1/55 units)	—	—	0.989 (0.866–1.130)

to the severity of left ventricular dysfunction, giving a potential pathophysiological mechanism for the prognosis of patients with depressive symptoms. Moreover, Carney et al. [31] suggested that the dys-regulation of the autonomic nervous system may partially mediate the increased risk for mortality in depressed myocardial infarction patients with frequent ventricular contractions. Furthermore, depression is associated with poor secondary prevention among patients who have had an acute ischemic event. In the large Heart and Soul study [32] of patients with depression and CHD, an association between depressive symptoms and adverse cardiovascular events was largely explained by behavioral factors, especially physical inactivity. It is also illustrated in other studies that unhealthy behaviors accompany depressive symptomatology and can mainly explain the occurrence of adverse cardiovascular events [33].

In the present work, when MedDietScore, that evaluates the level of adherence to a healthy dietary pattern, was included in the analysis, the depression variable lost its significant for the occurrence of adverse cardiac events during the short-term followup. Additionally, the 30-day outcome was inversely related to MedDietScore. The possible cardioprotective effects of Mediterranean diet became widely known for the first time in the 1970s from the Seven Countries Study [7]. Since then, there are numerous indications that adoption of a Mediterranean diet is associated with decreased all-cause mortality and improvements in cardiovascular risk factors levels [34, 35] due to the diet's antithrombotic, anti-inflammatory, and antioxidant effects [36, 37]. Among those studies, the HALE project revealed the protective effect of Mediterranean type of diet on cardiovascular and total mortality in elderly individuals [38]. It is known that inflammation and oxidative stress accompany the clinical presentation and course of an ACS, affecting infarct size. Infarct size determines postinfarction survival and prognosis, as it is the most important factor of ventricular remodelling process and left ventricular systolic function. Olive oil, which is the main source of fat in the Mediterranean type of diet, is rich in oleuropein, which has been shown to reduce the infarct size, in experimental models [39, 40], and also to protect reperfused myocardium from oxidative damage "in vivo," resulting in more preserved left ventricular systolic function [41]. In a recent study [9], it was revealed that ACS patients that had closer adherence to the Mediterranean diet preserved left ventricular systolic function, while they showed less in-hospital deaths and cardiovascular events during the two-years of followup. These findings were unaltered after controlling for several patient characteristics, like lifestyle behaviours, medical history as well as biological factors at hospital admission. Those cardioprotective mechanisms of Mediterranean diet might modify beneficially the adverse effects of depression symptomatology on cardiovascular system.

5. Limitations

The present work has several strengths mentioned above, but also some limitations. For example, only survivors of ACS were studied. Thus, there is no information from patients who died during the first two days of hospitalization (approximately 2% of the total hospitalizations). For the dietary evaluation, a holistic dietary approach using food patterns (i.e., Mediterranean diet) and not single food approach was used. The rationale of this approach was that overall diet assessment represents a broader picture of food and nutrient consumption of real life. Furthermore, dietary patterns capture the extremes of dietary habits, preempts nutritional confounding, possible effect modification among nutritional variables through the same procedure, and they do not tend to be biased.

6. Conclusion

This study highlights the effectiveness of adhering to the Mediterranean diet on cardiac events following ACS, especially for elderly individuals with depression. Regardless of

any drug treatment prescribed, clinicians should routinely advise patients with acute coronary syndromes to increase their frequency of consumption of Mediterranean foods, as it seems that this type of diet can attenuate the adverse effects of depression on cardiovascular health. Further studies are needed to investigate the most effective way to treat patients suffering from depressive symptoms and convince them to follow more healthy dietary patterns and a healthy lifestyle in general.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Research Article

Androidal Fat Dominates in Predicting Cardiometabolic Risk in Postmenopausal Women

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We hypothesized that soy isoflavones would attenuate the anticipated increase in androidal fat mass in postmenopausal women during the 36-month treatment, and thereby favorably modify the circulating cardiometabolic risk factors: triacylglycerol, LDL-C, HDL-C, glucose, insulin, uric acid, C-reactive protein, fibrinogen, and homocysteine. We collected data on 224 healthy postmenopausal women at risk for osteoporosis (45.8–65 y, median BMI 24.5) who consumed placebo or soy isoflavones (80 or 120 mg/d) for 36 months and used longitudinal analysis to examine the contribution of isoflavone treatment, androidal fat mass, other biologic factors, and dietary quality to cardiometabolic outcomes. Except for homocysteine, each cardiometabolic outcome model was significant (overall P-values from $\leq .0001$ to .0028). Androidal fat mass was typically the strongest covariate in each model. Isoflavone treatment did not influence any of the outcomes. Thus, androidal fat mass, but not isoflavonetreatment, is likely to alter the cardiometabolic profile in healthy postmenopausal women.

1. Introduction

Menopause is associated with an increase in intra-abdominal fat [1], which is considered a major risk factor of atherosclerotic cardiovascular disease (CVD) [2]. However, whether an increased risk of CVD in postmenopausal women is due to altered body composition, changes in reproductive hormones, or some other physiological process associated with menopause has not been clearly established. It is also uncertain as to what extent androidal fat mass may influence CVD risk factors in healthy nonobese women. The risk of chronic disease is perceived to be considerably higher in obese compared to normal weight adults. However, Gautier et al. [3] recently reported that the effect of waist circumference, reflecting androidal fat mass, in increasing the risk for diabetes was more profound among men and women with a normal body mass index (BMI) of less than 25 kg/m^2 than among those with above normal BMI. Thus, it appears that efforts to reduce abdominal fat accumulation would be beneficial regardless of BMI category.

This study was ancillary to the Soy Isoflavones for Reducing Bone Loss (SIRBL) study, a randomized, double-blind, placebo-controlled multicenter (Iowa State University (ISU) and University of California at Davis (UCD)) clinical trial funded by the National Institutes of Health (NIH) [4]. We examined contributors (androidal fat mass, duration of menopause, isoflavone treatment, family history of CVD, and dietary quality) to cardiometabolic risk in primarily normal and overweight healthy postmenopausal women. Cardiometabolic outcomes included circulating low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triacylglycerol, glucose, homeostatic model assessment (HOMA) of insulin resistance, uric acid, C-reactive protein (CRP), fibrinogen, and homocysteine

(Hcy). We hypothesized that consumption of soy isoflavones in tablet form would attenuate the anticipated increase in central fat (androidal) mass during the 36 months of treatment, which in turn may favorably modify circulating concentrations of cardiometabolic risk factors. We also hypothesized that androidal fat mass, other biologic factors, and dietary quality would influence these cardiometabolic risk factors, but that androidal fat mass would predominate.

2. Materials and Methods

2.1. Overall Study Design. The parent study examined the effect of two doses (80 versus 120 mg/day) of soy protein-derived isoflavone versus placebo tablets for 36 months on bone loss in healthy postmenopausal women (45 to 65 years of age) who were at risk for osteoporosis. The parent study included power analysis on the primary outcome (lumbar spine bone mineral density) in the methodology and has been previously reported [4]. This ancillary project focused on the relationship between body composition and cardiometabolic risk factors. Many of these cardiometabolic risk factors were tested throughout the study (LDL-C, HDL-C, TAG, glucose, and uric acid) whereas some were only tested through the 12 month time point (HOMA, CRP, fibrinogen, and Hcy). The respective Institutional Review Boards (IRB) at ISU (ID no. 02-199) and at UCD (ID no. 200210884-2) approved our study protocol, consent form, and all participant-related materials. Approvals for the dual-energy X-ray absorptiometry (DXA) procedures were obtained from each institution's IRB and State Department of Public Health in Iowa and California. At prebaseline, each participant received a detailed explanation of the study verbally and in writing before signing an informed consent form.

2.2. Participant Recruitment, Screening, and Selection. We recruited (2003 to 2005) women throughout the state of Iowa and in the greater Sacramento and Bay Area regions in northern California primarily through direct mailing lists, stories in local newspapers, and local/regional radio advertisements. Responders ($N = 5,255$) were initially screened via telephone to identify healthy women (without diseases or conditions, not taking hormones or medications) ≤65 years who had undergone natural menopause (cessation of menses 1 to 10 years), were not experiencing excessive vasomotor symptoms, nonsmokers (not currently smoking and who had not smoked in the past 6 months), and had a BMI between 18.5 through 29.9 (except for 9 women from UCD who did not meet the range of inclusion criterion: 8 women had BMI values that ranged from 30 to 32.7 and one woman had a BMI of 17.8, but were enrolled because they were deemed healthy).

The parent SIRBL project established the inclusion/exclusion criteria. We excluded vegans and high alcohol consumers (>7 servings/week), as well as those who were diagnosed with chronic disease, had a first-degree relative with breast cancer, or who chronically used medication (current: cholesterol-lowering and/or antihypertensive; past 3 months: antibiotics; past 6 months: estrogen/progestogen creams, calcitonin; past 12 months: oral hormones/estrogen or selective estrogen receptor modulators; ever: bisphosphonates).

Women who met the initial screening criteria ($N = 677$) were invited to the clinic for further eligibility screening, including BMD assessment using DXA. The SIRBL project focused on disease prevention rather than treatment; thus, women with BMD lumbar spine (L1-L4) and/or proximal femur T-scores that were low (>1.5 SD below young adult mean) or high (>1.0 SD above mean) or with evidence of previous or existing spinal fractures were excluded. Once each woman qualified based on BMD, fasting blood was drawn for a clinical chemistry profile. We excluded women with evidence of diabetes mellitus (fasted glucose ≥6.93 mmol/L (126 mg/dl)), abnormal renal, liver (elevated enzymes), and/or thyroid function, or elevated lipids (LDL-cholesterol >4.10 mmol/L (160 mg/dl); triacylglycerol >2.25 mmol/L (200 mg/dl)). Based upon our entry criteria, we randomized 255 women to treatment in the parent trial. We excluded 13 women at UCD from this analysis because they did not meet the entry criteria (11 had thickened endometrium, 1 had breast cancer, 1 could not provide a baseline blood sample). We excluded an additional 19 women who did not have body composition data at either 12, 24, or 36 months because they dropped out of the study, resulting in a sample size of 224 women based upon androidal fat as our primary covariate of interest in this ancillary project.

2.3. Randomization to Treatment and Tablet Formulation. To meet the objectives of the parent project, participants at each location (ISU, UCD) were stratified according to baseline proximal femur BMD (high, medium, and low) [4] based upon NHANES III database population values [5] and randomly assigned to one of three treatment groups: placebo control, 80 mg isoflavones, or 120 mg isoflavones. Tablets were provided by The Archer Daniels Midland Co. (Decatur, IL); tablet composition has been described previously [4]. An independent researcher (Patricia Murphy) at ISU confirmed that the actual isoflavone doses (mean ± SD, mg/d) were similar to those formulated and tested by Archer Daniels Midland, respectively: control = 0 compared with 0.3 ± 0.4; 80 mg = 89.5 ± 5.0 compared with 84.3 ± 4.5; 120 mg = 124.0 ± 7.7 compared with 122.5 ± 3.4. Participants in each group were instructed to take three compressed tablets/d. To preserve the double-blind nature of the study, bottles did not indicate treatment assignment.

2.4. Body Size and Composition Measures and Blood Sample Measures. For this study, we used anthropometric and body composition measurements that included weight, height, whole body lean and fat mass, and androidal fat mass, as well as fasting concentrations of lipids/lipoproteins, glucose, and uric acid. These outcomes were assessed at baseline, 12, 24, and 36 months. In addition, circulating insulin, HOMA (calculated as fasting glucose (mg/dL) × fasting insulin (μU/mL)/405), CRP, fibrinogen, Hcy, and red blood

cell (RBC) folate concentrations were assessed at baseline and 12 months.

Trained researchers obtained anthropometric measurements according to standard protocols. Standing height was taken twice (average value recorded) with a wall-mounted stadiometer (Model S100; Ayrton Corp., Prior Lake, MN) and weight was measured at ISU using a balance beam scale (ABCO Health-o-Meter; Bridgeview, IL) and at UCD using an electronic scale (Circuits and Systems Inc; E. Rockaway, NY). Women wore hospital scrubs or shorts and a t-shirt, and removed their shoes, belts, watches, and jewelry for the duration of assessment. To ensure standardized data collection, body composition measurements were obtained by certified cross-trained DXA operators using matching DXA instruments (Delphi W Hologic Inc; Bedford, MA) at each site that were calibrated daily. To further ensure quality control, one operator assessed overall composition from the whole body DXA scans for both sites. Regional adiposity analysis was performed by one analyzer (LR) who sectioned each whole body DXA scan into waist, hip, and thigh regions based on bone landmarks [6] using special software (Discovery Version 12.3:7). The waist region included the first lumbar through the fourth lumbar vertebrae. The hip region began below the fourth lumbar vertebrae and extended to the tip of the greater trochanter of the femur. Androidal fat mass (kg) for each participant was the sum of waist and hip fat mass.

Phlebotomists collected fasted (9 h) blood samples between 7:00 and 8:00 am. We separated serum (allowed to clot for 30 min prior to centrifugation) and plasma from whole blood and centrifuged samples for 15 minutes (4°C) at $1000 \times g$, storing aliquots at −80°C until analyses. Certified clinical laboratories (LabCorp; Kansas City, KS for ISU and UCD Medical Center; Sacramento, CA for UCD) performed a chemistry panel (including serum glucose, lipid profile, and uric acid) on each participant at each time point. We measured the remaining analytes (serum insulin, serum CRP, plasma fibrinogen, plasma Hcy, and RBC folate) for each participant in batch from ISU and UCD samples at baseline and 12 months in duplicate at ISU. We used sufficient in-house sera/plasma as quality-control samples (frozen at −80°C) to run with each kit to calculate interassay coefficient of variation (CV); we used duplicate samples to calculate intraassay CV. The low-to-normal and normal-to-high controls for each kit were well within the acceptable ranges. Serum insulin (μU/mL) concentration was determined with a radioimmunoassay kit (Linco Research, St Charles, MO, USA) using a Cobra II series autogamma counting system (Packard Instrument Company; Meriden, CT, USA). The intra- and interassay CV for insulin were 3.0% and 4.0%, respectively. Serum CRP (mg/L) concentration was determined with a high-sensitivity sandwich enzyme-linked immunosorbent assay kit (ALPCO Diagnostics; Salem, NH) and plasma (heparinized) fibrinogen (mg/mL) concentration was determined with a sandwich enzyme-linked immunosorbent assay kit (AssayPro; St. Charles, MO) using a microtiter plate reader (ELx808; Bio-Tek Instruments, Inc., Winooski, VT). The intra-assay CVs for CRP and fibrinogen were 3.7% and 2.7%, respectively; the interassay CVs for CRP and fibrinogen were 6.0% and 2.3%, respectively. Total Hcy (μmol/L) concentration was determined using a high-performance liquid chromatography (HPLC) method adapted from Araki and Sako [7] and Ubbink et al. [8]. The total Hcy in plasma consists of free Hcy (i.e., reduced plus oxidized Hcy in the nonprotein fraction of plasma) and protein-bound Hcy [9]. N-Acetylcysteine (1 mM) was added as an internal standard to the plasma samples prior to derivatization. The fluorescence intensities were measured with excitation at 385 nm and emission at 515 nm, using a JASCO FP-1520 fluorescence detector. Further assay details have been previously published [9]. The intra- and interassay CV for plasma Hcy were 3.8% and 6.3%, respectively. Intracellular (RBC) folate (ng/mL) was measured using a radioactive immunoassay kit (MP Biomedicals; Irvine, CA). Because four hematocrit values were missing, RBC folate could not be calculated for these four samples. In addition, three baseline samples were incorrectly processed; thus, RBC folate values have been presented for 217 women. The intra- and interassay CV for RBC folate were 3.2% and 11.8%, respectively.

2.5. Interviewer-Administered Questionnaires. During the enrollment phase, trained interviewers administered three questionnaires to participants: a health and medical history [10–12], a reproductive history [13], and a nutrition history [10, 11]. We also gathered data on prescription and over-the-counter medications at each time point, as well as previous and/or current use of herbal therapies or dietary supplements (which they were asked to discontinue prior to baseline testing). We assessed dietary intake at each time point using a semiquantitative food frequency questionnaire from Block Dietary Data Systems (Berkeley, CA). A Healthy Eating Index (HEI) score, with higher scores representing greater adherence to federal dietary guidelines, was calculated for each participant based on this questionnaire and included in the statistical analyses as a covariate.

2.6. Statistical Analysis. We performed statistical analyses using version 2.10.1 of the R software, including version 3.1.96 of the nlme package software and considered results statistically significant (two sided) at $P \leq .05$. Our 3-year longitudinal analyses of LDL-C, HDL-C, triacylglycerol, and glucose included women with complete data at all time points, baseline through 36 months. Our 1-year longitudinal analyses of fibrinogen, insulin, HOMA, Hcy, and CRP included women with complete data at baseline and 12 months. We reported descriptive statistics for 224 women using median and interquartile range. We constructed longitudinal models to identify significant contributors to each cardiometabolic risk factor (LDL-C, HDL-C, triacylglycerol, uric acid, glucose, insulin, HOMA, CRP, fibrinogen, and Hcy). Each final longitudinal model included these obligatory variables: treatment (control versus combined treatment with 80 mg or 120 mg of isoflavones or, in other words, no treatment versus treatment), time point (baseline versus 12, 24, or 36 months), treatment by time point interaction,

and site (ISU versus UCD), as well as potential covariates that included androidal fat mass (kg) adjusted for height, time since last menstrual period (TLMP) (yr) (calculated for each woman: baseline test date—date of her last menstrual period), family history of CVD coded as a categorical variable (none versus positive or none versus unknown), and HEI score. Additionally, the insulin model included glucose as a covariate, and the Hcy model included RBC folate as a covariate. Independent variables in modeling the outcomes of interest included those variables that were biologically plausible. Preliminary models also included dietary fat intake (determined using the Block Food Frequency Questionnaire) and physical activity (determined using the Paffenbarger physical activity recall [14]), but those variables did not emerge as remotely significant contributors to any of the cardiometabolic risk factors and thus were not included in the final models.

Separate height adjustments of fat and fat-free mass have been suggested for children by Wells and Cole [15]; accordingly, we found a significant impact of height on androidal fat mass among the participants in our study based on a log-log regression analysis (parameter estimate 0.8286, $P = .0058$). This suggested the use of height-adjusted androidal fat mass (androidal fat mass (g)/height (cm)) (exponent of 0.8286 for height changed to 1 for ease of interpretation). In other words, we adjusted androidal fat mass for height because taller women typically had greater waist circumferences due to their larger frame size and thus appeared to be at higher risk for CVD compared with shorter women, whereas this is not necessarily the case. We performed log transformation of variables with skewed distributions: triacylglycerol, HOMA, CRP, Hcy, and RBC folate.

Restricted maximum likelihood (REML) estimation was used to obtain estimates of variances and correlations between repeated measures. Model selection was guided by a stepwise backwards selection based on model diagnostics, such as Akaike's information criterion and Bayes information criterion. An overall model fit was obtained based on a likelihood ratio test of the (maximum likelihood fitted) model at hand and the more parsimonious model of only obligatory covariates. Significance indicates a failure to accept the null hypothesis of covariates contributing to the model in a random fashion. More specifically, significance indicates that the full model with all of the variables included explains a greater proportion of the variability in the outcome than the parsimonious model.

3. Results

3.1. Cardiometabolic Risk Factors Assessed during a 36-Month Period. Baseline values for body composition and cardiometabolic outcomes are summarized in Table 1. Body composition measurements, including androidal fat mass, did not change significantly during the course of the study. The isoflavone treatment did not have an effect on any of the body composition outcomes. Treatment compliance was verified using urinary isoflavone concentrations. Compliance was excellent [4]. The results of longitudinal analysis showed that each cardiometabolic outcome model was highly significant, with overall P-values $\leq .0001$ for all but the LDL-C model ($P = .002$). Significant covariates for each analyte are shown in Table 2. Androidal fat mass and site (ISU versus UCD) were consistent predictors of all analytes (36 month data) assessed, including lipids/lipoproteins, glucose, and uric acid. In general, androidal fat mass was typically the strongest covariate (positive) in each model (except the model with HDL-C as the outcome, where it was significantly and negatively associated). Time point also emerged as a significant covariate in the HDL-C and glucose models, indicating that the median concentrations of these analytes increased with time; however, the analyte concentrations at subsequent time points were not significantly different compared to baseline. The median glucose concentration was 85 mg/dL at baseline and 88 mg/dL at 36 months. The median HDL-C concentration was 64 mg/dL at baseline and 65 mg/dL at 36 months. Family history of CVD had a significant association with glucose: women who were unaware of their family history ("do not know," $n = 9$), taking into account key factors in the model, had on average a 6.8 mg/dL higher glucose concentration compared with women who indicated that they had a positive family history. Isoflavone treatment, TLMP, or HEI did not influence any of the 36 month analytes.

3.2. Cardiometabolic Risk Factors Assessed during a 12-Month Period. Similar to the 36 month outcomes, each 12 month outcome model was highly significant (overall model P-values $\leq .0001$), except for Hcy ($P = .23$, data not shown). Androidal fat mass was positively associated with each outcome (Table 3) and was the strongest covariate (positive) in each model. The parameter estimate for site was negative, indicating that the women from UCD had lower values than the women at ISU. In addition, TLMP ($P = .0020$) and TLMP-by-site interaction ($P = .0021$) contributed significantly, and a positive family history of CVD contributed marginally ($P = .070$) to fibrinogen concentration. As TLMP increased, the difference in fibrinogen concentration between the sites decreased. Glucose and time were significant covariates in the insulin model. As expected, a higher glucose concentration was associated with a higher insulin concentration. The unadjusted mean insulin concentration was significantly greater (2.86 μU/mL; $P \leq .0001$) at 12 months compared with baseline. Isoflavone treatment or HEI did not emerge as significant predictors in any of the 12 month models.

4. Discussion

The main objective of this study was to identify significant contributors to cardiometabolic risk in primarily normal and overweight (BMI < 30) healthy postmenopausal women. In agreement with our hypothesis, androidal fat mass was the strongest and most consistent predictor of all cardiometabolic outcomes (except for Hcy) examined in this study. Our participants, as a group, showed no

Table 1: Characteristics of participants at baseline[a].

		Quartile				
	N[b]	Median	First	Third	Min	Max
Age (y)	224	54.33	52.06	56.79	45.84	65.04
TLMP[c] (y)	224	2.76	1.76	5.02	0.79	10.02
Family History of CVD (n)	224					
No	88					
Yes	127					
Don't know	9					
Weight (kg)	224	66.35	59.98	73.70	43.70	93.10
BMI (kg/m^2)	224	24.46	22.33	27.03	17.84	31.66
Whole body fat mass[d] (%)	224	34.4	30.45	38.36	18.12	45.95
Androidal fat mass[d] (kg)	224	5.31	4.19	7.12	1.12	10.7
Serum total cholesterol (mg/dL)	224	206.5	189	226.2	142	297
Serum LDL-C (mg/dL)	224	127.5	109	141.2	62	192
Serum HDL-C (mg/dL)	224	64	55.75	76	30	111
Serum triacylglycerol (mg/dL)	224	76	59	98.25	18	290
Serum C-reactive protein (mg/L)	218	1.022	0.453	2.089	0.013	29.860
Plasma fibrinogen (mg/mL)	218	3.353	2.657	4.311	0.914	6.854
Plasma total homocysteine (μmol/L)	218	7.296	6.318	7.677	4.224	17.64
RBC folate (ng/mL)	217	10.45	8.896	12.82	4.595	40.13
Blood glucose (mg/dL)	224	85	80.75	90	57	117
Serum insulin (μU/mL)	218	11.39	8.437	13.96	0.104	36.14
HOMA[e]	218	2.362	1.694	3.006	0.022	9.458
Serum uric acid (mg/dL)	224	4.15	3.5	4.8	1.3	9
Systolic BP (mm/Hg)	224	119.5	112.8	132	93	170
Diastolic BP (mm/Hg)	224	74.5	68	80	49	111
Resting heart rate (bpm)	224	68	63	74	44	99
Healthy Eating Index score	224	67	56	76	37	95

[a]Baseline data are reported for the entire sample. Treatment groups did not differ significantly in any of the outcomes at baseline.
[b]The number of observations available at baseline
[c]Time since last menstrual period
[d]Assessed using dual-energy X-ray absorptiometery (DXA)
[e]Homeostatic model of insulin resistance

significant changes in body composition measurements, including androidal fat mass, during the course of the study. It should be noted, however, that the women were instructed to maintain their weight throughout the course of the study by following their usual diet and physical activity patterns, and hence, we did not expect to document overall or androidal fat mass change from baseline to 36 months. Similarly, with the exception of insulin, none of the cardiometabolic risk factors changed significantly between baseline and the time of final assessment (either 12 mo or 36 mo). Nevertheless, strong associations between androidal fat and cardiometabolic risk factors suggested that even a small increase in androidal fat mass may have considerable health consequences. Indeed, Biggs et al. [16] reported that the incidence of type 2 diabetes was 70% higher (a hazard ratio of 1.7) in adults 65 years of age and older who gained at least 10 cm in waist circumference over several years compared with those who remained within 2 cm of their baseline waist circumference. Although the Biggs's study did not specifically target postmenopausal women, it provided some insight into the magnitude of the impact of central adiposity on the incidence of type 2 diabetes.

Certain factors such as duration of menopause, isoflavone treatment, and diet quality that are recognized in the literature as influential with respect to cardiovascular health did not emerge as significant predictors of the cardiometabolic outcomes examined in this study. Some of our findings are consistent with previous reports. For instance, DeNino et al. [17] found that the relationship between age and blood lipids in nonobese women was abolished after controlling for visceral fat. Similarly, in our study, TLMP did not emerge in any model (except for fibrinogen) as a significant covariate, because time point took precedence over TLMP. Results also suggested that androidal fat mass in combination with other factors predominated in these cardiometabolic risk models. On the other hand, our findings for isoflavone treatment and dietary quality conflict with some of the previously published reports. The lowering effect of soy protein rich in isoflavones on blood lipids/lipoproteins, albeit modest

Table 2: Longitudinal analysis: covariates associated with each outcome variable[a] assessed from baseline through 36 months ($N = 224$).

Outcome variable	Independent variable	Likelihood ratio[b]	Parameter estimate	Std. error	t value	Pr(>t)
LDL-C	Androidal fat mass	8.93	0.274	0.092	2.99	0.0029
	Site		16.102	2.649	6.08	≤0.0001
HDL-C	Androidal fat mass	41.13	−0.337	0.052	−6.51	≤0.0001
	Site		−6.819	1.941	−3.51	0.0005
	Time point 12		1.479	1.065	1.39	0.17
	Time point 24		2.106	1.066	1.98	0.049
	Time point 36		3.607	1.066	3.38	0.0008
Triacylglycerol	Androidal fat mass	73.19	0.006	0.001	8.79	≤0.0001
	Site		−0.045	0.019	−2.37	0.019
Glucose	Androidal fat mass	36.13	0.165	0.031	5.28	0.0032
	Site		−2.310	0.894	−2.59	0.010
	Time point 12		2.802	1.015	2.76	0.0059
	Time point 36		3.599	1.015	3.55	0.0004
	FamHx "don't know"		6.868	2.303	2.98	0.0032
Uric Acid	Androidal fat mass	49.30	0.027	0.004	7.19	≤0.0001
	Site		0.427	0.112	3.81	0.0002

[a]Each final longitudinal model included obligatory variables: treatment (control versus combined treatment with 80 mg or 120 mg of isoflavones), time point (baseline versus 12, 24, or 36 months), treatment by time point interaction, and site (ISU versus UCD), as well as potential covariates that included androidal fat mass (kg) adjusted for height, time since last menstrual period (TLMP), family history of CVD (Fam Hx) coded as a categorical variable (none versus positive or none versus unknown), and Healthy Eating Index (HEI) score. This table shows only those covariates that were significant ($P \leq .05$) for each outcome variable or had a tendency ($P \leq .10$) to be significant.

[b]The likelihood ratio for each model represents the ratio of a model that includes only obligatory variables compared to the final model that includes obligatory variables and covariates. The overall P value for each model was ≤.0001, except the LDL model had a P value = .0028.

(≤6% reduction), has been documented [18, 19]. The effect is more profound in hypercholesterolemic individuals and in males. Similarly, the effect of diet quality on CVD outcomes is well known: a healthier diet (high in fiber and low in fat and sodium) is associated with a lower risk of CVD [20, 21]. We included both a HEI score as a measure of diet quality and isoflavone treatment in our analysis. None of the models retained either covariate. The lack of association between HEI and cardiometabolic outcomes in our study could be in part explained by a majority of women who had relatively healthy diets (median HEI of 67 out of 100). Very few studies have examined the association between HEI and cardiometabolic outcomes with mixed results. For instance, Kant and Graubard [22] reported that HEI emerged as a negative predictor of serum Hcy, CRP and plasma glucose ($P < .05$), whereas Fung and colleagues [23] did not find an association between HEI and CRP. In a recent study of 125 multiethnic overweight and obese women in early postpartum, the HEI scores were negatively associated with LDL-C and total cholesterol and positively related to HDL-C after adjustment for energy intake, body weight, and lactation status [24].

Based on the results of our study, HEI does not appear to be a predictor of cardiometabolic risk factors. On the other hand, the effects of dietary factors as well as isoflavone treatment on cardiometabolic outcomes may be mediated by androidal fat mass. We previously reported that soy isoflavone treatment for 12 months did not exert an effect on body composition, including androidal fat, in our sample of women [25]. With respect to diet, Fox et al. [26] determined that premenopausal women who participated in a 24 week diet and/or exercise program showed reductions in weight (~7 kg) and total percentage body fat (although it remained greater than 35% for all groups), but no significant improvements in blood lipids, glucose, or insulin concentrations. Further analysis revealed a lack of change in the waist-to-hip ratio, which in turn indicated that body fat distribution was not influenced by the intervention. To summarize, dietary interventions that are not sufficiently potent to reduce androidal fat mass are not likely to produce changes in cardiometabolic outcomes.

In addition to androidal fat mass, the other most common independent predictors of cardiometabolic outcomes in our study included time and site. Although concentrations of HDL-C and glucose did not change significantly during the study, both analytes showed an upward trend from baseline to 36 mo. The effect of time could be related to biological and/or behavioral factors that were not included in our models. In fact, TLMP was no longer significant when time was included, indicating that time was more important than TLMP. The site variable also emerged as a significant covariate in all models: compared with women at ISU,

Table 3: Multivariate linear regression: covariates associated with each outcome variable[a] assessed from baseline through 12 months.

Outcome variable[b]	Independent variable	Likelihood ratio[c]	Parameter estimate	Std. error	t value	Pr(>t)
CRP	Androidal fat mass	90.69	0.052	0.005	24.50	≤0.0001
	Site		−0.236	0.121	10.79	0.072
Fibrinogen	Androidal fat mass	31.63	0.012	0.004	4.32	≤0.0001
	Site		−1.469	0.227	−6.48	≤0.0001
	TLMP		−0.118	0.038	−3.13	0.0020
	TLMP × Site		0.159	0.051	3.12	0.0021
	Positive Fam Hist		0.204	0.112	1.82	0.070
Insulin	Androidal fat mass	51.16	0.143	0.024	5.95	≤0.0001
	Site		−4.516	0.588	−7.68	≤0.0001
	Time point 12		2.013	0.650	3.1	0.0022
	Glucose		0.095	0.028	3.4	0.0008
HOMA	Androidal fat mass	43.73	0.012	0.002	6.88	≤0.0001
	Site		−0.312	0.039	−7.92	≤0.0001
	Time point 12		0.011	0.004	3.44	0.0007

[a]The number of observations included in the analysis varied depending on the outcome: $N = 217$ for CRP and Hcy, $N = 218$ for fibrinogen, insulin, and HOMA. The Hcy model was not statistically significant and thus not shown in this table.
[b]Each final longitudinal model included these obligatory variables: treatment (control versus combined treatment with 80 mg or 120 mg of isoflavones), time point (baseline versus 12, 24, or 36 months), treatment by time point interaction, and site (ISU versus UCD), as well as potential covariates that included androidal fat mass (kg) adjusted for height, time since last menstrual period (TLMP), family history of CVD (FamHx) coded as a categorical variable (none versus positive or none versus unknown), and Healthy Eating Index (HEI) score. The fibrinogen model included TLMP by site interaction. The insulin model (but not other models) included glucose as a covariate. This table shows only those covariates that were significant ($P \leq .05$) for each outcome variable or had a tendency ($P \leq .10$) to be significant.
[c]The likelihood ratio for each model represents the ratio of a model that includes only obligatory variables compared to the final model that includes obligatory variables and covariates. The overall P-value for each model was ≤.0001.

women at UCD had lower concentrations of triacylglycerol, HDL-C, glucose, insulin, HOMA, CRP, and fibrinogen and higher concentrations of LDL-C and uric acid. The site effect may be in part explained by baseline characteristics: ISU women were slightly (albeit not significantly) heavier and younger compared with UCD women. It is also quite possible that the site effect was due to some inherent differences between the two geographic locations. We did not document a relationship between androidal fat mass, as well as other factors, and Hcy likely because the women in our study were well below the clinical cut-off of 15, and Hcy values did not indicate great variability.

Some of the strengths of our study were that we followed a relatively large number of women and monitored longitudinal changes (baseline to 12 or 36 mo) in cardiometabolic risk factors. Limitations were that these women were free-living (both a strength and limitation), lacked ethnic diversity, and underwent infrequent measurements (yearly). Women in this study were mainly nonobese based upon the BMI definition. However, BMI does not adequately reflect body composition. Thus, some of our women may have been identified as obese using other criteria, such as percentage body fat (35–40% = overweight, >40% = obese [27]). In conclusion, although cardiometabolic outcomes examined in this study were not affected by isoflavone treatment, each outcome (except for Hcy) had a strong, significant association with androidal fat mass. Thus, even small changes in androidal fat are likely to alter the cardiometabolic profile in healthy postmenopausal women.

Conflict of Interests/Financial Disclosures

Coauthors have not reported conflicts or disclosures.

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Research Article

Long-Term Effect of Mediterranean-Style Diet and Calorie Restriction on Biomarkers of Longevity and Oxidative Stress in Overweight Men

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We report the effects of a Mediterranean-style diet, with or without calorie restriction, on biomarkers of aging and oxidative stress in overweight men. 192 men were randomly assigned to either a Mediterranean-style diet or a conventional diet. The intervention program was based on implementation of a Mediterranean dietary pattern in the overweight group (MED diet group), associated with calorie restriction and increased physical activity in the obese group (lifestyle group). Both groups were compared with participants in two matched control groups (advice groups). After 2 years, there was a significant difference in weight loss between groups, which was −14 kg (95% CI −20 to −8) in lifestyle groups and −2.0 kg (−4.4 to 0) in the advice groups, with a difference of −11.9 kg (CI −19 to −4.7 kg, $P < .001$); moreover, there was a significant difference between groups at 2 years for insulin ($P = .04$), 8-iso-PGF2α ($P = .037$), glucose ($P = .04$), and adiponectin ($P = .01$). Prolonged adherence to a Mediterranean-style diet, with or without caloric restriction, in overweight or obese men is associated with significant amelioration of multiple risk factors, including a better cardiovascular risk profile, reduced oxidative stress, and improved insulin sensitivity.

1. Introduction

Data from observational and cohort studies indicate that longevity is greater in individuals adhering to healthy lifestyle practices [1] or in those with a favorable level of risk factors [2, 3]. Because of the limitations in feasibility for randomized trials to address the long-term effects of lifestyle on clinical outcomes, clinicians must rely mainly on a combination of epidemiological investigations and short-term clinical trials with intermediate end points. Whether long-term lifestyle changes add years to life and slow aging is not yet known. Some recent findings suggest that calorie restriction may have a positive effect on surrogate markers of longevity, including fasting insulin level and body temperature, as well as markers of oxidative stress [4]. Although the data were based on small number of subjects and limited follow-up (up to six months), the results were in line with the hypothesis that decreasing caloric intake by 30% or more in young or middle-aged laboratory animals prevents or retards age-related chronic diseases and significantly prolongs maximal life span [5, 6]. The quality of diet may also be important, as secondary prevention trials have indicated that Mediterranean-style diets reduced rates of heart disease and cardiovascular mortality in people with established coronary diseases [7, 8]. Moreover, increasing evidence suggests that diet may also be important in modulating inflammation [9, 10]. We are not aware of any trials assessing the long-term effect of the quality of diet on markers of longevity or oxidative stress in primary prevention. We report the effects of a Mediterranean-style diet, with or without calorie restriction, on biomarkers of aging and oxidative stress in overweight men.

2. Methods

2.1. Study Participants. Men were identified in our database of subjects participating in randomized controlled trials evaluating the effect of lifestyle changes [11, 12] and conducted

from October 2000 to January 2004. Men included in the present analysis were obese subjects with erectile dysfunction [11] or overweight subjects with metabolic syndrome [12] and had to have a complete follow-up in the respective study trial.

Participants were recruited from the outpatient practices of the Teaching Hospital of the Second University of Naples, Italy, and included persons of 18 years of age and older with a body mass index (BMI) of 26 kg/m^2 or greater. The subjects were sedentary (less than one hour per week of physical activity) with no evidence of participation in diet reduction programs and with a stable weight ($\pm$1 kg) within the last 6 months. The exclusion criteria were diabetes mellitus, impaired renal function (serum creatinine level greater than 1.5 mg/dL), hepatic disease, cardiovascular disease, psychiatric problems, a history of alcohol abuse (at least 500 g alcohol/week in the last year), and use of any medication. Subjects with the metabolic syndrome had to have three or more of the criteria recommended by the Adult Treatment Panel [13]. The study was approved by the institutional committee of ethical practice of our institution, and all the study subjects gave informed written consent.

2.2. Interventions. The intervention program was based on implementation of a Mediterranean dietary pattern in the overweight group (MED diet group), combined with calorie restriction and increased physical activity in the obese group (lifestyle group). Both groups were compared with two matched control groups (advice groups). Subjects were randomly assigned to either the intervention or advice groups using a computer-generated random number sequence. The program involved education on reducing dietary calories, personal goal setting, and self-monitoring (food diaries) through a series of monthly small-group sessions. The recommended composition of the dietary regimen was the following: carbohydrates 50% to 60%, proteins 15% to 20%, total fat $\leq$ 30%, saturated fat $<$ 10%; subjects were also advised to increase consumption of fruits, vegetables, nuts, and whole grains daily, and to increase the consumption of olive oil. Patients were in the program for 24 months and had monthly sessions with the nutritionist for the first year and bimonthly sessions for the second year. Compliance with the program was assessed by attendance at the meetings and completion of the diet diaries. Subjects in the lifestyle group also received guidance on increasing their level of physical activity, mainly walking for a minimum of 30 minutes per day, but also swimming or aerobic ball games. Subjects in the advice groups were given general oral and written information about healthy food choices both at baseline and at subsequent visits, but no specific individualized programs were offered to them.

2.3. Outcome Measures. Outcome measures were recorded at one and two years. The primary end point was change from baseline in insulin and 8-iso-$PGF_{2\alpha}$ between intervention and advice groups. Secondary analyses included the changed from baseline in body weight, total cholesterol, blood pressure, glucose, and adiponectin.

Height and weight were recorded with participants wearing lightweight clothing and no shoes using a Seca 200 scale with attached stadiometer (Seca, Hamburg, Germany). Twenty-four-hour nutrient intakes were calculated with food composition tables and patients' weekly diet diaries. All subjects were asked to complete for 3-day food record and to record occupational, household, and leisure time physical activity, to assess dietary adherence and exercise activity. Estimation of insulin sensitivity in the fasting state was assessed with HOMA (homeostasis model assessment) and calculated with the following formula: fasting plasma glucose (mmol/L) $\times$ fasting serum insulin (μU/mL)/25, as described by Matthews et al. [14]. Assays for serum total and high-density lipoprotein cholesterol, triglycerides, and glucose levels were performed in the hospital's chemistry laboratory. Plasma insulin levels were assayed by radioimmunoassay (Ares, Serono). Serum samples for adiponectin were stored at -80°C until assayed in duplicate using a high-sensitive, quantitative sandwich enzyme assay (Quantikine HS, R&D Systems, Minneapolis, MN). Plasma total 8-iso-$PGF_{2\alpha}$ levels were assessed by enzyme immunoassay (Assay Design Inc., Indianapolis, IN).

2.4. Statistical Analysis. Data are presented as mean $\pm$ SD unless otherwise stated. Unpaired (intervention versus advice) and paired (before versus after treatment) Student's t-tests were performed. The effect of treatments were tested by means of paired t-tests and a Wilcoxon matched test. The results of statistical analysis were also confirmed with ANOVA for repeated measures. Results were considered significant with two-tailed $P < .05$. All analyses were conducted using SPSS version 11.1 (SPSS Inc, Chicago, Ill).

3. Results

A total of 192 men enrolled in the study, 98 men in the intervention groups (46 MED diet, 52 lifestyle) and 94 men (44 MED diet, 50 lifestyle) in the advice groups. Both intervention groups were comparable with the corresponding advice groups, including the number of components of the metabolic syndrome, and relatively healthy. The prevalence of smokers was similar in the 2 groups: 27% in the intervention group and 31% in the control group ($P = .34$). Moreover, baseline data showed no important difference in the nutrient intake between the two groups (data not shown). After 2 years, subjects on the intervention groups consumed a greater percentage of calories from complex carbohydrates, polyunsaturated, and monounsaturated fat, had higher fiber intake, a lower ratio of omega-6 to omega-3 fatty acids, as well as lower energy consumption, saturated fat, and cholesterol intake than controls. Total fruit, vegetable, nuts, and whole grain intakes and olive oil consumption were significantly higher in the intervention groups. The level of physical activity increased more in the intervention group (from 39 [10] to 156 [30] min/wk) than in the control group (from 41 [9] to 74 [28] min/wk; $P < .001$).

After 2 years, there was a significant difference in weight loss between groups, which was -14 kg (95% CI -20 to -8)

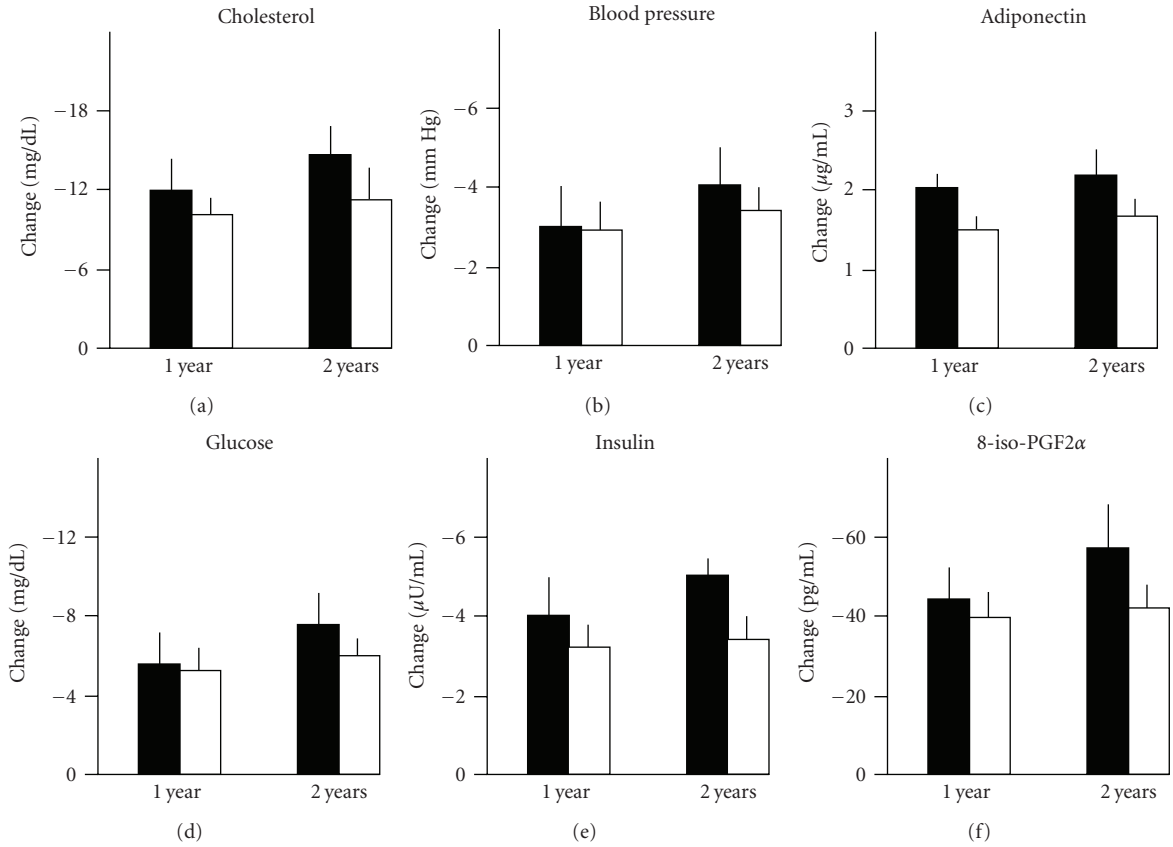

Figure 1: Changes in fasting plasma total cholesterol, glucose, insulin, mean blood pressure, insulin, adiponectin, and 8-iso-$PGF_{2\alpha}$ levels at year 1 and year 2 in subjects of intervention groups (black columns: lifestyle, white columns: MED diet). All parameters represent the net effect (intervention group, advice group) of treatments and were significantly reduced from baseline values at year 1 and year 2 in both groups.

in lifestyle groups and −2.0 kg (−4.4 to 0) in the advice groups, with a difference of −11.9 kg (CI −19 to −4.7 kg, $P < .001$). There was a significant association between change in body weight and HOMA ($r = 0.43$, $P = .01$), as well as between waist and HOMA ($r = 0.37$, $P = .01$).

Figure 1 shows the effect of treatments (change in intervention groups minus change in advice groups) on selected parameters at one year and two years. The effect of treatment was sustained as there was no trend to decrease at 2 years; moreover, there was a significant difference between groups (MED diet versus lifestyle) at 2 years for insulin ($P = .04$), 8-iso-$PGF_{2\alpha}$ ($P = .037$), glucose ($P = .04$), and adiponectin ($P = .01$) favouring lifestyle. There was no significant interaction of groups (intervention and advice) per time (years). The differences remained still significant after adjustment for the basal body weight.

4. Discussion

Our findings indicate that prolonged adherence to a Mediterranean-style diet, with or without caloric restriction, in overweight men resulted in reduced levels of biomarkers of ageing (insulin and glucose), oxidative stress (8-iso-$PGF_{2\alpha}$), and cardiovascular risk (cholesterol and blood pressure) and also produced a rise in circulating level of adiponectin, a protective factor against atherosclerosis and insulin resistance [15]. Long-term intervention studies of lifestyle changes on hard outcomes are unlikely to be performed. However, some of the surrogate markers evaluated in the present analysis are associated with extended life in observational studies [1–3].

Despite the fact that the role of oxidant stress in the pathogenesis of atherosclerosis is a hotly debated issue, in part because of a presumed failure of antioxidants to prevent the disease, current evidence suggests that isoprostanes represent a biomarker that has the potential to be of great importance in the assessment of human atherosclerotic cardiovascular disease. In particular, 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) is considered a reliable indicator of oxidative stress in vivo [16, 17]. Recent evidence suggests that their quantification may represent an independent marker of atherosclerotic risk [18]. Moreover, increasing evidence suggests an association between oxidative stress and obesity or insulin resistance. Keaney et al. [19] reported an association between increasing body mass index and increasing systemic oxidant stress; in nearly 3000 patients involved in the Framingham Heart Study, the authors showed enhanced IsoP formation in men and women, strongly associated with

increasing body mass index. Data from 2,002 nondiabetic subjects of the community-based Framingham Offspring Study indicate that systemic oxidative stress is associated with insulin resistance in individuals at average or elevated risk of diabetes (metabolic syndrome or IFG) even after accounting for BMI [20].

Short-term (up to six months) caloric restriction in overweight men and women produced significant body weight reduction associated with decreased DNA damage, considered a surrogate marker of oxidative stress [4]. The oxidative stress hypothesis of aging finds support from animal studies demonstrating reduced oxidative damage in longer-surviving, calorie-restriced rodents [21]. On the other hand, individuals at high cardiovascular risk who improved their diet toward a Mediterranean dietary pattern showed significant reductions in cellular lipid levels and LDL oxidation [22]. This recent observation adds evidence to the intriguing hypothesis that one important effect of Mediterranean-style diets in prolonging life [23, 24] may be associated with reduced oxidative stress and inflammation [9, 10].

Adiponectin plays an important role in modulating both insulin sensitivity and concentrations of circulating plasma glucose and nonesterified fatty acids. A lower concentration of circulating plasma adiponectin seems to be a good predictor of reduced insulin sensitivity and increased risk of type 2 diabetes [25]. In 987 diabetic women from the Nurses' Health Study with no history of cardiovascular disease, close adherence to a Mediterranean-type diet associated with higher adiponectin concentrations [26]. Of the several components of the Mediterranean dietary pattern score, alcohol, nuts, and whole grains show the strongest association with adiponectin concentrations. In insulin-resistant offspring of obese type 2 diabetic patients, a Mediterranean-style diet rich in monounsaturated fats (23% MUFA) improved insulin sensitivity, and this was associated with increased postprandial adiponectin mRNA gene expression in peripheral adipose tissue [27].

Interestingly enough, many of the parameters that are positively affected in the intervention groups are important risk factors for healthy survival in a large group of middle-aged men, including overweight, and high glucose, triglyceride, and blood pressure levels [3]. Given the difficulty of adopting a calorie restricted diet in the long-run, it seems important that such changes may be obtained, although to a lesser degree, with improved quality of diet. The public health burden of chronic diseases related to unhealthy diet is huge and on the rise, and argues for concomitant public health strategies and policies that affect entire populations.

In conclusion, prolonged adherence to a Mediterranean-style diet, with or without caloric restriction, in overweight or obese men is associated with significant amelioration of multiple risk factors, including a better cardiovascular risk profile (less blood pressure, less total cholesterol and triglycerides, higher HDL-cholesterol), reduced oxidative stress (less iso-8-$PGF_{2\alpha}$), and improved insulin sensitivity (reduced HOMA and increased adiponectin levels). These changes are amplified when MED diet is associated with calorie restriction and increased physical activity. As several potential risk factors for healthy and long survival in men are modifiable, common approaches that target multiple risk factors simultaneously and approaches that enhance insulin sensitivity may improve the probability of better health at older ages [3]. The choice of healthy diets, as the Mediterranean-style diet is thought to be, is critical to fighting the war against chronic disease and to add healthy years to life. This seems particularly important for individuals who carry additional risk factors, such as type 2 diabetes mellitus, obesity, and the metabolic syndrome, and fail, as most do, to have a consistent and long-term weight loss.

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Research Article

Possible Association of High Urinary Magnesium and Taurine to Creatinine Ratios with Metabolic Syndrome Risk Reduction in Australian Aboriginals

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Background. Because of the epidemic of metabolic syndrome (MS) in Australian Aboriginals known for their higher cardiovascular mortality and shorter life expectancy, we analyzed the possible relationship of their MS risks with the current dietary custom. *Methods*. The subjects were 84 people aged 16–79 years. The health examination was conducted according to the basic protocol of WHO-CARDIAC (Cardiovascular Diseases and Alimentary Comparison) Study. *Results*. The highest prevalence among MS risks was abdominal obesity (over 60%). After controlling for age and sex, the odds of obesity decreased significantly with high level of urinary magnesium/creatinine ratio (Mg/cre) (OR, 0.11; 95% CI, 0.02–0.57; $P < .05$). The significant inverse associations of fat intake with Mg/cre and of fast food intake with urinary taurine/creatinine ratio were revealed. *Conclusions*. The high prevalence of obesity in the Aboriginal people of this area may partly be due to the reduction of beneficial nutrients intake including Mg and taurine.

1. Introduction

The metabolic syndrome (MS) is composed of cardiovascular risk factors including abdominal obesity, high blood pressure (BP), dyslipidaemia and disturbed glucose metabolism. The people with MS would be more likely to have cardiovascular events and have a higher risk of mortality [1, 2]. An increased rate of MS in indigenous people than in nonindigenous people is becoming a serious problem [3]. Australian Aboriginals have the worse health status and life expectancy than nonindigenous people. Thompson et al. reported that a high proportion of urban Aboriginals revealed to be smokers, hypertensive, dyslipidaemic, overweight, obese or diabetes [4]. It was reported that the percentage of overweight in indigenous Australians was 5.5 times more than that in nonindigenous Australians. The prevalence of burden of cardiovascular diseases and diabetes were 4.6 and 5.4 times higher in indigenous people than in nonindigenous people in 2003 [5]. Both avoidable mortality and unavoidable mortality in indigenous people were much higher than those in nonindigenous people in Australia.

The high rate of cardiovascular diseases and obesity among Aboriginal people is thought to be caused by the combination of several factors including diet change, less activity, genetic susceptibility, and low level of living standard [5]. They hunted, fished, and gathered their food depending on local supply, before the introduction of western-style diets, high in fat and sugar and low in carbohydrate and nutrients [6]. They are not seemingly adaptable to the rapid dietary and lifestyle changes by adjusting their own homeostatic mechanisms, thus resulting in the development of MS.

Our objective in this survey including urine collection for Australian Aboriginals was to assess the prevalence of MS risks and their relationship with lifestyle factors especially

eating habit. Urinary biomarkers such as sodium (Na), potassium (K), magnesium (Mg), and taurine (Tau) would reflect their eating habit related to health and MS risks, however, there is few reports about them. We also expected to reveal possible triggers in their diets, if any, for the MS risks.

2. Method

2.1. Subjects. We carried out a health survey in an Aboriginal community located in Victoria, Australia. Participants were 84 people aged 16 to 79 years who were informed of the purpose and procedures about the study and signed an informed consent form. The study included BP and anthropometrical measurements, blood and spot urine collections and lifestyle questionnaires. This study was ethically approved by Mukogawa Women's University and supported by Framlingham Aboriginal Trust committees.

2.2. Data Collection. All measurements and blood sampling were performed by an experienced physician and a nurse at a local community healthcare centre or hospital. Body weight and height were checked for the subjects standing and wearing light clothes. From these results, body mass index (BMI; weight (kg)/height $(m)^2$) was calculated. Waist circumference (WC) was measured using a flexible steel measuring tape. BP and heart rates (HR) were measured after a 5- to 10-minute rest using an automatic digital BP measurement system (Omron Digital HEM-907, Tokyo, Japan). The mean of 2 readings was used in this analysis.

Blood analyses including serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting blood glucose, and haemoglobin A1c (HbA1c) were assessed at Gribbles Pathology (Victoria, Australia). Enzymatic methods for TC, HDL-C, LDL-C, and TG were performed. Spot urine was collected using a plastic cup and creatinine, Na, K, Mg and Tau were analyzed. Na and K were determined by electrode methods and creatinine was analyzed by enzymatic method. Mg was analyzed by spectrophotometric method. Tau was assessed using high performance liquid chromatography system with fluorescence detection consisted of two pumps (GL-7410, GL science, Tokyo, Japan), autosampler (GL-7420), and fluorescence detector (GL-7453A). *O*-phthalaldehyde solution (containing 5.96 mM *O*-phthalaldehyde and 0.1% 2-mercaptoethanol in borate buffer) was delivered at 0.5 ml/min and filtered urine samples were injected onto a *Hitachi #2619*-PH *column* (4.0 mm i.d. × 150 mm, *Hitachi*, Tokyo, Japan). Tau was monitored using an excitation wavelength of 360 nm and an emission wavelength of 450 nm. Sodium-potassium ratio (Na/K, (mmol/mmol)), sodium-creatinine ratio (Na/cre, (mmol/g)), potassium-creatinine ratio (K/cre, (mmol/g)), magnesium-creatinine ratio (Mg/cre, (mg/g)), and taurine-creatinine ratio (Tau/cre, (μmol/g)) were calculated by the measured values.

MS risks were defined according to the International Diabetes Federation (IDF) definition of the following: abdominal obesity (≥94 cm for men or ≥80 cm for women); high TG (≥1.7 mmol/L (150 mg/dL)); low HDL-C (<1.03 mmol/L (40 mg/dL) for men or <1.29 mmol/L (50 mg/dL) for women); increased BP (≥130 mmHg for systolic or ≥85 mmHg for diastolic). In this survey, high HbA1c (≥5.8%) was used as a definition of disturbed glucose metabolism instead of fasting glucose criteria because it remained possible that some participants drank soft drinks containing sugar before starting examination. Dyslipidaemia was defined as elevated TG and/or low HDL-C. BMI was categorized into 3 groups; under 25 as normal, 25 or more to under 30 as overweight, and equal to or over 30 as obesity.

For each participant, eating frequency was assessed using a food frequency questionnaire about 18 food items categorized into 4 or 5 levels: meat, fat, fish, milk, cheese, egg, fast food, bread, rice/pasta/noodles, legumes, soy products, fruits, vegetables, salt, coffee, tea, water, and soft drinks. Furthermore, information regarding employment, education, alcohol intake, smoking, medical history and physical activity were recorded.

2.3. Data Analysis. Differences between men and women were investigated using Student's *t*-tests. Prevalence rates of MS risks and intake frequency were compared using chi-square tests by age divided into 3 categories: young; under 30 years, middle-aged; 30 to 49 years and old; at least 50 years. Intake frequency was classified into two, high (once or more a week) and low (1, 2 times or less a month), which was applied to meat, fish, vegetables, and fast food. The intake frequency of soft drinks was classified into two, high (3 glasses or more a day) and low (2 glasses or less a day). The fat intake was categorized to two, "Yes" (eat fat or taken off after cooking) and "No" (taken off before cooking or eat no fat).

To compare urine Na/cre, K/cre, Mg/cre, Tau/cre and Na/K among three age groups, analyses of one-way variance was used. Multivariate logistic regression analysis was used to estimate the odds ratios (ORs) adjusted by age and sex on MS risks of the level of Na/cre, K/cre, Mg/cre, Tau/cre and Na/K in urine, which were divided into two groups, high and low, at the mean value. Differences in MS risks were investigated using Student's *t*-tests between high and low of urine Mg/cre and Tau/cre. The association of intake frequency to Mg/cre and Tau/cre was examined by a logistic regression adjusted with age and sex.

All statistical analyses were undertaken using the SPSS for windows package version 15 (SPSS Inc, Chicago, IL). Results are presented as means ± standard deviations. A *P*-value of.05 was set as the level of significance.

3. Results

3.1. Characteristics of the Study Population. Fifty percent of the total study subjects ($n = 84$) were men. Two men were excluded from all analyses because of the lack in blood and urine sampling. Urinary data of a man who did not provide adequate results was also eliminated. Baseline characteristics of study subjects are shown in Table 1. The mean age was 42 years for men (range, 16–77 years) and 37 years for women (range, 16–79 years). Men showed significantly higher levels in TC, LDL-C and SBP than women. The Na/Cre, K/Cre,

Table 1: Characteristics of study subjects.

	All	Men	Women	*P*-value
Biological variables	($n = 82$)	($n = 40$)	($n = 42$)	
Age (year)	39.6 ± 17.6	42.0 ± 18.2	37.4 ± 17.0	.23
BMI (kg/m^2)	28.2 ± 6.1	27.4 ± 4.7	28.9 ± 7.1	.27
WC (cm)	96.6 ± 14.5	94.5 ± 12.5	98.6 ± 16.0	.20
SBP (mmHg)	130.4 ± 16.4	135.3 ± 17.0	125.7 ± 14.5	<.01
DBP (mmHg)	73.9 ± 11.9	76.0 ± 12.4	72.0 ± 11.2	.12
HR (bpm)	75.8 ± 15.4	75.0 ± 16.6	76.6 ± 14.3	.65
TC (mmol/L)	4.6 ± 1.1	4.9 ± 1.2	4.3 ± 1.0	<.05
HDL-C (mmol/L)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.3	.60
LDL-C (mmol/L)	2.8 ± 1.0	3.1 ± 1.0	2.5 ± 0.9	<.01
TG (mmol/L)	1.5 ± 0.9	1.4 ± 0.7	1.5 ± 1.0	.69
HbA1c (%)	5.9 ± 0.9	5.8 ± 0.5	6.1 ± 1.2	.11
Ratios in urine	($n = 79$)	($n = 38$)	($n = 41$)	
Na/cre (mmol/g)	94.5 ± 60.2	86.0 ± 56.7	102.3 ± 62.9	.23
K/cre (mmol/g)	55.7 ± 28.4	53.7 ± 28.6	57.6 ± 28.4	.54
Mg/cre (mg/g)	44.9 ± 23.1	42.1 ± 25.3	47.6 ± 20.9	.30
Tau/cre (μmol/g)	1122.8 ± 2674.9	1590.3 ± 3770.8	689.5 ± 631.9	.14
Na/K (mol/mol)	1.97 ± 1.65	1.89 ± 1.55	2.04 ± 1.76	.69

Data are mean ± SD.

Mg/Cre, Tau/cre and Na/K ratios did not differ between the sex groups.

3.2. Age-Specific Prevalence. The frequency of MS risks and eating habit profiles among three age groups are presented in Figure 1 and Table 2. The highest percentage of obesity was shown in the old (young; 23.3%, middle-aged; 21.4%, old; 37.5%) and quite high frequency of abdominal obesity was shown at any age group (young; 66.7%, middle-aged; 67.9%, old; 66.7%). The prevalence of increased BP rose with age, from 60% of the young to 75% of the old, as well as high HbA1c, from 20% of the young to 62.5% of the old. On the other hand, the percentages of low HDL-C (41.7%) and high TG (25.0%) in the old were lowest of all, which resulted in the lowest percentage of dyslipidaemia (young; 66.7%, middle-aged; 67.9%, old; 50%, data not shown). Table 2 shows the dietary pattern of participants among age groups. The intake frequency of vegetables in the young was lower and that of soft drinks was higher than other age groups ($P < .01$ for both). On the other hand, the intake frequencies of meat and fast food in the old were significantly lower than those in younger groups ($P < .05$ and $P < .001$, resp.).

3.3. Urine Analyses. Table 3 shows logistic regression results of obesity and dyslipidaemia with urinary biomarkers adjusted with age and sex. High level of urine Mg/cre was associated with a much lower likelihood of obesity (OR, 0.11; 95% CI, 0.02–0.57; $P < .05$). Logistic regression results adjusted with age and sex on subjects with dyslipidaemia showed a significantly lower OR in the high level of urine Tau/cre (OR, 0.22; 95% CI, 0.07–0.73). High Tau/cre was associated with low TG ($P < .05$) and showed a tendency to be related with low WC and BMI ($P = .06$ and.09, resp.; Table 4). Table 5 shows the relationship of urine Mg/cre and Tau/cre with eating habits by logistic regression adjusted with age and sex. Compared to subjects who eat no fat, those who eat fat had a significantly lower likelihood of high Mg/cre level (OR, 0.12; 95% CI, 0.02–0.59) and a similar relationship was shown between intake frequency of fast food and Tau/cre level (OR, 0.11; 95% CI, 0.02–0.69).

4. Discussion

This study is the first to report on the relationship of MS risks with eating habit by spot urine analysis of nutritional biomarkers including Mg and Tau in Australian Aboriginals. It revealed a high prevalence of MS including abdominal obesity, increased BP and low HDL-C even at young age, and a quite high prevalence of high HbA1c in the old. The study confirms that an increased level of Mg/cre in spot urine is associated with a decreased likelihood of obesity, supported by lower BMI and WC in people with a higher level of Mg/cre. Restriction of magnesium intake decreased urinary loss [7] and a good correlation was observed between Mg/cre in spot urine and total 24-hour urine excretion ($R = 0.80$, $P < .05$) [8]. Considering both, low level of Mg/cre in spot urine would be caused by insufficient Mg intake and our finding is consistent to the previous studies that higher intake of Mg was associated with a marked reduction in the prevalence of obesity (OR, 0.78; 95% CI, 0.72–0.85), abdominal obesity (OR, 0.80; 95% CI, 0.76–0.85), and MS (OR, 0.83; 95% CI, 0.72–0.96) in the US people [9]. As it is

Table 2: Eating frequency by age groups.

Age	Young	Middle-aged	Old	*P*-value
(Men/Women)	$n = 30$ (13/17)	$n = 28$ (13/15)	$n = 24$ (14/10)	
Meat				<.05
Low	30.0 (9)	28.0 (7)	58.3 (14)	
High	70.0 (21)	72.0 (18)	41.7 (10)	
Fat				.56
No	36.0 (18)	30.0 (15)	34.0 (17)	
Yes	35.7 (10)	39.3 (11)	25.0 (7)	
Fish				.53
Low	46.7 (14)	32.0 (8)	37.5 (9)	
High	53.3 (16)	68.0 (17)	62.5 (15)	
Vegetables				<.01
Low	93.3 (28)	76.0 (19)	56.5 (13)	
High	6.7 (2)	24.0 (6)	43.5 (10)	
Fruits				.74
Low	20.0 (6)	16.0 (4)	25.0 (6)	
High	80.0 (24)	84.0 (21)	75.0 (18)	
Fast food				<.001
Low	20.0 (6)	28.0 (7)	70.8 (17)	
High	80.0 (24)	72.0 (18)	29.2 (7)	
Soft drinks				<.01
Low	36.0 (9)	68.4 (13)	80.0 (16)	
High	64.0 (16)	31.6 (6)	20.0 (4)	

Data are percentage (n). Young; under 30 years, Middle-aged; 30 to 49 years, Old; 50 years and older.

Table 3: Adjusted odds ratios of obesity and dyslipidaemia according to urinary biomarkers.

		Obesity		Dyslipidaemia	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Na/cre	Low	1		1	
	High	0.31 (0.08–2.26)	.31	0.75 (0.19–3.02)	.69
K/cre	Low	1		1	
	High	1.81 (0.39–8.40)	.45	0.56 (0.15–2.04)	.38
Mg/cre	Low	1		1	
	High	0.11 (0.02–0.57)	<.05	0.82 (0.27–2.48)	.73
Na/K	Low	1		1	
	High	5.68 (1.00–32.33)	.05	1.02 (0.25–4.20)	.98
Tau/cre	Low	1		1	
	High	0.36 (0.08–1.71)	.20	0.22 (0.07–0.73)	<.05

Data are adjusted by age and sex.

known, Mg is essential to many enzymatic reactions across the metabolic pathway of carbohydrate, lipid and electrolytes as a cofactor [10], and obesity is strongly inversely related to magnesium deficiency [11]. This may be partly due to the eating habit of obese people and the low consumption of rich

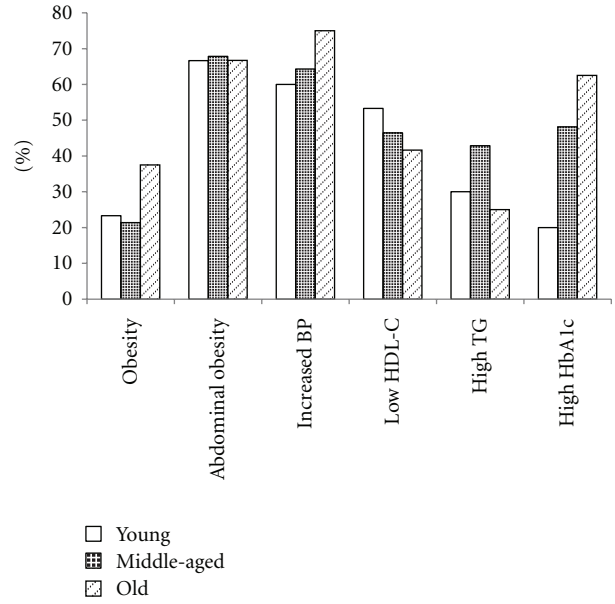

Figure 1: Prevalence of MS risks by age groups. young: under 30 years, middle-aged: 30 to 49 years, Old: 50 years and older. Obesity: BMI ≥ 30, abdominal obesity: ≥94 cm for men or ≥80 cm for women, Increased BP: ≥130 mmHg for systolic or ≥85 mmHg for diastolic, low HDL-C: <1.03 mmol/L, high TG: ≥1.7 mmol/L, high HbA1c: ≥5.8%.

in Mg foods such as whole grains, vegetables and seafood. The renal loss may be another mechanism contributing to Mg deficiency in obese people. Insulin plays a role in inducing Mg excretion [12]. Insulin resistance is the most common and could increase Mg excretion in people with MS risks [13].

In this study, urine Mg/cre was inversely associated with fat intake. It is reported that saturated fatty acids can cause a lipid-created plasma membrane abnormality because of incorporation into the cell membrane and the transition of Mg into cell may be reduced [14]. An accumulation of saturated fatty acids by diet may cause depletion of intracellular Mg, which might lead to diabetes [15]. Previous studies revealed that Mg deficiency was correlated with diabetes in indigenous Australians and US women [16, 17]. However, our study showed no significant association between urine Mg/cre and HbA1c. A possible reason is that HbA1c is a long-term indicator of hyperglycaemia, whereas, urine Mg/cre is a short-term indicator of diet.

Urine Tau/cre was associated with a decreased likelihood of dyslipidaemia. Fish is abundant source of Tau [18, 19] and omega-3 fatty acid. It was reported that the frequency of fish intake was positively correlated with the percent composition of omega-3 fatty acid in plasma phospholipids and negatively correlated with TC and LDL-C [20]. Fish oil such as eicosapentaenoic acid and docosahexaenoic acid are well known to lower the TG level [21]. The beneficial effects of Tau on lipid metabolism, such as hypocholesterolaemic and hypotriglyceridaemic activities, were observed both in rats and in humans [22, 23]. There was no significant

Table 4: MS risks according to urine levels of Mg/cre and Tau/cre.

	Mg/cre			Tau/cre		
	Low	High	*P*-value	Low	High	*P*-value
BMI (kg/m^2)	29.4 ± 6.3	26.1 ± 4.6	<.05	28.9 ± 6.1	26.4 ± 5.0	.09
WC (cm)	99.1 ± 14.6	91.8 ± 11.9	<.05	98.4 ± 14.3	91.8 ± 12.3	.06
SBP (mmHg)	128.1 ± 15.4	134.4 ± 18.0	.10	131.7 ± 17.7	128.3 ± 14.2	.41
DBP (mmHg)	74.1 ± 13.4	73.1 ± 9.7	.73	74.3 ± 11.8	72.4 ± 12.8	.53
HR (bpm)	75.9 ± 14.5	75.7 ± 16.4	.95	74.5 ± 11.0	79.5 ± 11.0	.19
TC (mmol/L)	4.5 ± 1.2	4.8 ± 0.9	.40	4.7 ± 1.1	4.4 ± 1.1	.29
HDL-C (mmol/L)	1.2 ± 0.3	1.2 ± 0.2	.65	1.2 ± 0.3	1.2 ± 0.2	.55
LDL-C (mmol/L)	2.7 ± 1.1	2.9 ± 0.8	.57	2.8 ± 1.0	2.7 ± 1.0	.52
TG (mmol/L)	1.4 ± 0.7	1.6 ± 1.0	.19	1.6 ± 0.9	1.2 ± 0.6	<.05
HbA1c (%)	6.0 ± 1.1	5.8 ± 0.6	.51	6.0 ± 1.1	5.7 ± 0.3	.15

Data are mean ± SD.

Table 5: Adjusted odds ratios of urine Mg/cre and Tau/cre according to eating habit.

		High Mg/cre		High Tau/cre	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Meat	Low	1		1	
	High	1.07 (0.19–6.05)	.94	2.06 (0.33–12.82)	.44
Fat	No	1		1	
	Yes	0.12 (0.02–0.59)	<.01	0.24 (0.04–1.30)	.10
Fish	Low	1		1	
	High	1.69 (0.42–6.83)	.46	3.17 (0.63–16.08)	.16
Vegetables	Low	1		1	
	High	1.87 (0.37–9.51)	.45	1.27 (0.20–8.06)	.80
Fruits	Low	1		1	
	High	1.18 (0.20–6.77)	.86	0.31 (0.05–2.15)	.24
Fast food	Low	1		1	
	High	0.80 (0.17–3.90)	.78	0.11 (0.02–0.69)	<.05
Soft drinks	Low	1		1	
	High	1.16 (0.29–4.71)	.83	0.93 (0.20–4.38)	.92

Data are adjusted by age and sex.

association between elevated urine Tau/cre and obesity in this study. However, the subjects with high Tau/cre showed a weak tendency to be low BMI and WC, which is supported by the previous study showing that Tau prevented obesity in high-fat-induced and/or genetically obese mice [24].

Contrary to our expectation, no association was detected between the intake frequency of fish and Tau/cre. It may be due to out of consideration to the volume of fish consumption and the lack of question about seafood other than fish, especially to shellfish, the most abundant source of Tau. Furthermore, no association was detected between Tau/cre and HbA1c in this study. Our previous report revealed that the excretion volume of Tau in 24-hour urine was inversely associated with fasting blood glucose in African men [25]. A population-based prospective cohort study in England also showed that fish consumption would be effective in reducing risk of diabetes [26]. The same reason for the lack of relationship between Mg/cre and HbA1c in this study is supposed to be applicable to between Tau/cre and HbA1c again.

Aboriginal people used to eat Mg rich food, such as nuts, vegetables, and unrefined cereals. These plant foods also contain other minerals, vitamins, fibre, and omega-3 fatty acids [27]. Their modern diet, however, includes foods that are rich in fat and sugar, which may result in excessive energy intake and unhealthy condition. This study revealed Aboriginal people in this area were at extremely high risks of abdominal obesity, consistent with health report in

Australian Aboriginals [5]. Our data also confirmed previous findings from the DRUID (Diabetes and Related conditions in Urban Indigenous people in the Darwin region) study that the percentages of increased BP and TC in men were higher than in women and that the prevalence of diabetes and the mean of HbA1c rose strongly with age [28]. Aboriginals also used to have eating habit of fish and shellfish [6]. However, this study showed that the fish intake frequency in nearly the half of the subjects was less than once a week. The inverse relationship between Tau/cre and the intake frequency of fast food, as well as between Mg/cre and fat intake, would demonstrate that Western eating habit have caught on in this area. The percentage of high TG showed no association with age, which may be accounted for by lower eating frequencies of meat and fast food and a higher eating frequency of vegetables in the old than in both the young and middle aged. These results from eating frequency revealed increasing westernization of diet in the young and middle-aged, indicating the increase of diabetes in future.

Recently, Yamori et al. reported that Mg and Tau showed a synergistic effect on preventing cardiovascular risks [29]. Tau is an abundant and semiessential free amino acid in human and has beneficial effects on MS risks such as hypertension, dyslipidaemia, and diabetes [30]. Previous reports showed Mg intake was inversely associated with the incidence of ischemic stroke [31]. Beneficial effects on endothelial function of Mg, and Tau were also reported [32, 33]. To prevent MS risks, it would be recommended to promote diet rich in Mg and Tau to Australian Aboriginals.

There are some limitations in this study. First, the number of the participants was small and age showed wide variance, yet the number and mean age of each sex was nearly equal. Secondly, it was impossible to analyze the excretion volume of Na, K, Mg and Tau a day because the number of participants successful in a collection of 24-hour urine was inadequate. Consequently, we analyzed those excretion levels of spot urine instead of 24-hour urine, because the good correlation between creatinine ratio of Tau in spot urine and the total volume in 24-hour urine was detected in previous study [34] as well as Mg [8]. We supposed that Mg/cre and Tau/cre in spot urine could be useful for alternative markers of one-day excretion volume of Mg and Tau respectively and that could be available for evaluating risks of coronary heart diseases and diabetes.

The main implication of our results is that low urinary Mg and Tau levels predict increased MS risks in Australian Aboriginals. Mg deficiency would lead less activity of enzymes and insulin resistance. Tau has beneficial effects for lipid metabolisms. In addition, both Mg and Tau have cardioprotective and antihypertensive effects. These data support the hypothesis that diet rich in Mg and Tau may help to prevent MS risks. It is needed to confirm the association of Mg and Tau with MS risks in additional large prospective studies.

5. Conclusion

In conclusion, low urine Mg/cre and/or Tau/cre could be associated with MS prevalence in Australian Aboriginals, in part, via the effects on obesity and dyslipidaemia.

Abbreviations

BMI:	Body mass index
BP:	Blood pressure
CARDIAC Study:	Cardiovascular Diseases Alimentary Comparison Study
CI:	Confidence interval
DBP:	Diastolic blood pressure
K/cre:	Potassium-creatinine ratio
HbA1c:	Haemoglobin A1c
HDL-C:	High-density lipoprotein cholesterol
HR:	Heart rate
IDF:	The International Diabetes Federation
LDL-C:	Low-density lipoprotein cholesterol
Mg/cre:	Magnesium-creatinine ratio
MS:	Metabolic syndrome
Na/cre:	Sodium-creatinine ratio
Na/K:	Sodium-potassium ratio
OR:	Odds ratio
SBP:	Systolic blood pressure
Tau:	Taurine
Tau/cre:	Taurine-creatinine ratio
TC:	Total cholesterol
TG:	Triglycerides
WC:	Waist circumference.

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Research Article

Cardiovascular Disease-Related Lifestyle Factors among People with Type 2 Diabetes in Pakistan: A Multicentre Study for the Prevalence, Clustering, and Associated Sociodemographic Determinants

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Background. We evaluated the prevalence and clustering pattern of cardiovascular disease (CVD) related lifestyle factors and their association with CVD among patients with type 2 diabetes. We also examined the association of these factors with various sociodemographic characteristics. *Methods*. A total of 1000 patients with type 2 diabetes were interviewed in a cross-sectional, multicenter study in out-patient clinics in Karachi, Pakistan. *Results*. In this study 30.3% study participants had CVD. Majority of the patients were physically inactive and had adverse psychosocial factors. Forty percent of the study participants were exposed to passive smoking while 12.7% were current smokers. Only 8.8% of study subjects had none of the studied lifestyle factor, 27.5% had one, while 63.7% had two or three factors. CVDs were independently associated with physical inactivity, adverse psychosocial factors, passive smoking and clustering of two or three lifestyle factors. Physical inactivity was more prevalent among females and patients with no/less education. Proportion of adverse psychosocial factors were higher among females, elders and patients with no/less education. Clustering of these lifestyle factors was significantly higher among females, elderly and no/less educated patients. *Conclusion*. These results suggest the need of comprehensive and integrated interventions to reduce the prevalence of lifestyle factors.

1. Introduction

Cardiovascular disease (CVD) is known to be the leading cause of mortality worldwide resulting in 17.1 million deaths, with 13 million deaths attributed to coronary heart disease and stroke alone; of these, more than 80% of deaths has occurred in low- to middle-income countries [1]. It is projected that by the year 2030, CVD-related mortality will rise up to 25 million, mainly from heart disease and stroke [1]. Similarly, global statistics on diabetes are also alarming, as the disease is rapidly increasing worldwide and future projections of its burden are reported to rise particularly in Pakistan and other developing countries [2, 3].

It is evident that diabetes is an independent risk factor for CVD, and people with diabetes are three to four times more likely to develop CVD [4, 5]. The development of CVD in diabetic patients is a cause of concern, as it is a major reason for hospitalization, premature morbidity, disability,

and mortality [6, 7] which lead to an increased cost of care. It is reported that over 70% of the cost attributed to diabetes care is associated with its cardiovascular complications [6].

Lifestyle behaviors such as lack of exercise, psychosocial factors, and exposure to smoking further increase the risk of developing CVD [8–12] and are also highly prevalent in less developed countries [13, 14]. On the other hand, prevention and modification of these unhealthy behaviors can lead to reduction in CVD and resultant mortality [13, 15]. Literature reveals that at least 80% of CVD (coronary heart disease and cerebrovascular diseases) could potentially be avoided by adopting healthy lifestyle [1, 15].

The clustering of such unhealthy lifestyle practices has very important implications for both public health practitioners as well as for clinicians. It is well known that the risk of developing CVD multiplies many folds when related lifestyle risk factors coexist as compared to their individual risk [13]. Numerous studies have identified the clustering pattern of CVD-related factors among various groups of population [16, 17]. A study from Japan reported the clustering of cardiovascular risk factors, but the study mainly focused on biological risk factors such as glucose intolerance, dyslipidemia, and hyperuricemia [17]. Recently, Khuwaja and Kadir reported the clustering of lifestyle risk factors in Pakistan [13], but the study participants did not include a high-risk population for CVD such as patients having diabetes. We therefore conducted this study among diabetic patients to assess the prevalence and clustering pattern of CVD-related lifestyle risk factors and their associations with CVD. We also aimed to identify the sociodemographic characteristics associated with these lifestyle risk factors.

2. Materials and Methods

This multicentre cross-sectional study was conducted in four outpatient clinics in Karachi, the largest city and economic hub of Pakistan with a population of over 16 million, which represent all ethnicities and socioeconomically diverse populations in the country. An attempt to capture a wide spectrum of clinical and socioeconomic factors was made by enrolling study participants from four different clinics including family medicine, internal medicine, specific diabetes care, and endocrinology clinics representing both public and private sectors.

All patients having type 2 diabetes visiting their respective clinics for follow-up visits were consecutively recruited till the final sample size was achieved. We considered patients having type 2 diabetes who were labeled as "type 2 diabetic patients" by their treating physician and recorded in their medical files. However, patients suffering from type 1 diabetes or women with gestational diabetes were excluded. In this study, we were not expecting any adverse event to study participants; even so, prior to enroll in the study, consent was obtained from all the study participants. Participants were assured about the confidentiality and anonymity of their information, and all efforts were made to ensure privacy. After reviewing the study protocol and questionnaire, permission was granted from all the concerned clinics to conduct this study in their clinics.

Face-to-face interviews were conducted to get the required information, and each interview took about 20 minutes. Pretested structured questionnaire was used to obtain information about sociodemographic (gender, age, and education level) and lifestyle risk factors (level of physical activity, psychosocial history, smoking status, and exposure to passive smoking). Physical activity was assessed by using International Physical Activity Questionnaire (IPAQ) [18]. Having either anxiety and/or depression was used as proxy indicator for adverse psychosocial factors. The questionnaire used to assess the presence of anxiety and depression was Hospital Anxiety and Depression Scale (HADS) [19]. This tool is validated in national language of Pakistan (Urdu) [20] and was used extensively to study anxiety and depression among various outpatient as well as inpatient settings. One of its main features is that the items, which could relegate to problems such as insomnia, unemployment, eating disorders, headache, and fatigue, have been excluded, in order to avoid false positive cases among persons with somatic diseases. The HADS-D (Depression) covers mostly anhedonia and loss of interest, which form the core of depression symptoms, whereas HADS-A (Anxiety) covers mainly the fields of tension and worry. The HADS questionnaire consists of 14 items (sentences-questions) with answers in four grades on a Likert scale. It has seven questions regarding anxiety and seven for depression. Maximum sum was 21 for each scale. HADS uses >8 as a "cutoff" score. A score up to 8 indicates that the individual is free of symptoms, and a score beyond 8 defined that the symptomatology of anxiety or depression is present.

The variables which included blood pressure, glycemic levels, lipid profile, height, and weight were noted/verified from patients' medical records. Body mass index (BMI) was calculated as weight in kilograms divided by height in meter squares. Study participants were classified as obese if their BMI $> 25\,\text{kg/m}^2$. Hypercholesterolaemia was defined according to ATP III criteria (≥ 200 mg/dL). Individuals were classified as hypertensive if they were previously diagnosed and currently on antihypertensive medication. However, participants in whom elevated levels of blood pressure were discovered for first time at the day of interview (indexed visit) were not included in hypertensive category, as it is recommended to have at least two elevated blood pressure readings at two different times. Cardiovascular disease (coronary artery disease and/or stroke) was considered to exist if there was a history of coronary heart disease (angina, myocardial infarction) verified through medical records of a prior episode and confirmed by work-up including electrocardiography, echocardiography, and exercise treadmill test, while having stroke was solely labeled on the basis of patient's history along with file note verification of treating physician. CVD-related lifestyle factors such as physical inactivity were defined as not doing moderate to vigorous activity for 30 minutes or more, at least 4 days in a week, and participants falling in this group were categorized as "physically inactive." Patients having anxiety and or depression were categorized positive for "adverse psychosocial factor." Persons smoking

any number of cigarettes per day were classified as "current smokers." Passive smoker for this study was defined as any person who has been exposed to second-hand smoke for at least 30 minutes in a day, for at least 5 days of the week either at home and or at work place, for last six months, and more.

To analyze the defined objectives of this study, the initial required sample size was 895 study participants. However, we approached 1000 consecutively eligible type 2 diabetic patients from the four clinics to participate in the study. In total, 87 patients refused to participate in the study, while the required information was incomplete and missing for 26 patients. Therefore, the final analysis was performed on 887 study participants. All the data was collected within eight-month duration. All the data was collected, cleaned, and validated by medical graduates specifically trained for this task.

The data was analyzed using the Statistical Package for Social Sciences (SPSS) version 19. Mean and standard deviations (SD) for continuous variables and percentages for categorical variables and lifestyle factors were calculated separately. Clustering of lifestyle factors was studied as none, one, and two or three. In model I, multivariable analysis using multiple logistic regressions was carried out to evaluate the association of combined effect of lifestyle factors with CVD among patients with type 2 diabetes, while in model II, the association of clustering pattern of lifestyle factors with CVD was assessed. Age, sex, educational status, and body mass index are well known confounders for lifestyle factors and CVD [7, 13]; we therefore adjusted these variables in both models to evaluate the independent association of CVD with lifestyle risk factors and their clustering pattern. Cross-tabulation and chi-square test of significance was applied to identify the association of lifestyle factors and clustering pattern by gender, age, and educational status. All smokers in this study were men; hence, we did not include it in the final model.

3. Results

Baseline characteristics of the study participants are presented in Table 1. In all, 43.6% of the study participants were up to the age of 50 years, and there was a preponderance of females (57.4%). The majority of patients (59.4%) had diabetes for more than five years. Over 78% of study participants were non smokers, while 9% were past smokers. About half of the patients reported family history (siblings, parents, and grandparents) of diabetes. In all, 41% of the diabetic patients were also concurrently diagnosed to have hypertension; however, overall mean systolic and diastolic blood pressure levels of study participants were substantially high. There were also higher mean values of lipid profile (total cholesterol, low-density lipoproteins, and triglycerides) and body mass index. Similarly, the glycemic levels were substantially high among study participants. Over 80% of the study participants were taking oral hypoglycemic agents, while one-third of the patients were also taking low-dose aspirin on regular basis.

Table 1: Background characteristics of study participants.

Characteristics	$N = 887$
Age (in years)	
Up to 50	387 (43.6)
More than 50	500 (56.4)
Sex	
Females	509 (57.4)
Males	368 (42.6)
Diabetes duration*	
1 to 5 years	360 (40.6)
More than 5 years	527 (59.4)
Status of smoking	
Nonsmoker	694 (78.3)
Past smoker	80 (9.0)
Current smoker	113 (12.7)
Type of treatment for glycemic control	
Diet and exercise	85 (9.6)
Single oral drug	351 (39.5)
More than one oral drug	367 (41.4)
Insulin therapy	84 (9.5)
Taking low-dose aspirin	
Yes	294 (33.1)
No	593 (66.9)
Family history of diabetes	
Yes	420 (47.2)
No	467 (52.8
Coexist hypertension	
Yes	363 (40.9)
No	524 (59.1)
Systolic blood pressure	134.1 ± 18.2
Diastolic blood pressure	83.9 ± 11.4
Total cholesterol	202.1 ± 34.1
Low density lipoproteins	155.4 ± 45.1
Triglycerides	209.4 ± 86.1
Fasting blood glucose	198.6 ± 79.7
Postprandial blood glucose	256.2 ± 106.5
HbA_1C**	7.9 ± 1.4
Body mass index	27.7 ± 5.1

Data are presented in means ± SD or n (%).
*Duration since diagnosis of diabetes; ** $n = 285$.

In Table 2, proportion distribution and clustering pattern of lifestyle factors and their associations with CVD are described. Amongst all, 30.3% (95% CI = 27.2–33.2) of the diabetic patients had CVD. Over 65% of participants were physically inactive, 71.4% had anxiety and/or depression, and 40.1% were exposed to passive smoking. In the univariate analysis, all the three studied lifestyle factors and their clustering pattern were found to be significantly associated with CVD (physical inactivity: crude OR = 1.7, 95% CI = 1.2–2.3; psychosocial factors: crude OR = 2.2, 95% CI = 1.6–3.2; passive smoking exposure: crude OR = 1.7, 95% CI = 1.3–2.3; clustering of any two or three lifestyle factors: crude OR = 6.1, 95% CI = 2.7–13.7). However, the confounders

Table 2: Proportion distribution and clustering pattern of lifestyle risk factors and their associations with CVD among study participants.

Characteristics	Overall *n*	Having CVD *n* (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Model I				
Physical activity				
Yes	309	72 (23.3)	1	1
No	578	197 (34.1)	1.7 (1.2–2.3)	1.6 (1.2–2.3)
Psychosocial factors				
No	254	49 (19.3)	1	1
Yes	633	220 (34.8)	2.2 (1.6–3.2)	1.9 (1.4–2.8)
Passive smoking				
No	531	136 (25.6)	1	1
Yes	356	133 (37.4)	1.7 (1.3–2.3)	1.7 (1.2–2.3)
Model II				
Clustering of lifestyle factors				
No factor	78	7 (9.0)	1	
1 factor	244	51 (20.9)	2.7 (1.2–6.2)	
2 or three factors	565	211 (37.3)	6.1 (2.7–13.7)	

After adjustment for age, sex, educational status, and body mass index.

(age, sex, educational status, and body mass index) reported in the literature were not fulfilling the criteria of being a confounding factor in this study except age which was confounded by the exposures of physical inactivity and clustering of lifestyle factors.

In model I of the final multivariable analysis (Table 2), the odds of having CVD were higher among those who were physically inactive (adjusted OR = 1.6; 95% CI = 1.2–2.3) and had anxiety and/or depression (Adjusted OR = 1.9; 95% CI = 1.4–2.8), and among those exposed to passive smoking (adjusted OR = 1.7; 95% CI = 1.2–2.3) while adjusted for age, sex, educational status, and body mass index. In another model, the odds of having CVD increased with the clustering of lifestyle factors: for having any one factor (adjusted OR = 2.7; 95% CI = 1.2–6.2) and for clustering of two or three factors (adjusted OR = 6.1; 95% CI = 2.7–13.7) after adjusting for the similar factors described in the first model.

The association of sociodemographic characteristics with CVD-related lifestyle factors and their clustering pattern are presented in Table 3. In comparison to males, females were more physically inactive (57.1% versus 71.1%; $P < 0.001$). Similarly those with no/less education were more inactive compared to their counterparts having education of more than five years (77.7% versus 53.6%; $P < 0.001$). Significant majority of study participants having anxiety and/or depression were females (74.5%), elderly (77.0%), and having no/less education (75.6%) compared to their counterparts. Exposure of passive smoking was almost equally distributed among all groups of sociodemographic classes. Clustering of two or three CVD-related lifestyle factors was significantly higher among females compared to males (69.9% versus 55.3%; $P < 0.001$) and elderly compared to younger patients (68.1% versus 58.0%; $P = 0.004$). Clustering of these factors was also higher among study participants having no/less education compared to those with more education (71.8% versus 56.2%; $P < 0.001$).

4. Discussion

It is well known that modifiable lifestyle factors such as physical inactivity, psychosocial stress, and smoking result in an increased risk of CVD, while control of the same substantially decreases the development of CVD [1, 15]. The results of our study are consistent with those of previous studies and highlight the importance of adequate control of these lifestyle factors, particularly among high-risk people like diabetics, to prevent the development and progression of CVD and its consequences.

In a recently conducted study on healthy Canadian adults [21], only 10% of the study population was found to be physically inactive, as opposed to 60% healthy adults in Pakistan [13]. The presence of such high levels of physi-cal inactivity is particularly harmful among people with diabetes, as the presence of diabetes itself confers increased cardiovascular risk, and the coexistence of physical inactivity further amplifies this risk. The high prevalence of physical inactivity in an earlier study from Pakistan [13] and in our study may be attributed to the lack of awareness regarding the role and benefits of exercise in preventing CVD as highlighted from the earlier studies in Pakistan [22]. Furthermore, watching television and playing computer games have considerably risen in this part of the world, along with unavailability of safe playgrounds and walking tracks rendering majority of the population physically inactive [13].

Furthermore, the burden of psychosocial factors which predispose to anxiety and depression is also reported to be more prevalent in developing countries [23]. By using HADS

Table 3: The association of clinical and sociodemographic determinants with CVD-related lifestyle factors and their clustering pattern among study participants.

Lifestyle factors	Gender			Age (in years)			Education (in years)			Current Smoking			Obesity			Hypercholesterolaemia		
	Male	Female	*P* value	Up to 50	> 50	*P* value	> 5	0 to 5	*P* value	Yes	No	*P* value	Yes	No	*P* value	Yes	No	*P* value
Physical activity			<0.001			0.18			<0.001			0.33			0.41			0.26
Yes	42.9	28.9		36.6	33.5		46.4	22.3		38.9	34.2		35.8	32.7		36.6	32.9	
No	57.1	71.1		63.4	66.5		53.6	77.7		61.1	65.8		64.2	67.3		63.4	67.1	
Psychosocial factors			0.02			<0.001			0.007			0.001			0.29			0.07
No	32.8	25.5		35.8	23.0		32.5	24.4		15.9	30.5		27.6	31.0		26.0	31.5	
Yes	67.2	74.5		64.2	77.0		67.5	75.6		84.15	69.5		72.4	69.0		74.0	68.5	
Passive smoking			0.40			0.51			0.42			0.22			0.03			0.06
No	59.3	60.3		59.8	59.9		60.3	59.4		65.5	59.0		62.4	54.4		62.8	56.6	
Yes	40.7	39.7		40.2	40.1		39.7	40.6		34.5	41.0		37.6	45.6		37.2	43.4	
Clustering of lifestyle factors			<0.001			0.004			<0.001			0.35			0.87			0.55
No factor	12.7	5.9		11.3	6.8		12.4	4.9		5.3	9.3		8.7	8.9		8.0	9.7	
1 factor	32.0	24.2		30.7	25.1		31.5	23.2		30.1	27.1		28.1	26.3		28.6	26.3	
2/3 factors	55.3	69.9		58.0	68.1		56.2	71.8		64.6	63.6		63.2	64.8		63.4	64.0	

Data is presented in percentages.

scale, our study showed that more than 70% of the study participants were suffering from anxiety and/or depression. However, results of a study conducted in the United Kingdom using the same scale revealed substantially lesser proportion of these disorders among diabetic patients [24]. This sharp difference in prevalence of mood disorders may be attributed to the high levels of poverty, poor socioeconomic conditions, and scarce health care facilities and resources in developing countries.

It is evident that smoking is a strong risk factor for developing CVD in general [1] and among diabetics in particular [7]. It is also reported that passive smoking also increases the risk of chronic diseases including CVD [8, 10]. A community-based survey recently reported that about half of the study participants in Pakistan were exposed to passive smoking [25]. Using the same definition of pas-sive smoking in our study, over one-third of the diabetic population was found to be exposed to passive smoking. This high proportion of exposure reflects the lack of awareness about the hazards of passive smoking among the general population. In Pakistan, in spite of laws and constitutions to restrict smoking at public places, people freely smoke in public transport, shopping malls, restaurants, and even many of the work places and offices. This dreadful scenario exposes higher proportion of people to passive smoking. It is documented that, in Pakistan, up to 34% adults smoke cigarettes [25]. However, in our study, 13% of the study participants were reported as being current smokers and all of them were males. This lower prevalence can be attributed to the fact that in this study, interviews were conducted in the presence of patients' family members/attendants, raising the possibility that majority of the participants did not admit that they smoked, as it is viewed as a socially unacceptable habit in this part of the world. Another possible explanation for the lower prevalence of smoking may be due to the fact that patients might have given up smoking after developing diabetes and its complication. Furthermore, previous work reported was done only in men [25], and it is well reported that when compared to women, smoking among men is more prevalent in both developed as well as in developing countries [13, 26].

Recently, data collected from a multisite five Asian countries survey [27] revealed that a substantial proportion of study population had clustering of lifestyle risk factors, and similar findings were also reported in a community-based study from urban Pakistan [13]. In our study, a very small proportion of the participants were found to have none of CVD-related lifestyle factors, while one-fourth had one of these risks, and majority had clustering of two or three factors. This pattern of unhealthy lifestyle clustering reflects the possibility of poor awareness and harmful attitude and practices regarding healthy behaviors. Results of this study also endorse the existing literature that physical inactivity, adverse psychosocial factors, and exposure to smoking are strongly associated with CVD [1, 15], and clustering of these factors enhances the risk further [13, 28].

With the increase in prevalence of CVD-related modifiable lifestyle factors among high-risk population like diabetics in developing countries, identification of specific target groups within such population is important in order to introduce comprehensive and integrated preventive strategies aimed to reduce CVD. The presence of cardiovascular risk factors in both the genders has been studied extensively. Though literature from the Western world has identified females to have a lower risk of developing CVD [29], evidence from South Asia reveals that both men and women bear an equal risk of developing these diseases [30]. Furthermore, a study from Pakistan reports women to have a greater risk of developing CVD than men [31]. The results of our study reveal that all the CVD-related lifestyle factors and their clustering are significantly higher among women. Hence, the female population in our study was found to be at higher risk of developing CVD owing to increased prevalence of unhealthy lifestyle behaviors. The presence of increased CVD-related risk factors in women can be attributed to the fact that up to 50% males have been reported to smoke at home [25], thus exposing the females to passive smoking as well. Furthermore, the social status of women in our patriarchal culture leads to increased prevalence of psychosocial risk factors among them. Moreover, cultural restrictions limit females to going outside their homes with-out an accompanying male family member resulting in decreased likelihood for joining sport physical and exercise centers and gymnasiums.

It is well known that increasing age is associated with increased cardiovascular risk due to acceleration of atherosclerosis [32] and other cardiovascular risk factors [16]. This study showed that up to 80% of the older population was found to have anxiety and/or depression. This increased psychosocial suffering may be attributed to the presence of more chronic illnesses and CVD as well as challenging life situations such as being more isolated and dependent. Clustering of two or more lifestyle risk factors was also found to be present in up to 70% of the elderly patients, providing further explanation for increased cardiovascular risk in this age group. These results are in accordance with results of various studies conducted elsewhere [16, 27].

It has been reported that higher level of education has a protective role with regard to healthy lifestyle and behaviors [33, 34] as it leads to greater awareness and improved conscience regarding health. The results of our study also suggest low prevalence of CVD-related factors such as physical inactivity and anxiety and/or depression among people having more years of education. Similarly, clustering of these risk factors was in lesser proportion among the educated participants, reinforcing the fact that people with less education have an increased risk of unhealthy lifestyle practices.

The overall metabolic control (blood pressure levels, glycemic control, lipid levels, and body mass index) of our study participants was poor. It is well reported that the management and control of diabetes is a real challenge for health care providers as well as people having diabetes [7, 22]. Many possible reasons and explanations exist for poor control of disease, like lack of knowledge about the disease among diabetic patients [35], poor quality of care

provided by treating physicians [22], and excessive cost for the management of diabetes [6, 36] which many patients cannot afford in resource-constrained countries.

This study also has certain limitations. Since this study employs a cross-sectional study design, temporal relation between CVD and its lifestyle factors could not be identified. Coronary artery disease is often silent with regards to symptoms in diabetic subjects, and therefore noninvasive studies (such as myocardial scintigraphy and dobutamine stress echocardiography) should have been performed for a thorough evaluation of the cardiac status. However, due to cost and resource limits, we have not evaluated the cardiac status using these tests. Similarly, HbA_1C, another comparatively costly test, is recommended to evaluate the overall glycemic control, but it was only reported in 285 patients. Therefore, we cannot comment about the overall glycemic control of study participants during the period of time. All the smokers in this study were male; hence, this important factor was not included in the final analysis. Possibility of recall bias exists regarding some information stated by patients. We did not inquire about the dietary habits of study participants which is an imperative lifestyle factor for CVD. All the study centers were from one metropolitan city; therefore, it may not be possible to generalize the findings to the rural population that might have different behaviors. Furthermore, being a cross-sectional study, we cannot assess the impact of successful medical treatment on the occurrence of CVD. Age, sex, educational status, and body mass index are well known confounders for lifestyle factors with CVD [7, 13, 37]; however, in this study except for the age, other established confounders were not found to be associated with CVD, lifestyle risk factors, and their clustering pattern.

5. Conclusion

This multicenter study highlights very high prevalence and clustering of CVD-related lifestyle factors, particularly physical inactivity, anxiety, depression, and exposure to passive smoking. The presence of such a high burden of these factors among diabetic patients is a cause of concern and requires urgent interventions in order to prevent and control CVD. These interventions should be based on a comprehensive and integrated approach covering all of these lifestyle factors rather than any single factor to anticipate their cumulative effects. We recommend that health care providers should provide awareness and education regarding CVD risk factors and their prevention to patients and their families/caregivers. Furthermore, safe walking tracks, playgrounds, and relaxation avenues should also be made available to allow more people to engage in physical activities and relaxation programs. Laws should be strictly imposed to prohibit smoking at public places. Women should be empowered and be allowed to follow a healthy lifestyle. Further research is suggested to explore this very important avenue in more detail and to design and test interventions accordingly.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Research Article

Lifestyle Practices and Cardiovascular Disease Mortality in the Elderly: The Leisure World Cohort Study

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Modifiable behavioral risk factors are major contributing causes of death, but whether the effects are maintained in older adults is uncertain. We explored the association of smoking, alcohol consumption, caffeine intake, physical activity, and body mass index on cardiovascular disease (CVD) mortality in 13,296 older adults and calculated risk estimates using Cox regression analysis in four age groups (<70, 70–74, 75–79, and 80+ years). The most important factor was current smoking, which increased risk in all age-sex groups. In women, alcohol consumption (≤3 drinks/day) was related to decreased (15–30%) risk in those <80 years old; in men, 4+ drinks/day was associated with reduced (15–30%) risk. Active 70+ year olds had 20–40% lower risk. Both underweight and obese women were at increased risk. Lifestyle practices impact CVD death rates in older adults, even those aged 80+ years. Not smoking, moderate alcohol consumption, physical activity, and normal weight are important health promoters in our aging population.

1. Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in the United States [1]. It kills one American every 38 seconds and accounts for 1 of every 2.9 deaths, more deaths than any other major cause of death. The 2006 overall death rate due to CVD was 262.5, but the rate increases substantially with age. It is estimated that more than 1 in 3 men and around 1 in 4 women aged 75 and over currently live with the condition. This age group is the fastest growing segment of the US population.

Although CVD is the leading cause of death, modifiable behavioral risk factors are major contributing or actual cause of this mortality [2]. In both younger and older age groups the five key risk factors for CVD are hypertension, high serum cholesterol, diabetes, body mass index, and smoking. Additional lifestyle practices including alcohol consumption and exercise are also related to the disease. The majority of studies of alcohol intake have found J- or U-shaped risk curves with light to moderate drinkers having a lower risk of atherosclerotic CVD than nondrinkers or heavy drinkers [3]. For physical activity, a dose-response relationship exists between duration and intensity of activity and CVD disease risk, with even relatively low levels of physical activity providing some benefit compared with inactivity [4].

Although these lifestyle practices have substantial health benefits and reduce mortality, few studies have examined their impact in combination and on survival beyond age 75. As part of a prospective cohort study of the effect of modifiable lifestyle practices on longevity and successful aging, we explored the association of smoking, alcohol consumption, caffeine intake, physical activity, and body mass index on CVD mortality in a large cohort (over 13,000) of elderly (median age 74 years) men and women followed for 26 years.

2. Materials and Methods

The Leisure World Cohort Study was established in the early 1980s when 13,978 (8877 female and 5101 male) residents of a California retirement community (Leisure World Laguna Hills) completed a postal health survey. The population

and the cohort are mostly Caucasian, well educated, upper-middle class, and elderly.

The baseline survey asked about demographic information (birth date, sex, marital status, number of children, height, weight); brief medical history (high blood pressure, angina, heart attack, stroke, diabetes, rheumatoid arthritis, fractures after age 40, cancer, gallbladder surgery, glaucoma, cataract surgery); medication use (hypertensive medication, digitalis, nonprescription pain medication); personal habits (cigarette smoking, exercise, alcohol consumption, vitamin supplement use); usual frequencies of consumption of 58 food (or food groups) that are common sources of dietary vitamin A and C; beverage intake (milk, regular coffee, decaffeinated coffee, black or green tea, and soft drinks).

2.1. Lifestyle Factors. Based on their reported smoking history we classified participants as never, past, or current smokers.

Consumption of alcoholic beverages was asked separately for wine (4 oz.), beer (12 oz.), and hard liquor (1 oz.), each equivalent to about 1/2 oz. of alcohol. Response choices for average weekday consumption were never drink, less than 1, 1, 2, 3, and 4 or more drinks. Total alcohol intake per day was calculated by summing the number of drinks consumed of each type [5]. Individuals were then categorized into four groups: 0, $\leq$1, 2-3, and 4+ drinks/day.

We estimated daily caffeine intake by summing the frequency of consumption of each beverage and chocolate multiplied by its average caffeine content (mg/standard unit) as 115, 3, 50, 50, and 6 for regular coffee, decaffeinated coffee, tea, cola soft drinks, and chocolate, respectively [6]. Caffeine intake was categorized as <50, 50–99, 100–199, 200–399, 400+ mg/day.

Body mass index (weight (kg)/height $(m)^2$) was calculated based on self-reported height and weight at baseline and categorized according to federal guidelines: underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (30+) [7, 8].

The amount of time spent on physical activities was ascertained by asking, "On the average weekday, how much time do you spend in the following activities?—***active outdoor activities*** (e.g., swimming, biking, jogging, tennis, vigorous walking), ***active indoor activities*** (e.g., exercising, dancing), ***other outdoor activities*** (e.g., sightseeing, boating, fishing, golf, gardening, attending sporting events), ***other indoor activities*** (e.g., reading, sewing, crafts, board games, pool, attending theater or concerts, performing household chores), ***watching TV***." For each question, the response categories were 0 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3-4 hours, 5-6 hours, 7-8 hours, 9 hours or more per day. The time spent per day in active exercise was calculated by summing the times spent in active outdoor activities and active indoor activities and in other activities by summing the times spent in other outdoor activities and other indoor activities.

2.2. Determination of Outcome. Followup of the cohort is maintained by periodic resurvey and determination of vital status by search of governmental and commercial death indexes and ascertainment of death certificates. Participants were followed to death or December 31, 2007, whichever came first. To date 55 cohort members have been lost to follow up; search of death indices did not reveal that these individuals were deceased. Cause of death was determined from death certificates or by codes provided by the California Department of Vital Statistics. We included as CVD deaths those coded 390–459 in *International Classification of Diseases 9* (years 1981–1998) and I00–I99 in *International Classification of Diseases 10* (years 1999–2007).

2.3. Statistical Analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained using Cox regression analysis [9]. For the Cox models, chronological age was used as the fundamental time scale with study entry being the age when the survey was completed and the event of interest being age at CVD death. Separate analyses were performed for four age groups (<70, 70–74, 75–79, and 80+ years) within the two sexes. HRs were calculated for each lifestyle factor adjusted for age (continuous) and then additionally adjusted for the other lifestyle variables plus seven separate histories (no, yes) of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). No adjustment in the P values was made for multiple comparisons.

To account for the possibility that recent disease development may have influenced lifestyle practices as well as be related to mortality, we repeated the analyses excluding the first five years of followup.

Previous reports present details of the methods and validity of exposure and outcome data [10–15]. The Institutional Review Boards of the University of Southern California and the University of California, Irvine approved the study.

3. Results

After excluding 682 subjects with missing information on the lifestyle factors, we analyzed data on 13,296 subjects (8444 women and 4852 men). At study entry, the participants ranged in age from 44 to 101 years (median: 74 years). By December 31, 2007, the subjects had contributed 180,122 person-years of followup (median: 13.5 years), and 11,929 (7367 women and 4562 men) had died. Age at death ranged from 59 to 108 years (median: 87 years). Over half of all deaths were due to CVD: 4575 women and 2656 men.

Table 1 presents selected characteristics for the participants by sex. Differences between males and females were highly statistically significant ($P < .001$) for all variables except caffeine ($P < .01$). Because of these differences as well as the different patterns of smoking (amount and duration), alcohol (type), activities (type), and body-build between men and women and the fact that women live longer on average than men and for comparison with other studies limited to a single sex, we performed separate analyses for men and women.

Tables 2 and 3 show the age-adjusted and multivariable-adjusted HRs of CVD mortality for the various lifestyle variables for women and men, respectively. Adjustment

Table 1: Characteristics of the cohort by sex.

	Women (n = 8444)		Men (n = 4852)	
	Mean	SD	Mean	SD
Age at baseline (years)	73	7.4	74	7.2
Age at last followup (years)	88	7.1	86	6.9
Followup years	15	7.4	12	7.1
Active activities (hrs/day)	0.91	1.1	1.0	1.3
Other activities (hrs/day)	4.4	2.6	3.6	2.7
Alcohol (drinks/day)	1.2	1.2	1.6	1.5
Caffeine (mg/day)	169	166	177	172
Body mass index (kg/m^2)	23	3.5	24	2.9
	No.	%	No.	%
Medical history				
High blood pressure	3433	41	1764	36
Angina	806	9.6	714	15
Heart attack	560	6.6	798	16
Stroke	308	3.7	344	7.1
Cancer	1078	13	452	9.3
Diabetes	421	5.0	405	8.3
Rheumatoid arthritis	564	6.7	218	4.5
Smoke				
Never	4627	55	1618	33
Past	2750	32	2812	58
Current	1067	13	422	9
Deceased	7367	87	4562	94
Deceased from cardiovascular disease	4525	54	2656	55

for potential confounders increased the observed HRs for smoking but had limited effect on the others, generally attenuating the observed HRs.

Although caffeine intake showed no consistent effect, the other modifiable factors were related to CVD death. Current smokers had significantly increased (about 40–130%) risk compared with never smokers in all age-sex groups. In women, alcohol consumption ($\leq$3 drinks/day) was related to decreased (about 15–30%) risk compared with abstainers in all but the oldest age group. In men, 4+ drinks/day was associated with reduced (about 15–30%) risk in all but those aged 70–74 years. Women and men aged 70+ years old who participated in active activities, even as little as 1/2 hour/day, had 20–40% lower risk of CVD death compared to those who reported no active activities. The risk decreased with increasing time spent in active activities. Participation in other activities was also associated with reduced risk. However, more time in these activities was needed to show the same reduced risk as for active activities. Underweight and obese women in all age groups were at increased risk of CVD death (though not all groups showed statistically significant effects). Notably overweight women had no increased risk. Underweight men also appeared to be at increased risk, though the number of such men was small (n = 81). Risk was also increased in overweight men aged <75 years compared with their normal weight peers. No effect was seen in older men.

Exclusion of the first five years of followup (including 1826 early deaths) changed the findings slightly. The multivariate-adjusted risk estimates changed by less than 10 percent except for current smokers aged 80+ years (women 1.46 to 1.28, men 2.20 to 2.50), underweight women aged 70–74 years (1.29 to 1.13), obese women aged 75–79 years (1.09 to 1.21), underweight men (aged <70 years, 1.75 to 1.49; aged 70–74 years, 2.76 to 1.84; aged 75–79 years, 1.48 to 1.72; and aged 80+ years, 1.12 to 0.84), obese men aged 80+ years (1.40 to 1.91). HRs for active and other activities in men aged 75+ years were generally attenuated to 1.0, and all became nonsignificant.

4. Discussion

Our study extends the available literature on the CVD survival benefits of several lifestyle practices to the very old. We confirmed the beneficial effect of not smoking, participating in activities, drinking alcohol, and having a normal body mass index. Each of these was associated with reduced CVD death in our elderly men and women, even those aged 80 years and older. Many of the factors were

Table 2: Hazard ratios (HRs) for cardiovascular disease mortality by lifestyle practices, Leisure World Cohort Study, 1981–2007, women by age group.

	No.	Model 1*		Model 2*		No.	Model 1*		Model 2*		No.	Model 1*		Model 2*		No.	Model 1*		Model 2*	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
	Age at entry <70 years (n = 2599)					Age at entry 70–74 years (n = 2151)					Age at entry 75–79 years (n = 2051)					Age at entry 80+ years (n = 1643)				
Smoking																				
Never	1108	1.00		1.00		1060	1.00		1.00		1233	1.00		1.00		1226	1.00		1.00	
Past	986	1.11	0.96–1.29	1.12	0.96–1.30	792	1.02	0.90–1.15	1.03	0.91–1.17	627	1.22	1.08–1.38	1.25	1.10–1.42	345	1.10	0.95–1.28	1.13	0.97–1.31
Current	505	1.86	1.56–2.22	2.04	1.69–2.45	299	1.44	1.21–1.72	1.50	1.25–1.81	191	1.64	1.36–1.98	1.71	1.40–2.09	72	1.29	0.96–1.73	1.46	1.07–1.98
Alcohol consumption drinks/day																				
0	607	1.00		1.00		576	1.00		1.00		544	1.00		1.00		609	1.00		1.00	
≤1	901	0.75	0.63–0.89	0.78	0.65–0.93	721	0.84	0.73–0.97	0.92	0.79–1.06	758	0.83	0.73–0.95	0.85	0.74–0.98	609	0.93	0.81–1.06	1.00	0.87–1.15
2-3	598	0.78	0.64–0.94	0.75	0.61–0.92	485	0.84	0.71–0.98	0.87	0.73–1.02	449	0.75	0.64–0.87	0.72	0.61–0.84	265	0.87	0.73–1.04	0.92	0.76–1.11
4+	493	0.93	0.76–1.13	0.88	0.71–1.08	369	0.95	0.80–1.13	0.95	0.79–1.14	300	0.81	0.68–0.96	0.74	0.62–0.90	160	0.94	0.76–1.16	1.01	0.81–1.27
Caffeine consumption mg/day																				
<50	640	1.00		1.00		559	1.00		1.00		602	1.00		1.00		558	1.00		1.00	
50–99	330	0.90	0.71–1.13	0.95	0.76–1.20	322	0.89	0.74–1.07	0.90	0.75–1.09	286	0.99	0.83–1.18	1.03	0.86–1.22	240	0.90	0.75–1.08	0.91	0.76–1.09
100–199	592	0.95	0.79–1.15	0.97	0.80–1.17	560	0.87	0.75–1.02	0.88	0.76–1.03	535	0.95	0.82–1.10	1.00	0.86–1.16	433	0.88	0.76–1.03	0.89	0.76–1.04
200–399	716	0.91	0.75–1.09	0.92	0.76–1.11	529	0.84	0.72–0.98	0.87	0.74–1.02	486	1.03	0.89–1.19	1.07	0.92–1.25	327	0.77	0.65–0.91	0.75	0.63–0.90
400+	321	1.11	0.89–1.40	1.15	0.92–1.45	181	0.77	0.61–0.98	0.76	0.69–0.97	142	0.88	0.70–1.10	0.90	0.71–1.14	85	0.88	0.67–1.15	0.85	0.64–1.12
Active activities hrs/day																				
None	392	1.00		1.00		372	1.00		1.00		466	1.00		1.00		582	1.00		1.00	
≤1/2	716	0.94	0.76–1.16	0.99	0.80–1.22	642	0.82	0.69–0.97	0.82	0.69–0.97	661	0.84	0.73–0.98	0.83	0.72–0.97	545	0.86	0.74–0.99	0.89	0.77–1.04
3/4–1	992	0.77	0.63–0.94	0.82	0.67–1.01	772	0.72	0.61–0.84	0.75	0.63–0.89	689	0.76	0.66–0.88	0.80	0.69–0.93	414	0.68	0.58–0.79	0.71	0.60–0.83
2+	499	0.73	0.58–0.92	0.76	0.61–0.97	365	0.66	0.66–0.81	0.70	0.58–0.86	235	0.72	0.59–0.88	0.81	0.66–0.99	102	0.64	0.49–0.83	0.71	0.54–0.93
Other activities hrs/day																				
<2	238	1.00		1.00		197	1.00		1.00		242	1.00		1.00		268	1.00		1.00	
2-3	881	0.92	0.72–1.17	0.95	0.74–1.21	810	0.90	0.73–1.10	0.88	0.71–1.09	837	0.90	0.76–1.08	0.93	0.77–1.11	702	0.76	0.64–0.90	0.84	0.70–1.00
4-5	754	0.93	0.73–1.18	0.98	0.76–1.25	619	0.78	0.63–0.96	0.83	0.66–1.03	549	0.84	0.70–1.02	0.87	0.72–1.05	408	0.73	0.61–0.88	0.82	0.68–0.99
6+	726	0.84	0.65–1.07	0.85	0.66–1.09	525	0.69	0.55–0.86	0.68	0.54–0.84	423	0.77	0.63–0.94	0.81	0.66–0.99	265	0.65	0.52–0.80	0.72	0.60–0.89
Body mass index kg/m^2																				
<18.5	89	2.19	1.59–3.02	2.36	1.70–3.26	102	1.27	0.96–1.67	1.29	0.96–1.67	124	1.36	1.09–1.70	1.34	1.07–1.69	152	1.45	1.18–1.79	1.50	1.22–1.86
18.5–24.9	1773	1.00		1.00		1473	1.00		1.00		1464	1.00		1.00		1188	1.00		1.00	
25–29.9	580	1.17	1.00–1.37	1.03	0.88–1.21	487	1.06	0.92–1.21	0.97	0.84–1.11	400	0.97	0.84–1.11	0.87	0.75–1.00	261	0.92	0.78–1.09	0.91	0.78–1.08
30+	157	1.39	1.05–1.83	1.13	0.85–1.50	89	1.55	1.19–2.00	1.38	1.06–1.79	63	1.34	0.99–1.81	1.09	0.80–1.48	42	1.44	1.03–2.03	1.39	0.98–1.97

*Model 1: adjusted for age at entry; Model 2: adjusted for age at entry, smoking, alcohol, caffeine, active activities, other activities, body mass index, high blood pressure, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer

Table 3: Hazard Ratios (HRs) for cardiovascular disease mortality by lifestyle practices, Leisure World Cohort Study, 1981–2007, men by age group.

	No.	Model 1*		Model 2*		No.	Model 1*		Model 2*		No.	Model 1*		Model 2*		No.	Model 1*		Model 2*	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
	Age at entry <70 years (n = 1224)					Age at entry 70–74 years (n = 1207)					Age at entry 75–79 years (n = 1289)					Age at entry 80+ years (n = 1132)				
Smoking																				
Never	402	1.00		1.00		372	1.00		1.00		424	1.00		1.00		420	1.00		1.00	
Past	655	1.15	0.95–1.39	1.19	0.97–1.44	709	1.00	0.84–1.18	0.95	0.79–1.13	775	1.16	0.99–1.35	1.13	0.96–1.32	673	1.20	1.03–1.41	1.24	1.05–1.47
Current	167	2.08	1.59–2.73	2.31	1.72–3.10	126	1.57	1.17–2.09	1.47	1.09–2.00	90	1.20	0.87–1.67	1.41	1.00–1.99	39	1.77	1.13–2.76	2.20	1.39–3.49
Alcohol consumption drinks/day																				
0	265	1.00		1.00		224	1.00		1.00		272	1.00		1.00		287	1.00		1.00	
<=1	280	0.94	0.74–1.20	0.91	0.71–1.17	296	0.97	0.76–1.23	1.03	0.81–1.31	311	0.88	0.72–1.08	0.99	0.80–1.22	320	0.87	0.71–1.06	0.81	0.66–1.00
2-3	350	0.63	0.49–0.81	0.64	0.49–0.83	325	0.84	0.67–1.07	0.98	0.76–1.25	353	0.90	0.74–1.10	0.94	0.76–1.16	283	0.86	0.70–1.05	0.77	0.62–0.96
4+	329	0.84	0.66–1.08	0.75	0.58–0.96	362	0.91	0.72–1.15	0.95	0.74–1.21	353	0.78	0.64–0.96	0.77	0.62–0.96	242	0.67	0.53–0.84	0.67	0.52–0.85
Caffeine consumption mg/day																				
<50	274	1.00		1.00		314	1.00		1.00		353	1.00		1.00		355	1.00		1.00	
50–99	182	1.12	0.85–1.49	1.16	0.87–1.54	174	1.11	0.87–1.41	1.02	0.80–1.32	209	0.98	0.79–1.22	0.93	0.74–1.15	161	0.97	0.76–1.24	1.06	0.83–1.35
100–199	265	1.12	0.87–1.45	1.15	0.89–1.50	293	0.87	0.70–1.08	0.88	0.70–1.09	287	0.87	0.71–1.06	0.89	0.73–1.09	272	1.02	0.83–1.24	1.00	0.81–1.22
200–399	327	0.96	0.75–1.23	1.11	0.86–1.43	319	0.93	0.75–1.14	0.97	0.78–1.20	350	0.78	0.64–0.94	0.75	0.61–0.92	260	0.80	0.65–0.99	0.86	0.69–1.08
400+	176	0.98	0.73–1.32	0.93	0.66–1.27	107	0.90	0.66–1.23	0.88	0.64–1.22	90	0.80	0.57–1.10	0.86	0.61–1.20	84	1.00	0.73–1.37	1.09	0.79–1.52
Active activities hrs/day																				
None	179	1.00		1.00		208	1.00		1.00		189	1.00		1.00		306	1.00		1.00	
≤1/2	329	0.97	0.73–1.30	1.01	0.76–1.36	347	0.75	0.59–0.94	0.73	0.57–0.93	523	0.74	0.59–0.92	0.73	0.58–0.91	358	0.90	0.74–1.10	0.90	0.73–1.10
3/4–1	456	1.24	0.95–1.62	1.31	0.99–1.72	414	0.67	0.53–0.84	0.67	0.53–0.84	419	0.69	0.56–0.86	0.66	0.52–0.82	336	0.75	0.61–0.91	0.78	0.64–0.96
2+	260	0.89	0.65–1.21	1.03	0.75–1.41	238	0.56	0.43–0.73	0.58	0.44–0.75	258	0.65	0.51–0.83	0.71	0.55–0.91	132	0.77	0.59–1.01	0.78	0.59–1.02
Other activities hrs/day																				
<2	274	1.00		1.00		261	1.00		1.00		321	1.00		1.00		341	1.00		1.00	
2-3	401	0.76	0.60–0.96	0.74	0.58–0.94	447	0.84	0.68–1.03	0.85	0.69–1.05	474	0.88	0.73–1.06	0.92	0.76–1.11	453	0.81	0.68–0.97	0.80	0.66–0.96
4-5	328	0.87	0.68–1.11	0.91	0.71–1.16	302	0.76	0.61–0.95	0.83	0.66–1.05	321	0.83	0.68–1.01	0.88	0.72–1.08	219	0.89	0.72–1.11	0.90	0.71–1.12
6+	221	0.89	0.68–1.15	0.82	0.63–1.08	197	0.77	0.59–0.99	0.79	0.61–1.03	173	0.84	0.66–1.06	0.96	0.75–1.22	119	0.62	0.47–0.82	0.67	0.51–0.89
Body mass index kg/m^2																				
<18.5	11	1.41	0.45–4.40	1.75	0.55–5.57	14	2.84	1.41–5.74	2.76	1.34–5.67	20	1.33	0.73–2.43	1.48	0.80–2.71	36	1.23	0.80–1.90	1.12	0.71–1.75
18.5–24.9	624	1.00		1.00		725	1.00		1.00		836	1.00		1.00		813	1.00		1.00	
25–29.9	530	1.24	1.04–1.48	1.32	1.10–1.58	432	1.17	1.00–1.38	1.20	1.02–1.42	397	1.09	0.94–1.27	1.06	0.91–1.24	264	0.81	0.68–0.97	0.86	0.72–1.04
30+	59	1.14	0.76–1.71	1.11	0.73–1.67	36	1.55	0.98–2.47	1.50	0.94–2.40	36	0.97	0.62–1.52	1.02	0.64–1.61	19	1.64	0.96–2.80	1.40	0.81–2.42

*Model 1: adjusted for age at entry; Model 2: adjusted for age at entry, smoking, alcohol, caffeine, active activities, other activities, body mass index, high blood pressure, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer

correlated, but each independently predicted risk. The most important single factor was current cigarette smoking.

We previously reported the effects of several of these lifestyle practices on all-cause mortality in this cohort [5, 6, 8, 15]. Although not age stratified, results were similar to those found in the present analysis. Smoking increased risk in both men (1.95) and women (1.67). Alcohol intake showed a small beneficial effect (15% reduction in risk) in both men and women, while a shallow U-shaped association of caffeine intake with mortality was observed in both sexes. The curves for the association of body mass index and all-cause mortality were almost identical for men and women with being underweight increasing risk about 50% and being obese increasing risk 20–25%.

We acknowledge several limitations in our study. The indices of physical activities, alcohol and caffeine intake, and smoking used in this study are crude and self-reported and their reliability and validity were not ascertained. Although our data on other variables are also self-reported, previous studies in our population and others support the reliability of medical history of major chronic disease [10, 13] and of self-reported height and weight [10]. Another limitation is that changes over time in all potential risk factors may affect outcome. Additionally, the subjects in our study were mostly white, highly educated, and of middle social-economic class and therefore not representative of the general population. Although this may limit the generalizability of our results, it offers the advantage of reduced potential confounding by race, education, social-economic class, and presumed access to health care. Additionally, although we adjusted for other risk and potential confounding factors, unrecognized and uncontrolled confounders cannot be ruled out in this or any observational study

This cohort has the advantages of population-based prospective design, large sample size, inclusion of men and women, and data on several lifestyle factors and important confounders, including factors previously found to be related to mortality. The long and almost complete followup of the cohort resulted in a large number of outcome events.

Previous studies have identified lifestyle factors that promote health and increase longevity, including absence of current smoking, drinking a moderate amount of alcohol, participating in moderate exercise, and being of normal body mass index. However, few studies have investigated the combined effect of these lifestyle factors and even fewer have included the very old or, if they did, did not show age-stratified results. In the HALE Project of European subjects aged 70 to 90 years, adherence to a Mediterranean diet (HR = 0.71) and healthful lifestyle (moderate alcohol use (HR = 0.74), physical activity (HR = 0.65), and nonsmoking (HR = 0.68)) was associated with a lower rate of cardiovascular mortality [16]. In the Nurses' Health Study of middle-aged women, those who did not smoke cigarettes, were not overweight, maintained a healthful diet, exercised moderately or vigorously for half an hour a day, and consumed alcohol moderately had an incidence of coronary events that was more than 80 percent lower than that in the rest of the population [17]. In the SENECA (Survey in Europe on Nutrition and the Elderly: A Concerted Action) study of those aged 70–75 years, a high-quality diet, nonsmoking, and physical activity were positively related to 10-year survival in both men and women [18]. For men, the mortality risk for a low-quality diet was 1.25, for inactivity was 1.36, and for smoking was 2.06. For women, the mortality risk for smoking was 1.76 and for inactivity 1.75, much higher than the risk associated with a low-quality diet 1.26. In the NHANES I Epidemiologic Followup Study, smoking predicted survival in middle-aged (45–54 years old) and older (65–74 years old) men and middle-aged women; nonrecreational physical activity predicted survival in older men and women; low body mass index was also associated with shorter survival in older men and middle-aged and older women; drinking was associated with shorter survival in older men [19].

Experimental, clinical, and epidemiological studies suggest mechanisms that provide a biological basis for causal relations between these behavioral risk factors and lower rates of CVD and death. Alcohol increases high-density lipoprotein cholesterol concentrations, decreases platelet aggregation, and affects tissue plasminogen activator and other components of clotting and fibrinolysis [3]. Likewise, physical activity reduces blood pressure, increases high-density lipoprotein cholesterol, decreases triglycerides, improves cardiorespiratory fitness, and produces beneficial changes in inflammatory/hemostatic factors [4].

The reason for increased mortality among the underweight elderly is not clear. Previous all-cause and CVD mortality studies in the elderly have found persons in the lowest weight category at increased risk of death [20, 21]. Being lean, especially in the elderly, may represent a real risk because of nutrient deficiency and physical, functional, and psychological impairment. A balanced and healthful diet may be difficult for some elderly to maintain.

Evidence from epidemiologic studies indicates that the same factors that are associated with increased risk of CVD in middle-aged people are relevant in older adults. Although much effort has focused on the pharmacologic management of hypertension and blood lipid levels with proven success, lifestyle can also affect CVD mortality. Changing these risk factors in older adults can help reduce CVD risk as it does in middle-aged adults and without side effects, high cost, or medical intervention. Together avoidance of smoking, sensible drinking habits, regular physical activity, and maintenance of a healthy body weight may prevent much of the CVD in Western populations. With increasing age, the elderly, however, may become limited by comorbid conditions, decreased functional ability, impaired cognition, and emotional instability and therefore need special programs providing increased physical and social activities and balanced and healthful nutrition. Of course, the greatest benefit will be achieved by adopting these habits early in life and maintaining them throughout the life course.

5. Conclusion

Results in this large elderly cohort with long followup showing a decreased risk of cardiovascular mortality with

several lifestyle practices suggest that maintenance of these is an important health promoter in aging populations.

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Review Article

Molecular Mechanisms in Exercise-Induced Cardioprotection

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Physical inactivity is increasingly recognized as modifiable behavioral risk factor for cardiovascular diseases. A partial list of proposed mechanisms for exercise-induced cardioprotection include induction of heat shock proteins, increase in cardiac antioxidant capacity, expression of endoplasmic reticulum stress proteins, anatomical and physiological changes in the coronary arteries, changes in nitric oxide production, adaptational changes in cardiac mitochondria, increased autophagy, and improved function of sarcolemmal and/or mitochondrial ATP-sensitive potassium channels. It is currently unclear which of these protective mechanisms are essential for exercise-induced cardioprotection. However, most investigations focus on sarcolemmal KATP channels, NO production, and mitochondrial changes although it is very likely that other mechanisms may also exist. This paper discusses current information about these aforementioned topics and does not consider potentially important adaptations within blood or the autonomic nervous system. A better understanding of the molecular basis of exercise-induced cardioprotection will help to develop better therapeutic strategies.

1. Introduction

It is generally accepted that regular exercise is an effective way for reducing cardiovascular morbidity and mortality [1]. Physical inactivity and obesity are also increasingly recognized as modifiable behavioral risk factors for a wide range of chronic diseases, including cardiovascular diseases. Furthermore, epidemiologic investigations indicate that the survival rate of heart attack victims is greater in physically active persons compared to sedentary counterparts [2]. Several large cohort studies have attempted to quantify the protective effect of physical activity on cardiovascular and all cause mortality. Nocon et al. [3] in a meta-analysis of 33 studies with 883,372 participants reported significant risk reductions for physically active participants. All-cause mortality was reduced by 33%, and cardiovascular mortality was associated with a 35% risk reduction. Exercise capacity or cardiorespiratory fitness is inversely related to cardiovascular and all-cause mortality, even after adjustments for other confounding factors [4–6].

The American College of Sports Medicine defines exercise as "*Any and all activity involving generation of force by the activated muscle(s) that results in disruption of a homeostatic state*". Exercise is classified by the type, intensity, and duration of activity. Endurance exercise reflects prolonged and continuous periods of contractile activity (high repetition) against low resistance whereas resistance exercise (strength training) involves short periods of contractile activity (low repetition) against a high opposing resistance, while sprint exercise occurs during short periods of maximal (intense) repetitive contractile activity, where there is a short period of exercise against a low resistance, such as running a 100-m sprint race. However, sprint training can also be performed against high resistance, which results in a combination of resistance and endurance modalities, for example, running with added weights [7].

Although it is clear that exercise promotes a cardioprotective phenotype, a detailed understanding of the cellular mechanisms responsible for this cardioprotection remains incomplete. The cytoprotective mechanisms that have garnered most attention are inducible heat shock proteins and antioxidant enzymes, especially superoxide dismutase (SOD) [8–11]. However, there are numerous clues suggesting that other mechanisms may also be part of exercise-induced

cardioprotective phenotype, and they may have significant roles in the protective process. Improving our understanding of the molecular basis for exercise-induced cardioprotection will play an important role in developing optimal exercise interventions for primary and secondary prophylaxis. The objective of this paper is to summarize the body of knowledge related to the molecular basis of cardioprotective effects of exercise and the evidence for other potential mediators. We mainly focused on adaptations within the cardiac muscles and will briefly examine coronary adaptations as well. However, it should be noted that other adaptive mechanisms in the blood, humoral and autonomic nervous system, muscles, and so forth can also affect this process.

2. Exercise-Induced Expression of HSPs in the Heart

The ability of organisms to respond to various stressors was first described by Selye in 1936, who suggested a series of programmed events that help organisms to cope with the situation [12]. The heat shock response is a common cellular reaction to external stimuli such as ischemia [13], hypoxia [14], acidosis [15], oxidative stress [16], protein degradation [17], increased intracellular calcium [18], and energy depletion [19] (Table 1). Therefore, the terms "stress proteins" and "cellular stress response" reflect the array of stressors known to initiate heat shock protein (HSP) expression [20]. It is generally accepted that exercise increases the expression of cardiac HSPs. Locke et al. [21] performed a comprehensive study of the effects of acute exercise on myocardial expression of HSPs and showed that the expression of HSPs can begin within 30–60 min after an exercise bout in the rat myocardium. The mechanistic link between exercise and myocardial expression of HSPs is unclear. However, a variety of stresses associated with exercise, including heat stress and hypoxia, reduced intracellular pH, reactive oxygen and nitrogen species (ROS and RNS) production, and depletion of glucose and glycogen stores, increase in cytosolic calcium levels and cardiomyocyte stretching can all contribute to HSP elevation in cardiac muscle [22]. Several stress proteins such as HSP10, HSP40, HSP60, and HSP90 are thought to play cardioprotective roles [23, 24], with some detailed understanding of the role of the HSP70 family [25]. Production of HSP70 in the rat myocardium during treadmill running is mediated by an increase in the activation of heat shock transcription factor 1 (HSF 1), which then binds to the heat shock element of HSP70 genes and results in increased levels of HSP70 mRNA [26]. In an attempt to provide additional insights, Melling et al. showed that protein kinase A (PKA), and not protein kinase C, plays a key role in exercise-induced regulation of HSP70 gene expression [27]. Activation of PKA mediates the suppression of an intermediary protein kinase, extracellular signal regulated kinases (ERK1/2), which phosphorylates and suppresses the activation of the HSF1. However, following exercise training, ERK1/2 regulates the transcriptional activation of several genes involved in cell growth and proliferation and has been shown to be associated with training-mediated myocardial hypertrophy. In another study, Melling et al. [28] reported increased expression of HSP70 following a single bout of exercise in the presence of elevated ERK1/2 in trained animals. These results suggest that training results in adaptations that allow for the simultaneous initiation of both proliferative and protective responses. In addition, HSP72 (a member of HSP70 family) augments myocardial antioxidant capacity [29]. During ischemia/reperfusion (I/R) insult, HSP72 preserves mitochondrial function and provides cellular protection against apoptosis [30, 31]. Moreover, by prevention of protein aggregation and denaturation, HSP72 also enhances recovery from acute cellular injury and so protects cells from subsequent injury [32].

Although exercise induces cardiac HSP72 expression (which is cardioprotective), there are some reports demonstrating that the beneficial effects of exercise on cardiac muscle is independent of HSPs formation [33]. Hamilton et al. postulated that exercise associated cardioprotection may depend, in part, on increases in myocardial content manganese superoxide dismutase (MnSOD), rather than HSP levels [34], while studies by Quindry et al. suggest that exercise-induced myocardial protection against I/R is unrelated to increases in cardiac levels of HSP10, HSP27, HSP40, HSP60, HSP72, HSP73, or HSP90 [35, 36]. One explanation for these findings is the activation of cardioprotective mechanisms through different pathways that then converge on common distal pathways, suggesting that exercise-induced cardioprotection could be achievable through multiple mechanisms.

3. Exercise and Myocardial Antioxidant Capacity

Cells have evolved highly complex antioxidant systems (enzymic and nonenzymic), which work synergistically to protect cells and organ systems of the body against free radical-induced damage. The most efficient enzymatic antioxidants involve glutathione peroxidase, catalase, and superoxide dismutase. Nonenzymatic antioxidants include vitamins E and C and thiol antioxidants (glutathione, thioredoxin) [38]. Each of these antioxidants is capable of combining with reactive oxidants to produce other less reactive spices. Superoxide dismutase promotes the dismutation of the superoxide radical to form hydrogen peroxide (H_2O_2) and oxygen. While glutathione peroxidase (GPx) uses reduced glutathione (GSH), as a reducing equivalent, to reduce H_2O_2 to form oxidized glutathione and water. Furthermore, GSH can remove selected oxygen radicals directly and assist in the recycling of vitamin C and E (Table 2).

Catalase converts H_2O_2 to water and oxygen. The newly identified peroxiredoxin family represents a group of peroxidases that also catalyze the reduction of H_2O_2. They include at least six isoforms in mammalian cells [39]. Among them, peroxiredoxin III is synthesized with a mitochondrial targeting sequence, as is MnSOD.

The effects of exercise on myocardial antioxidant enzyme activities has been widely investigated but with variable conclusions. For example, while some studies report that exercise-induced increases in GPx activity [40, 41], others

Table 1: Cellular location and function of selected heat shock proteins (HSPs) [22, 23, 32, 37].

Family	Members	Cellular location	Proposed function (comment)
Ubiquitin	Ubiquitin	Cytosol	Protein degradation (ubiquitin levels in cells increase following cellular injury)
HSP10	HSP10	Mitochondria	Molecular chaperons, cofactor for HSP60
HSP27	HSP27, HSP26, and so forth	Cytosol, nucleus	Microfilament stabilization, antiapoptotic (variable in size and number in different organisms)
HSP60	HSP60	Mitochondria	Refolds proteins and prevents aggregation of denatured proteins, proapoptotic.
HSP70	HSP72, HSP73, HSP75, HSP78	Cytosol, nucleus, mitochondria, endoplasmic reticulum	Molecular chaperons, protein folding, and cytoprotection (HSP72 postulated to play an important role in myocardial protection against I/R injury).
HSP90	HSP90, HSP100, Grp94	Cytosol, nucleus, ER	May function as a molecular chaperone during maturation of steroid receptors and assists in the folding of newly synthesized peptides, protein translocation.

suggest that myocardial GPx activity is not altered by exercise [42, 43]. Such equivocal results have also been reported for myocardial catalase, with increased [44, 45] and decreased [33, 43] levels. Although there is no clear explanation for these discrepancies, it is possible that the use of exercise protocols that differ in duration and intensity may be an important underlying factor. The strongest evidence to directly link increases in myocardial antioxidants and exercise-induced cardioprotection implicates a contributory role for MnSOD. It is generally believed that even short-term endurance exercise results in a rapid increase in myocardial MnSOD activity [43, 46, 47] as shown in studies that employed antisense oligonucleotide techniques to silence MnSOD genes and so prevent exercise-induced increases in myocardial MnSOD activity [46, 48]. For example, Yamashita et al. [46] reported that inhibition of exercise-induced increases in cardiac MnSOD abolished protection against myocardial infarction, findings that were confirmed by Hamilton et al. [49] who concluded that MnSOD plays a key role against I/R-induced cardiac arrhythmias. In contrast, Lennon et al. [50] reported that exercise-induced increases in cardiac MnSOD activity is not essential to achieve exercise-mediated protection against myocardial stunning. It is possible that mechanisms responsible for exercise-induced protection against myocardial stunning are different from those involved in myocardial arrhythmias and infarction [51] (Figure 1).

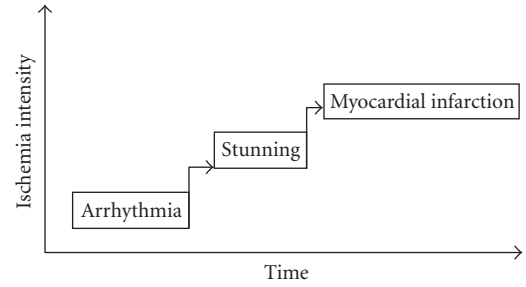


Figure 1: Sequence of pathologic events in ischemia reperfusion injury.

4. Additional Mechanisms Involved in Exercise-Induced Cardioprotection

The induction of myocardial HSPs and upregulation of cardiac antioxidant enzymes are well-studied aspects of the response to exercise. Other related responses to exercise-induced cardioprotection include anatomical and physiological changes in the coronary arteries, increased myocardial cyclooxygenase-2 (COX-2) activity, elevated endoplasmic reticulum stress proteins, nitric oxide production, increased autophagy, and improved function of sarcolemmal and/or mitochondrial ATP sensitive potassium (sarco K_{ATP} and/or mito K_{ATP}) channels [52] (Figure 2).

5. Myocardial Collateral Circulation

Exercise-induced adaptation of the coronary circulation can be divided into two major processes: (a) angiogenesis, which is an expansion of the capillary network by the formation of new blood vessels and occurs at the level of capillaries and resistance arterioles, but not in large arteries and (b) arteriogenesis, which is as enlargement of existing vessels [53].

5.1. Angiogenesis. It has been speculated that endurance exercise stimulates angiogenesis by either a division of preexisting endothelial cells or by bone marrow-derived endothelial progenitor cells and monocyte or macrophage derived angiogenic cells [54]. Some reports indicate that physical activity improves the mobilization of endothelial progenitor cells in healthy subjects and in patients with cardiovascular risk and coronary artery disease [55, 56]. Indeed, angiogenesis is regulated by a net balance between positive (angiogenic) and negative (angiostatic) regulators of blood vessel growth. A balance favoring predominantly positive regulators are an angiogenic phenotype whereas a shift favoring negative regulators is an angiostatic phenotype. Therefore, an impaired regulation of angiogenesis is often associated with the development of angiogenesis-dependent diseases such as atherosclerosis.

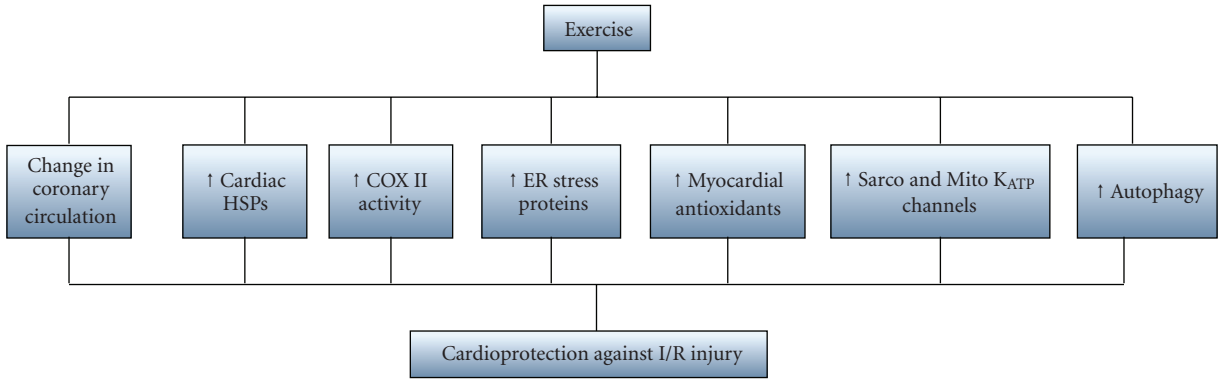


Figure 2: Proposed mechanisms for exercised-induced cardioprotection.

Endostatin is an endogenous angiostatic factor identified originally in conditioned media of murine hemangioendothelioma cells [57, 58]. Many studies have shown that the proteolytic release of endostatin from collagen XVIII is mediated by proteases of many classes, such as cysteine proteases, matrix metalloproteases, and aspartic proteases [59, 60]. The potent antiangiogenic effects of endostatin are mediated via a combination of effects on endothelial cells, where endostatin inhibits cellular proliferation and migration and stimulates apoptosis [61, 62]. The biological effects of endostatin are mainly attributed to its antagonism of vascular endothelial growth factor (VEGF) signaling [63].

Angiogenesis has both beneficial and deleterious effects in atherosclerosis. While increased angiogenesis in cardiac tissue may be a favorable sign in the healing of the ischemic tissues [64], progressive angiogenesis in a primary atherosclerotic lesion could be a cause of plaque expansion [65, 66]. There are several studies showing that exercise induces a local angiogenic phenotype characterized by overexpression of VEGF in skeletal muscle [67] and heart [64]. This phenomenon can prevent ischemia in these tissues. Exercise can also exert beneficial effects against atherosclerosis by increasing circulating endostatin, which inhibits development of atherosclerotic plaque through blocking angiogenesis in the plaque tissue [68]. Meanwhile, Brixius et al. also reported that endurance activity improves angiogenesis by reducing endostatin plasma levels [69]. Even though the different exercise protocols in these experiments can explain these discrepant results, further studies are needed to elucidate the precise mechanisms.

5.2. Arteriogenesis. Exercise training increases the diameter of large arterioles, small arteries, and conduit arteries. Another important aspect of exercise-induced changes in capillarity is the onset and persistence of exercise-induced arteriogenesis. The induction of arteriogenesis is an important vascular adaptation [70], since arteriogenesis leads to the formation of large conductance arteries capable of compensating for the loss of function of occluded arteries. Animal studies and clinical observations provide evidence for a significant correlation between regular physical exercise and increased coronary artery lumen diameter [71, 72]. In one study, an 8-week training programme increased the contractile response to low doses of dobutamine in patients with chronic coronary artery disease and having a left ventricular ejection fraction below 40%. This implies that short-term exercise training can improve quality of life by improving left ventricular systolic function during mild to moderate physical activity in patients with ischemic cardiomyopathy [73]. Moreover, eight patients with coronary heart disease and exertional angina pectoris successfully completed an 11–15 week programme of endurance exercise conditioning. Angina threshold was determined by upright bicycle ergometer exercise and by atrial pacing. The product of heart rate and arterial systolic blood pressure at the exercise angina threshold was higher after conditioning, suggesting that conditioning increased the maximum myocardial oxygen supply during exercise [74].

6. Cyclooxygenase II and Exercise-Induced Cardioprotection

The phenomenon of ischemic preconditioning whereby brief episodes of sublethal ischemia renders the myocardium resistant to subsequent ischemic stress occurs in two phases: (i) an early phase that starts within a few minutes after the initial ischemic stimulus, lasts for 2-3 h, and is due to adenosine and bradykinin release and (ii) a second phase, which begins 12–24 h later and lasts for 3-4 days [75, 76]. This later phase of ischemic preconditioning is caused by the simultaneous activation of multiple stress responsive signaling pathways, including COX-2 and the inducible form of nitric oxide synthase (iNOS), resulting in the heart developing a phenotype that confers sustained protection against both reversible (stunning) and irreversible (infarction) myocardial I/R injury [76]. Similar to ischemic stimuli, both short- (1–3 days) and long-term (weeks—months) exercise protocols are equally effective in conferring cardioprotection against I/R injury [77, 78].

Given the phenotypic similarities between ischemic and exercise preconditioning, and since COX-2 and iNOS are required to achieve the late phase of ischemic preconditioning-induced cardioprotection against both I/R stunning

Table 2: Major antioxidants.

	Name	Role	Remarks
Endogenous enzymes	Superoxide dismutase (SOD) (a) mitochondrial (b) cytoplasmic (c) extracellular	Dismutase superoxide to H_2O_2	(a) Contains manganese (MnSOD) (b) Contains copper and zinc (CuZnSOD) (c) Contains copper (CuSOD)
	Catalase	Dismutase H_2O_2 to H_2O	Present in peroxisomes
	Glutathione peroxidase	Removes H_2O_2 and lipid peroxides	Selenoproteins (contains Se^{2+}) Primarily in the cytosol also mitochondria
Nonenzymatic substance	Vitamin E	Lipid peroxidation, scavenges superoxide, hydroxyl and lipid peroxide	Fat soluble
	Vitamin C	Scavenges superoxide, hydroxyl radicals and H_2O_2, contributes to regeneration of vit E. Neutralizes oxidants from stimulated neutrophils	Water soluble
	β-carotene (provitamin A)	Scavenges $\cdot OH$, $O_2^{\cdot -}$ and peroxy radicals Prevents oxidation of vitamin A Binds to transition metals	Water soluble

and infarction [76, 79], it had been postulated that COX-2 activity, and subsequent prostanoids production, may also be essential for exercise-induced cardioprotection [80]. However, Nagy et al. reported that COX II inhibition did not prevent exercise-induced cardioprotection against ventricular arrhythmias after coronary occlusion in dogs [81]. Accordingly, studies by Quindry et al. [82, 83] revealed that exercise does not elevate cardiac COX-2 activity. Therefore, we conclude that different mechanisms may be responsible for cardioprotection afforded by ischemia preconditioning and aerobic exercise.

7. Exercise-Induced Cardioprotection by Endoplasmic Reticulum Stress Proteins

Another candidate mechanism explaining exercise-induced cardioprotection is through a family of cardioprotective protein collectively called endoplasmic reticulum (ER) stress proteins. During a cardiac I/R insult, the ER helps cellular homeostasis by maintaining intracellular calcium regulation and protein folding [84]. Malfunction of the ER during an I/R event can lead to both mitochondrial-dependent and mitochondrial-independent cell death due to disruption of calcium homeostasis and/or impaired protein folding [85]. The two most important ER stress proteins are Grp78 and Grp94 which belong to HSP families and are overexpressed in cultured cardiomyocytes during oxidative stress and calcium overload [86]. Martindale et al. suggested that the unfolded protein response (UPR) is activated in the heart during I/R, where formation of "Activation of Transcription Factor 6 (ATF6)" induces the expression of proteins such as Grp78 and Grp94, which in turn reduces I/R-induced necrosis and apoptosis in the heart [87]. Since overexpression of these ER stress proteins provide ER protection during an I/R insult, it may be that these proteins contribute to exercise-induced cardioprotection. However, studies by Murlasits et al. demonstrate that at least short-term exercise training does not elevate ER stress proteins, and therefore, short-term exercise-induced cardioprotection may not be linked to ER stress adaptation [88].

8. Nitric Oxide and Exercise-Induced Cardioprotection

Nitric oxide plays a fundamental role in protecting the heart against I/R injury. Specifically, it plays a critical bifunctional role as a trigger and a mediator of late phase of preconditioning. Increased production of NO by eNOS is an important trigger in the late phase of ischemia and exercise-induced preconditioning, and enhanced NO production by iNOS is mandatory in the mediation of the antistunning and antiinfarct actions of late preconditioning [89]. In other words, the heart responds to ischemia by using two types NOS isoforms in a harmonized manner; it uses preexisting eNOS for a prompt burst of NO production, while at the same time, there is upregulation of iNOS to switch to a defensive phenotype by a sustained enhancement of NO biosynthesis. The exact cardioprotective mechanisms of NO during I/R is a subject of much debate; however, hypothesized mechanisms include inhibition of calcium influx into myocytes [90], antagonism of β-adrenergic stimulation [91], reduction in cardiac oxygen consumption [92, 93], and actions on sarco K_{ATP} channels [94].

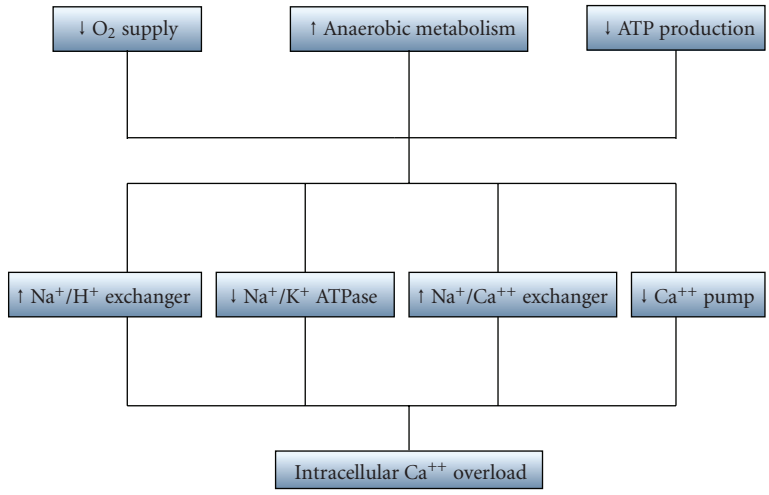
Although there are many studies on the cardioprotective effect of nitric oxide in I/R-induced preconditioning, there are less investigations evaluating the protection afforded by nitric oxide in exercise-induced cardioprotection. Exercise increases the expression and activity of eNOS, likely due

to changes shear stress, which modulates the production of NO [95–97]. Besides its vascular and metabolic effects (vasodilation, altered carbohydrate metabolism) [98], NO possess a number of physiological properties which makes it a cardioprotective molecule in the setting of myocardial I/R injury. For example, NO reversibly inhibits mitochondrial respiration [99] and apoptosis [100]. This effect results in a reduction in mitochondrial-induced cardiac injury in the failing human heart. Babai et al. showed that even a single period of exercise affords delayed protection against I/R-induced ventricular tachycardia and other ischemic changes that are mediated by NO [101]. Further evidence for a central role of eNOS in exercise physiology comes from experiments with eNOS deficient mice ($eNOS^{-/-}$). Running capacity in these animals is 50%–60% less than age-matched wild-type mice [102, 103]. de Waard et al. found that the beneficial effects of exercise after MI on LV remodeling and dysfunction depends critically on endogenous eNOS. They observed that the lack of one eNOS allele is sufficient to negate all beneficial effects of exercise, strongly suggesting that the beneficial effects of exercise depends on full eNOS expression [104]. Taylor et al. in an in vitro setting showed that exercise can render a cardioprotective phenotype against I/R insult even in the presence of blockade of all NOS isoforms with L-NAME, leading them to conclude that acute exercise-induced preconditioning is not mediated by NOS (or either increases in HSP 72 or other antioxidant enzymes) [105]. These discrepant findings can be accounted for by considering the role of nitrite and nitrates in the physiology of the cardiovascular system. For example, it has been shown that nitrite (and nitrates) acts as a storage reservoir on NO so that under pathological conditions such as ischemia and hypoxia, nitrite can readily be reduced to NO [106, 107]. The beneficial effect of nitrite therapy (which generates NO-independent of eNOS) has been shown in animal models of cardiac I/R injury [108, 109]. Nitrite levels are increased following exercise in both rodents and humans [110, 111]. Since nitrite accumulated in the heart can provide cardioprotection during an ischemic event by being reduced to NO, it is likely that NO produced from endothelial cells during exercise can be oxidized to nitrite, transported in the plasma to then affect the heart or vasculature. In the case of myocardial ischemia, nitrite can be reduced back to NO and exert cardioprotection in an NO-dependent manner [112]. This hypothesis potentially could be applied to all the experiments in which exercise-induced cardioprotection was not abolished in the presence of an inhibitor of NOS [105, 113]. To add to the importance of NO in exercise physiology is its ability to activate K_{ATP} channels through cGMP-PKG signaling [114, 115] and to increase expression of HSP70 [116] during exercise.

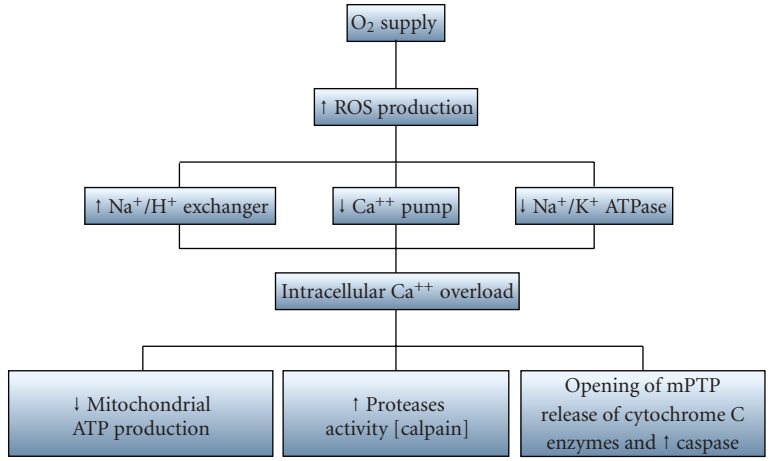
9. Role of Sarco and Mito K_{ATP} Channels in Exercise-Induced Cardioprotection

Several lines of evidence indicate that sarco K_{ATP} channels are involved in cardiac I/R injury. The K_{ATP} channel was first described in 1983 and was named for the inhibitory effect of cytosolic ATP on potassium channel opening [117]. During ischemia, heart cells become energy depleted, which leads to increased anaerobic glycolysis to compensate for ATP depletion. The resulting acidosis increases the influx of Na via the Na/H exchanger and inhibits the ATP-dependent sarcolemmal Na/K ATPase to augment the initial accumulation of Na [118]. The high intracellular Na concentration prompts the Na/Ca exchanger to work in the reverse mode, producing cytosolic and mitochondrial Ca overload [119]. Upon reperfusion, a burst of ROS is generated by mitochondria, while intracellular Na overload continues as a result of the impaired function of Na/K ATPase (Figure 3(a) and 3(b)).

The Na/K ATPase pump is a transmembrane heterodimer protein composed of α and β subunits. The cytoplasmic domain of α subunit interacts with ankyrin, a protein that connects the Na/K ATPase to the fodrin-based membrane skeleton [120]. Ankyrin and fodrin are major components of the membrane cytoskeleton in a variety of nonerythroid cells [121]. They are also substrates of calpains, a group of nonlysosomal Ca-dependent proteases. Previous studies demonstrated activation of calpain leading to the degradation of both ankyrin and fodrin during reperfusion [120]. The resulting increased intracellular concentrations of Na and Ca, along with low ATP levels, lead to additional mitochondrial ROS production and to activation of other proteases, which result in decreased sarcoplasmic reticulum calcium transport and dysfunctional contractile proteins [122]. Increased cytosolic Ca levels also contribute to the opening of the mitochondrial permeability transition pore (mPTP), resulting in a loss of mitochondrial membrane potential and reduced ATP production [123]. The decrease in ATP production leads to opening of K_{ATP} channels on both the sarcolemmal and mitochondria. It was Noma [117] who initially hypothesized that opening of sarco K_{ATP} channels induced by hypoxia, ischemia, or pharmacological K_{ATP} openers shortens the cardiac action potential duration by accelerating phase III repolarization. An enhanced phase 3 repolarization would inhibit Ca entry into the cell via L-type channels and prevent Ca overload. Furthermore, the slowing of depolarization would also reduce Ca entry and slow or prevent the reversal of the Na/Ca exchanger. These actions would increase cell viability via a reduction in Ca overload during ischemia and early reperfusion. Additional evidence supporting the protective role of sarco K_{ATP} channels was provided by other investigators [123–127]. Exercise training increases the expression of cardiac sarco K_{ATP}, and moreover, pharmacological blockage of these channels impairs cardioprotection [128]. The sex-specific and exercise acquired resistance to myocardial I/R injury is dependent on sarco K_{ATP} activity during ischemia [129]. Interestingly, female animals have higher sarco ATP sensitive potassium channel expression [130] and estrogen can upregulate the expression of these channels [131]. Administration of HMR-1098, a sarcolemmal K_{ATP} channel blocker, abolished the sex-dependent differences in infarct size [132, 133]. It is likely that the smaller infarct size in female hearts reported in some studies may be related to an increase activity of protein kinases B (also known as Akt) and C [134], which cause increased recruitment of K_{ATP} in myocyte



(a) Ischemia



(b) Reperfusion

Figure 3: (a, b) Pathophysiological consequences of (a) ischemia and (b) reperfusion. (mPTP, mitochondrial permeability transition pore).

sarcolemma. Inhibition of these kinases before ischemia expanded infarct size in female (but not male) hearts. Recent studies suggest that inhibition of K_{ATP} channels and of PKC are not additive, suggesting that activation of PKC and K_{ATP} channels are different components of the same signaling pathway [135]. Activation of PKC by adenosine downregulates K_{ATP} channels [136]. It is possible that on type of PKC is active following exercise which upregulates K_{ATP} channels, while the activation of adenosine receptors activate another type of PKC which downregulates these channels [137]. The fact that PKC mediated activation of sarco K_{ATP} channels is sex dependent suggests the presence of regulatory component(s) that either may not be present, or regulated in a different manner, in males. These findings show the complexity of signaling pathway(s) that regulate the density and function of sarco K_{ATP} channels in preconditioned and nonpreconditioned hearts in a gender-dependent manner. A full understanding of the mechanisms underlying regulation of sarco K_{ATP} is an exciting task for the future that certainly will have a significant impact on therapeutic strategies for the prevention and treatment of cardiovascular diseases.

Several lines of evidence confirm the role of mitochondrial K channels in protection against I/R injury [138–140]. Prostacyclin analogs protect cardiac myocytes from oxidative stress mainly via activation of type 3 of PE_2 receptors during I/R injury. Activation of these receptors primes the opening of mitochondrial K_{ATP} channels [141]. However, there is some controversy about the role of mito k_{ATP} channels in exercise preconditioning of the heart. For example, Domenech et al. reported that the early effect of exercise preconditioning of the heart is mediated through mito k_{ATP} channels [142], while Brown et al. reported that mito k_{ATP} channels are not an essential mediator of exercise-induced protection against I/R-induced myocardial infarction [128]. It has also been recently suggested that mito K_{ATP} channels provide antiarrhythmic effects as part of exercise-induced cardioprotection against I/R injury [143]. It should be mentioned that the molecular characteristics of

mito k_{ATP} channels remains elusive. Additional research is needed before definitive conclusions can be drawn.

10. Exercise and Cardiac Mitochondria

There is an important role for mitochondria in I/R injury. Exercise training results in cardiac mitochondrial adaptations that result in decreased ROS production, increasing their ability to tolerate high calcium levels. Lifelong voluntary wheel running reduced cardiac subsarcolemmal and interfibrillar mitochondrial hydrogen peroxide production in rats [144]. Similarly, endurance exercise reduces ROS production in myocardial mitochondria, resulting in less calcium influx upon reperfusion [145]. Reduction in ROS production could be related to decreased superoxide production or increased mitochondrial antioxidant enzyme activity. A study by Judge et al. [144] indicated that MnSOD activity was significantly lowered in subsarcolemmal and interfibrillar mitochondria, leading to the suggestion this may reflect a reduction in mitochondrial superoxide production. However, this issue is currently a matter of considerable debate.

Mitochondria of exercised animals are able to tolerate higher levels of calcium. Mitochondria isolated from hearts of exercised animals are more resistant to calcium-induced mPTP opening [146]. Furthermore, exercise training induces a mitochondrial phenotype that is protective against apoptotic stimuli [147]. These changes include increases in the protein levels of primary antioxidant enzymes in both subsarcolemmal and interfibrillar mitochondria, attenuation of ROS-induced cytochrome c release, reduced maximal rates of mPTP opening (V_{max}), and prolonged time to $V_{(max)}$ in both subsarcolemmal and interfibrillar mitochondria, and increased levels of antiapoptotic proteins including the apoptosis repressor with a caspase recruitment domain. These results are consistent with the concept that exercise-induced mitochondrial adaptations contribute to exercise-induced cardioprotection and are compatible with our study on the effect of exercise on renal mitochondria in diabetic mice [148].

Monoamine oxidase enzymes are located on the outer mitochondrial membrane and are divided into 2 major forms A and B based on genetic criteria, substrate specificity, and inhibition by synthetic compounds. The degradation of biogenic amines (serotonin and catecholamines) is the major physiological function of these enzymes [149] and MAO-A, which is the predominant isoforms expressed in cardiac ventricle, also represents an important source of ROS in the heart [150]. Moreover, its ability to produce ROS increases with aging and its expression is upregulated during cardiac hypertrophy and failure [151]. A study by Bianchi et al. investigating the potential role of ROS generated by MAO-A during 5-HT degradation in cardiomyocyte death and its role in post-I/R damage showed that MAO is responsible for receptor-independent apoptotic effects of 5-HT in cardiomyocytes and post-ischemic myocardial injury. They also provided evidence that H_2O_2 production by MAO-A plays a critical role in post I/R events leading to cardiac damage [152]. Another *in vivo* study using MAO-A knockout mice showed that these animals were protected from I/R-induced cardiac damage and this protection was related to significantly lower ROS generation following I/R injury [153]. Interestingly, Kavazis et al. showed that MAO-A protein levels were significantly reduced in both subsarcolemmal and intermyofibrillar mitochondria following exercise training [154]. They proposed that down regulation of MAO-A protein expression following endurance exercise is one of the mechanisms for exercise-induced cardioprotection.

Other effects of exercise on cardiac mitochondria relates to proteins involved in bioenergetics. This regulation may help to meet the increased energy demands during exercise or improved cardiac function during resting conditions. Thus, repeated bouts of exercise increase the mitochondrial levels of several enzymes such as acyl-CoA dehydrogenase, hydroxyacyl-CoA dehydrogenase, and $\delta(3,5)$- $\delta(2,4)$-dienoyl-CoA isomerase that are involved in the β-oxidation of fatty acids [51] (Figure 4).

11. Exercise and Autophagy

Autophagy or autophagocytosis is a universal, dynamic process that takes place in all eukaryotic cells and helps to maintain a balance between the synthesis, degradation and subsequent recycling of cellular products. This process consists of three phases: (a) formation and engulfment of the target by a double-membrane vesicle called an autophagosome, (b) delivery of autophagosomes to lysosomes, and (c) degradation of the autophagosomes and its content by lysosomal proteases [155]. Autophagy plays an important role in the basal turnover of intracellular proteins and organelles and production of amino acids in nutrient emergency. These functions guarantee rejuvenation and adaptation to changing or adverse conditions and even underlie dynamic processes such as development or metamorphosis. The autophagic pathway is crucial for maintaining cell homeostasis and disruption to the pathway can be a contributing factor to many diseases. During nutrient starvation, increased levels of autophagy lead to breakdown of nonvital components and the release of nutrients, ensuring that vital processes can continue. Mutant yeast cells that have a reduced autophagic capability rapidly perish in nutrition deficient conditions [156]. In brief, autophagy is a mechanism by which cells, in times of nutrient shortage, can degrade protein for metabolic needs and simultaneously eliminate unwanted, damaged, or redundant cell membranes and organelles including mitochondria, endoplasmic reticulum, and peroxisomes; in this regard, autophagy contrasts with the accumulation of damaged cells that naturally occurs during the process of aging. Decreased autophagy can promote the development of cancer [157] and neurodegenerative conditions including Alzheimer's [158] and Parkinson's disease [159]. In the heart, autophagy can protect against apoptosis activated by ischemic injury [160], and its chronic perturbation is causative in genetic forms of heart disease [161]. Conversely, autophagy can also be a form of programmed cell death linked to, but distinct from, apoptosis [162, 163].

The inductive effect of caloric restriction and suppression of autophagy by excessive caloric intake can also play roles

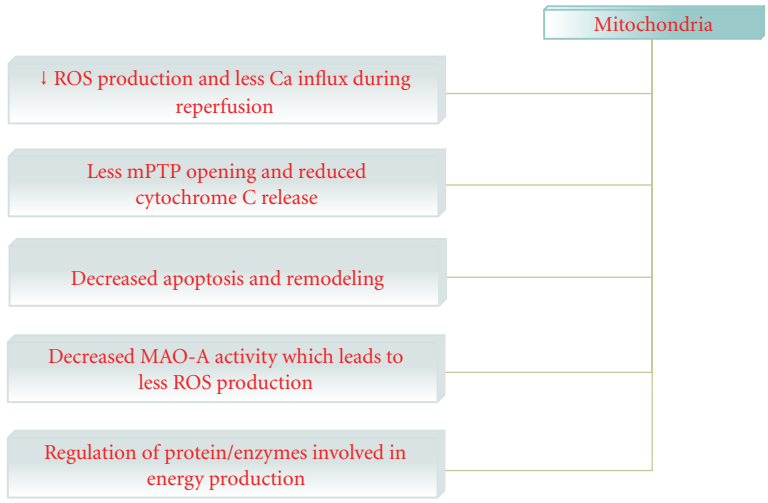


Figure 4: selected exercise-induced mitochondrial change in cardiac muscles. (Mitochondrial permeability transition pore, mPTP).

in the metabolic syndrome, type II diabetes, and aging [164, 165].

We conclude that exercise mediates its cardioprotective effects, in part, by induction and up regulation of autophagy [166–169]. Exercise-induced autophagic responses are diminished in people with the metabolic syndrome, type II diabetes, or sedentary life styles. Agents known to induce pharmacological conditioning, such as adenosine and diazoxide, are also inducers of autophagy [170]. Autophagy is upregulated in the chronically ischemic myocardium, where there is an inverse relationship with the extent of apoptosis [171]. Myocardial protection elicited by adaptation to ischemia is mediated at least in part via upregulation of autophagy [160, 172].

12. Summary

There is firm evidence from observational and randomized trials that regular exercise contributes to the primary, secondary and tertiary prevention of cardiovascular and several other lifestyle-dependent diseases and that regular exercise is associated with a reduced risk of premature death. The detailed molecular mechanisms behind this favorable effect remain unknown and continue to be actively investigated at various levels although there is significant evidence favoring redox homeostasis during cardioprotection. For the sake of clarity, we propose to divide the potential mechanisms into two major categories: those mechanisms that mainly decrease ROS production and other mechanisms that are more effective in repair and housekeeping (Table 3). These molecular adaptations lead to better physiological function and enhanced resistance to oxidative stress.

Among the proposed mechanisms for exercise-induced cardioprotection, changes in mitochondrial function and sarco K_{ATP} channel regulation play more significant roles. Indeed, mitochondria are important determinants of survival in cardiac myocytes exposed to I/R [173, 174]. Therefore, its adaptations during exercise can have a greater impact on cardiac muscles. Just as important is the protective role of NO, which in addition to matching blood flow to metabolic demands also has antiatherosclerotic properties (inhibits inflammatory cells and platelets from adhering to the vascular walls) and can increase the expression of HSP70 and activate K_{ATP} channels. It seems likely that other unknown cardioprotective mediators also exist and may contribute to exercise preconditioning, stressing the need for additional research to determine how the integration of the different pathways can lead to cardioprotection. Another important consideration is to better understand the impact of different exercise protocols (type, duration, and intensity) and gender differences on the time course and extent of exercise-induced cardioprotection, as this will have implications for both ongoing preventative health care as well as for developing therapeutic strategies, for example, in the management of some patients with cardiac diseases.

Table 3: Proposed mechanisms in exercise-induced cardioprotection.

Mechanisms which mainly decrease ROS production	Mechanisms which mainly repair cellular damages
(i) Sarco K_{ATP} channles (and possibly mito K_{ATP} channles) (ii) ↑NO (iii) Mitochondrial adaptations, including ↑MnSOD	(i) HSPs (ii) ↑Autophagy (iii) ↑ER stress proteins

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Review Article

Physical Inactivity and Mortality Risk

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In recent years a plethora of epidemiologic evidence accumulated supports a strong, independent and inverse, association between physical activity and the fitness status of an individual and mortality in apparently healthy individuals and diseased populations. These health benefits are realized at relatively low fitness levels and increase with higher physical activity patterns or fitness status in a dose-response fashion. The risk reduction is at least in part attributed to the favorable effect of exercise or physical activity on the cardiovascular risk factors, namely, blood pressure, diabetes mellitus and obesity. In this review, we examine evidence from epidemiologic and interventional studies in support of the association between exercise and physical activity and health. In addition, we present the exercise effects on the aforementioned risk factors. Finally, we include select dietary approaches and their impact on risk factors and overall mortality risk.

1. Introduction

The conventional wisdom since antiquity has been that a healthy lifestyle leads to prolonged and healthy life. Although a precise definition of a healthy lifestyle is not established, data acquired from the Framingham Heart Study have helped identify several behaviors that predispose an individual to a higher risk for future cardiovascular events and early mortality. These behaviors, coined as risk factors, include age, gender, heredity (nonmodifiable) and diabetes mellitus, hypertension, dyslipidemia, smoking, physical inactivity, and obesity referred to as modifiable risk factors.

The modifiable risk factors are influenced by a number of variables including diet and exercise. In this review, we present a synopsis of some of the most influential studies examining the effects of physical activity and diet and the traditional CV risk factors and mortality. Finally, we consider the clinical applications of this evidence.

2. Physical Activity and Health

Interest in the relationship between physical activity, fitness, and health was generated by the landmark work by Morris and coworkers who reported significantly lower mortality rates in civil servants with physically demanding occupations when compared to desk clerks [1]. The plethora of evidences accumulated since then from occupational, leisure time and fitness assessment studies support a strong, inverse, and independent association between physical activity, health, and cardiovascular (CV) and overall mortality in apparently healthy individuals [2–26] and in those with documented CV disease [23]. The association is as robust as that of established risk factors [2]. A detailed account of the most influential studies in each category follows.

3. Occupational and Leisure Time Studies

The findings of occupational studies on 6,351 longshoremen [3] and those of 16,963 Harvard alumni support an inverse association between physical work and cardiovascular mortality [6, 7]. The findings of these studies support a sharp reduction in fatal and nonfatal heart attack rates with increase in weekly energy expenditure of $\geq$2000 Kcal per week. Those who expended less than 2,000 Kcal per week had 64% higher risk for a heart attack. An important finding of this study was that reduction in risk was only

evident if physical activity was maintained throughout life. Those who played varsity sports, but did not maintain a physically active lifestyle had higher mortality rate compared to those who maintained a physically active lifestyle in adulthood. Moreover, those who avoided athletics in college but subsequently took up a more active lifestyle also had similarly low rates of mortality [6].

In the next two reports that followed on the same cohort, a consistent, inverse, and graded trend towards lower all-cause mortality rate was noted. As physical activity-related caloric expenditure increased from 500 Kcal to 2000 Kcal per week the mortality rate decreased. More specifically, the mortality risk for men whose weekly energy expenditure from leisure time activities total 2000 Kcal or more had about 25% to 33% lower mortality rate compared to those with caloric expenditure less than 2000 Kcal per week. An interesting observation of this study was that the mortality risk tended to increase slightly in those expending more than 3,500 Kcal per week suggesting that exercise beyond a certain level may be harmful to some [7]. This will be equivalent to about 30–35 miles of jogging per week.

In the more recent study, the relative risk of death based on different types of physical activity that included walking (miles/week), stair-climbing (floors), and sports playing in 10,269 Harvard alumni over a 9-year period was examined [8]. Particularly noteworthy in this study was the 30% to 40% reduction in mortality risk, evident in those individuals engaging in moderate to vigorous activity levels (≥4.5 METs) with only minimal additional benefits achieved by engaging in activities of greater intensity. The reduction was similar, when physical activity was expressed as kilocalories per week (the sum of walking, stair climbing, and sports participation) suggesting that a 40% reduction in mortality occurs by engaging in modest levels of activity (1,000 to 2,000 kcal/week, equivalent to three to five 1-hour sessions of activity).

Collectively, the findings of these studies [3, 6, 8] provided evidence in support of an exercise intensity threshold of about 5-6 METs and an exercise volume threshold somewhere between 1,000 to 2000 Kcal per week for significant reduction in mortality risk. Furthermore, the findings suggest that most of the benefits occur at moderate exercise volumes and moderate intensities.

Fatal and nonfatal coronary events were also assessed in 5,288 men and 5,229 women who lived in 58 settlements called kibbutzim [4]. A unique aspect of this study is that these settlements (kibbutzim) provided communal dining facilities and similar medical care for a relatively homogeneous group. Thus, many of the confounding factors present in epidemiologic studies were eliminated. In addition, risk factors were similar in between physically active and sedentary groups. The relative risk for coronary events of this 15-year followup study was 2.5-times higher in men in sedentary occupations compared to the men who performed more physically demanding jobs. For women, the risk was 3.1-times greater for the corresponding occupations [4].

Similar results have been reported from large studies that have followed cohorts for CHD morbidity and mortality in the range of 10 to 20 years among British civil servants, U.S. railroad workers, San Francisco longshoremen, nurses, physicians, other health care workers, and other cohorts. The findings of these studies are summarized in two comprehensive reviews [9, 10].

The influence of genetic factors in the reduction of the mortality risk cannot be dismissed. A valid agreement can be made that it is not the physical activity that provides protection, but the genetic composition of these individuals. In this regard, the independent association of physical activity and mortality and the influence of genetic and other familial factors were assessed in a cohort of same-sex twins born in Finland before 1958 and with both alive in 1967 [12]. In 1975, healthy men ($n = 7,925$) and women ($n = 7,977$) responded to a questionnaire on physical activity, occupation, smoking habits, body weight, alcohol use, and physician-diagnosed diseases. Individuals who reported engaging in a brisk walk for a mean duration of 30 minutes, at least 6 times per month were classified as physically active. Those who reported no leisure time activity were classified as sedentary. The remaining individuals were classified as occasional exercisers. When compared to the sedentary twins, the adjusted risk of mortality was 33% lower among the twins who exercised occasionally and 44% lower among the physically active twins. These findings suggest that physical activity is associated with lower mortality independent of genetic and other confounding factors.

In contrast to these reports, a Finnish study found that the rate of coronary heart disease mortality was greater among lumberjacks compared to less active farmers of the same region [5]. However, these finding must be interpreted with caution for two reasons. Although farmers may have been less active than lumberjacks, they were not sedentary. Thus, the study compared highly active individuals (lumberjacks) to somewhat less active (farmers). This along with the higher fat consumption and smoking rates among lumberjacks is likely to have attenuated the positive effects of physical activity in the lumberjacks and showed more favorable outcomes for the farmers.

Clearly, the accumulated evidence from observational studies provided strong support for the existence of a strong inverse relationship between physical exercise and coronary heart disease risk. In a recent review that included 44 observational studies from 1966 to 2000, the findings are summarized as follows. First, there is strong evidence of an inverse linear dose-response relationship between volume of physical activity and all-cause mortality. Second, an exercise volume threshold can be defined beyond which a significant reduction in mortality risk occurs. Such threshold appears to be at caloric expenditure of approximately 1,000 Kcal per week was defined as the threshold for an average reduction of 20% to 30% in mortality risk. Further reductions in risk are observed with higher volumes of energy expenditure. The independent contribution of the exercise components of intensity, duration, and frequency to the reduction of mortality risk was not clear and the need for more research to better understand the contribution of each component is emphasized [11]. Efforts to define the intensity, duration, frequency, volume, and type of exercise necessary for cardiovascular health and longevity continue.

4. Physical Fitness Studies

A shift from assessing physical activity by questionnaires to a more objective assessment was provided by Blair and coinvestigators [13]. In study, 10,224 men and 3,120 women underwent a maximal exercise test exercise. They were then grouped into five fitness categories based on the MET level achieved. In a follow-up period of over 8 years, the adjusted relationship between exercise capacity, cardiovascular, and all-cause mortality inverse, and graded for both men and women. The major reduction in mortality risk occurred when moving from the least fit (<6 METs) to the next fit category of 7 METs, continued to decline with higher fitness levels and appears to plateau at approximately 9 to 10 METs for women and men, respectively. These findings suggest that health benefits are realized at relatively moderate fitness levels attainable by a brisk walk of 30 to 60 minutes each day. The investigators also reported similar findings in much larger cohort when the impact of fitness was assessed within groups who possess specific risk factors such as hypertension, diabetes, or smoking [14].

Although the physical activity-mortality relationship is well established by now, information on the intensity, duration, and type of physical activity is still speculative. An exercise intensity threshold of about 6 METs for a reduction in risk has been suggested by some [15]. Others have shown an independent effect of exercise type, intensity, and duration on the risk for coronary heart disease. It is noteworthy that this is the first study to provide evidence on the efficacy of weight training or resistance exercise on coronary heart disease risk reduction. The risk reduction was similar to that provided by a brisk walking 30 or more minutes [16].

Although exercise intensity, duration, and volume were inversely related to coronary heart disease, the much stronger association between intensity and risk suggests that walking intensity has a stronger effect on risk reduction than duration [16].

5. A Dose-Response Association

Recently, several studies have reported a more precise quantification of the dose (amount of exercise or degree of fitness) and response (mortality risk-reduction) relationship by expressing exercise capacity in the context of survival benefit per MET. These studies present the change in mortality risk for each 1-MET increases in exercise capacity assessed by a maximal exercise test. The reduction in mortality risk per 1-MET increase in exercise capacity ranges between 10% and 25% [17–27]. This is evident in both men and women. There is also evidence to suggest that the strength of exercise capacity in predicting risk of mortality may even be greater among women than men, reporting [19, 25].

It is well documented that the age-adjusted all-cause mortality rates in African-Americans are as much as 60% higher when compared to Caucasians. In a recent study we assessed the association between physical activity, exercise capacity, and mortality among 6,749 African-American and 8,911 Caucasian men [24]. We found exercise capacity to be a more powerful predictor of risk for all-cause mortality than established risk factors (smoking, dyslipidemia, diabetes, and hypertension) among both African-Americans and Caucasians after adjusting for cardiac medications. The risk for mortality was 13% lower for every 1-MET increase in exercise capacity for the entire cohort with similar reductions observed for those with and without CVD. When fitness groups were considered, the relative risk for all-cause mortality was approximately 20% lower in those with an exercise capacity of 5–7 METs (Moderate-Fit category) when compared to those achieving <5 METs. The mortality risk was 50% lower for those with an exercise capacity 7.1 to 10 METs and 70% lower for those with an exercise capacity of more than 10 METs. This gradient for a reduction in mortality with increasing fitness was similar in African-Americans and Caucasians in the entire cohort and in individuals with and without CVD.

Similar findings were reported in men 65–92 years of age during a 20-year follow-up period. To account for the possibility that the higher mortality rates observed in the low-fit categories were the result of underlying diseases (such as cachexia), musculoskeletal, or peripheral vascular issues and not low fitness per se (reverse causality), the investigators undertook three approaches: (1) excluded those who died within the initial two years of followup, (2) excluded those who were not treated with beta-blockers but did not achieve at least 85% of their age-predicted maximal heart rate (to account for factors that may have impaired exercise performance), and (3) excluded those in the two lowest fit categories (≤5 METs) with BMI < 20; and finally excluded all those who met all three conditions. We then repeated the survival analyses separately (for each exclusion), as well as with all exclusions combined. In all four scenarios, the association between exercise capacity and mortality risk remained robust and the risk reduction did not deviate substantially from that observed in the entire cohort. The similarity in trends and magnitude of risk reduction observed between the findings of the entire cohort and these four separate analyses argues against the likelihood of reverse causality and supports the validity of fitness and mortality risk association. Another noteworthy finding in this study is that the mortality risk of individuals who were unfit during the initial evaluation but became fit during the followup was 35% when compared to those who remained unfit [26]. These finding are similar to those reported by Blair et al. [17].

These findings have significant public health implications. Mortality risk can be cut in half regardless of age or race by just engaging in brisk walk for 2-3 hours per week or 30 minutes per session 4-5 days per week. Collectively, the findings of the aforementioned studies support the concept that exercise capacity should be given as much attention by clinicians as other major risk factors.

6. Physical Activity, Risk Factors, and Mortality

As mentioned previously, the exercise-related health benefits are in part related to favorable modulations in CV risk factors that have been observed with increased physical activity

patterns or structured exercise programs [27]. In this regard, we present data to support the effects of physical activity or exercise capacity on select cardiac risk factors.

7. Hypertension and Physical Activity

Chronic hypertension is recognized as a major and the most common risk factor for developing cardiovascular disease [28–30]. This relationship is direct, strong, continuous, graded, consistent, predictive, and independent [31]. The mortality risk doubles for every 20 mm Hg increase systolic blood pressure above the threshold of 115 mm Hg and for every 10 mm Hg increase in diastolic blood pressure threshold of 75 mm Hg [32]. For an individual with normal blood pressure at the age of 55 years, the risk of developing hypertension during the remainder of his or her life is estimated to be 90% [33].

The potential of increased physical activity to lower elevated blood pressure or to prevent/attenuate the development of hypertension was suggested by several epidemiologic studies that used habitual physical activity as reported by the participants [34–36] or assessed more objectively by an exercise treadmill test [37]. The relative risk for developing hypertension in sedentary individuals with normal blood pressure at rest is approximately 35% to 70% higher when compared to their physically active peers [38–40].

8. Exercise Interventional Studies

The aforementioned epidemiologic evidence, an overwhelming number of well-controlled studies that followed have consistently shown that regularly performed aerobic exercise of mild to moderate intensity lowers blood pressure in patients with mild to moderate essential hypertension [41–43].

An overwhelming number of these studies reported that regularly performed aerobic exercise lowers blood pressure in patients with essential hypertension when compared to nonexercising controls. Although some variability exists among the several reviews and metaanalyses, the general conclusion is that aerobic exercise training is effective in lowering blood pressure in hypertensive individuals for all ages and both genders [41–44]. The average exercise-related blood pressure is about 7–10 mm Hg for systolic and 4–8 mm Hg for diastolic blood pressure [41, 42]. We also observed significantly lower blood pressure in individuals with Stage 2 hypertension after 16 weeks of exercise training. In addition, blood pressure in the exercise group was still significantly lower from baseline even after a 33% reduction in antihypertensive medication was achieved in those who exercised for an additional 16 weeks [45]. It is now well-recognized that a sedentary lifestyle increases the risk for hypertension whereas increased occupational or leisure time physical activity is associated with lower levels of blood pressure [31, 46]. Increased physical activity is now strongly recommended as part of the lifestyle modification along or as adjunct to pharmacologic therapy proposed by the Joint National Committee [29, 30].

9. Physical Activity and Mortality Risk in Hypertensive Individuals

We assessed the association between exercise capacity and mortality in 4,631 hypertensive men with and without additional cardiovascular risk factors. During a follow-up period of 7.7 ± 5.4 years (35,629 person-years), the adjusted mortality rate was 34% lower for the group next to the lowest fit individuals, and 59% and 71% for the next two highest fit categories, respectively. Exercise capacity was the strongest predictor of all-cause mortality. The adjusted mortality risk was 13% lower for every 1-MET increase in exercise capacity.

When additional risk factors were considered, the mortality risk was 47% higher for individuals within the lowest-fit category with additional risk factors, compared to individuals with no risk factors. This risk was eliminated for those in the next fitness category and was progressively reduced for the highest-fit categories regardless of the presence or absence of additional risk factors. These findings support that exercise capacity is a strong predictor of all-cause mortality in hypertensive males. The increased risk imposed by low fitness and additional cardiovascular risk factors is eliminated by relatively small increases in exercise capacity and declines progressively with higher exercise capacity [47]. Similar findings were observed in those with high to normal blood pressure [48] and in prehypertensive individuals [49].

10. PA and Mortality in Individuals with Type 2 Diabetes Mellitus

Findings from randomized, well-controlled exercise training studies supports that both aerobic and anaerobic (resistance training) exercises improve glucose uptake and insulin sensitivity after only a few weeks of training [50–53]. There is also evidence to suggest that resistance training may be more effective in lowering blood glucose levels [50–52].

11. Exercise and Diabetes Prevention

Strong evidence from large cohort studies also supports that exercise and physical activity in general, are highly effective in delaying or averting the development of diabetes. In addition, physical activity has been shown to reduce the risk of mortality in diabetics [54–57]. Support of the epidemiologic findings is provided by two interventional studies [58, 59]. In one study [58], overweight men ($n = 172$) and women ($n = 350$) with impaired glucose tolerance randomly assigned to either the intervention group or control group. The intervention group was instructed to follow a healthy diet, reduce weight, and increase physical activity. At the end of the follow-up period (3.2 years), the cumulative incidence of diabetes was 11% for the intervention group and 23% in the control group. The risk for diabetes was reduced by 58% in the intervention group. The investigators concluded that the observed changes in the incidence of diabetes were the direct result of the implemented lifestyle modifications.

In the Diabetes Prevention Program Research Group [59], 3,234 nondiabetic individuals with elevated fasting

blood glucose levels were randomly assigned to one of three groups: lifestyle-modification, metformin, and placebo. The lifestyle-modification group included weight reduction of at least 7% of initial body weight through a heart-healthy diet and engaging in moderate intensity physical activity (brisk walking) for at least 150 minutes per week. At the end of the follow-up period (2.8 years), both medication (metformin) and lifestyle interventions were equally effective in lowering blood glucose concentrations when compared to the placebo group. However, lifestyle intervention was significantly more effective in preventing the incidence of diabetes than metformin (58% versus 31% for lifestyle-modification and metformin groups, resp.). To prevent one case of diabetes, the investigators calculated that 6.9 persons have to participate in the lifestyle-modification group and 13.9 would have to receive metformin. Finally, lifestyle intervention resulted in more participants maintaining normal blood glucose values over a period of 4 years than the metformin or placebo groups.

12. Exercise Capacity and Mortality Risk

Poor exercise capacity is a well-established independent predictor of cardiovascular and overall mortality among healthy subjects, and patients with diabetes mellitus and/or cardiovascular disease (CVD) [23, 24, 60–65] whereas increased physical activity and higher cardiorespiratory fitness confer health benefits in proportion to the level of fitness [23, 24, 60–65], independent of body mass index (BMI) [60, 61, 64, 65]. Increases in physical activity patterns, have, thus, emerged as an integral part of the prevention and management of type 2 diabetes mellitus [60–65]. We assessed the association between exercise capacity and mortality risk in African-American ($n = 1,703$) and Caucasian ($n = 1,445$) diabetic men during a mean follow-up period of over 7 years. We noted a graded reduction in mortality risk with increased exercise capacity for both races. The association was stronger for Caucasians. Each 1-MET increase in exercise capacity yielded 19% lower risk for Caucasians and 14% for African-Americans. Similarly, the risk was 43% lower for moderate-fit and 67% for high-fit Caucasians. The comparable reductions in African-Americans were 34% and 46%, respectively. Our findings support that exercise capacity is a strong predictor of all-cause mortality in African-American and Caucasian men with type 2 diabetes. The exercise capacity-related reduction in mortality appears to be stronger and more graded for Caucasians than for African-Americans [65]. These findings support previous reports of an inverse relationship between aerobic fitness and total mortality in both healthy and diabetic populations [23, 24, 60–64]. They also confirm a previous report in predominantly male Caucasian diabetics that the largest proportional reduction in risk occurs between the least fit and the moderate fit categories [61].

13. Physical Activity and Obesity

Prior to 1998, obesity was not considered an independent risk factor for CHD. In June 1998, the AHA reclassified overweight and obesity as a major, modifiable risk factor for CHD comparable in status to the other well-established CHD risk factors [66].

Obesity not only increases directly the CHD risk, but also amplifies it indirectly by the adverse effects of obesity on several established CHD risk factors. Evidence from multiple studies agreed that both BMI ≥ 27 and the distribution of fat in the abdomen region as indicated by a waist to hip ratio $>$ 0.85 in women and 0.98 cm in men or a waist circumference of $\geq$98 cm and $\geq$85 cm for men and women, respectively, are associated with hypertension, diabetes, abnormal lipids, and increased CHD mortality [67–72].

14. Physical Activity and Weight Loss

Weight reduction is principally determined and directly related to the net deficit in energy balance, either through a reduction in energy intake or an increase in energy expenditure regardless of the diet composition [73]. Both genetic factors and lifestyle are likely to contribute significantly to variability of body weight in humans [74]. A chronic energy imbalance that favors weight gain may be the outcome of a complex interaction between genetic and environmental factors [75, 76]. However it is virtually impossible to blame genes for the increase in obesity of epidemic proportion in the United States in the past 20 years, since the gene pool has not changed significantly [75]. It is more likely that the genetic makeup may not necessarily cause obesity, but in the presence of powerful environmental influences, the propensity for obesity is enhanced. The predominant environmental factors for obesity appear to be over-consumption of calories and reduction in physical activity. Of the two, physical inactivity appears to play the predominant role. According to the USA federal report on obesity, total caloric intake over the last two decades has not substantially increased while physical activity has decreased significantly [77].

The theoretical mechanism that chronic exercise promotes a reduction in body fat is by increasing total daily energy expenditure without a corresponding increase in energy intake [78]. Exercise alone results in favorable but modest reduction on body weight and body fat distribution [79]. This exercise-induced weight reduction is achieved by long-term aerobic exercises or physical activity of sufficient intensity, duration, and frequency. However, when the energy intake is held constant, exercise alone can achieve significant weight losses [78]. This was shown in at least one study where the investigators achieved 7.6 lbs of weight over a period of three months when an energy deficit of 700 Kcal per day was achieved by exercise only and energy intake was held constant to pre-exercise levels [80].

The effectiveness of exercise to induce weight loss is directly related to the total number of kcal expanded [81]. In this regard, the duration of exercise becomes important. In a recent 18-month exercise study, overweight women exercising more than 200 minutes per week realized a significantly greater weight reduction (-13.1 kg) than those exercising 150 to 200 minutes/week (-8.5 kg) or less than 150 min/week (3.5 kg). This suggests a dose-response relationship between

amount of exercise and long-term weight loss and that a minimum of 150 minutes of exercise per week may be necessary for enhanced weight loss [82].

Although the exercise-induced losses in body weight may be viewed as relatively small and disappointing by some, it is worth pointing out that weight loss must be viewed as a long-term process. Excess weight accumulation did not occur over night and expectations that it will shed quickly are not realistic. In this regard, long-term exercise-induced weight loss is promising. In an 8-week-diet or diet-plus-exercise program consisting of 35–60 minutes of aerobic activity 3 days per week, weight losses were similar in both groups. However, those who did not exercise during the 18-month follow-up period gained about 60% of the weight back in 6 months and 92% of the weight back at 18 months. For those who continued to exercise during the 18-month follow-up period, body weight did not change significantly [83]. Finally, increased physical activity combined with a prudent diet and behavior modification is likely to be a more effective a way to maximize weight loss [84, 85]. Furthermore, the exercise program should focus on long duration and low intensity, tailored for expending calories rather than improving fitness [84].

Despite the small changes in weight reduction associated with physical activity, a number of studies provide convincing evidence that reduction in mortality risk is evident and inversely related to exercise capacity regardless of BMI levels [86–89]. Furthermore, in a number of these studies, fitness emerged as a more powerful predictor of mortality than BMI [86–88] independent of overall and abdominal obesity [87] and of comparable importance with that of diabetes mellitus and other cardiovascular risk factors [88].

15. Dietary Approaches to Lower Risk

Comprehensive dietary approaches favorably affect cardiometabolic risk factors, (diabetes, high blood pressure, obesity) and reduce CVD. They are now widely recommended and implemented in the prevention and treatment of cardiovascular disease [90, 91]. Decreased saturated fats and cholesterol and increased consumption of fruits, vegetables, and whole grain products are advocated in most dietary approaches. In this regard, data from the Lyon Diet Heart Study [92, 93] supports as much as 50% to 70% reduction in recurrent heart disease and all-cause mortality and suggests that a Mediterranean-style diet may be superior to the health benefits of step I diet advocated by the National Cholesterol Education Program committee (NCEP) [90]. Several studies now support health benefits associated with the Mediterranean or Mediterranean-type diet. Consequently, such dietary patterns are presented as an alternative to the less practical for most people, vegetarian diet [92–100]. The traditional Mediterranean diet is characterized by a high consumption of olive oil, legumes, cereals, fruits, vegetables, moderate to high consumption of fish, moderate consumption of wine, dairy products, mostly as cheese and yogurt, and low consumption of meat and meat products. This diet is low in saturated fat (less than about 9% of energy), with total lipid intake ranging from less than 30% to more than 40% of energy from one area to another. Moreover, the ratio of monounsaturated to saturated fats is about two. The high content in the diet of vegetables, fresh fruits, and cereals, and the liberal use of olive oil guarantee an adequate intake of carotene, vitamin C, tocopherols, a linolenic acid, and various important minerals.

The unusually lower mortality rates reported by epidemiologic studies in Mediterranean populations are in support of suggestions [95] that such dietary pattern may be associated with lower risk of hypertension, coronary heart disease, and cancer. Recently, evidence from the CARDIO2000 study [97, 101] showed that the adoption of Mediterranean diet was related with an adjusted 7% to 10% reduction on the coronary risk in treated, untreated, or uncontrolled hypertensive subjects. In large prospective survey involving over 22,000 middle age and older Greeks, an inverse association was observed between death due to coronary heart disease and greater adherence to the Mediterranean diet regardless of sex, smoking status, level of education, body mass index, and level of physical activity [99].

Although the evidence strongly supports that Mediterranean dietary patterns lead to health benefits, some doubt that such dietary pattern is practical or can be adopted by other populations due to differences in cultural and environmental conditions [102]. Others, however, express optimism that the Mediterranean dietary pattern can easily be translated into other cultures, since it can utilize other food options to increase the intake of monounsaturated fats and consequently lead to similar effects in the health status [103]. Although this debate is likely to continue, current evidence strongly argues that the use of products that utilize olive oil instead of saturated fats should be encouraged in all cultures. In this regard, an ingenious and potentially promising approach to increase the consumption of olive oil has been introduced recently by at least one company. Saturated fats are removed from meat products (ham, cold cuts, etc.) and are substituted with olive oil. Similar findings have been reported by the Dietary Approaches to Stop Hypertension (DASH) clinical trial [94] that utilized very similar to the Mediterranean dietary pattern in hypertensive adults. The investigators reported that the diet, rich in fruits and vegetables, and contains reduced saturated and total fat, sodium held constant, was superior in reducing blood pressure [94] and lowering the risk of CHD and stroke among middle-aged women during 24 years of follow-up [104].

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Review Article

Special Needs to Prescribe Exercise Intensity for Scientific Studies

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There is clear evidence regarding the health benefits of physical activity. These benefits follow a dose-response relationship with a particular respect to exercise intensity. Guidelines for exercise testing and prescription have been established to provide optimal standards for exercise training. A wide range of intensities is used to prescribe exercise, but this approach is limited. Usually percentages of maximal oxygen uptake (VO_2) or heart rate (HR) are applied to set exercise training intensity but this approach yields substantially variable metabolic and cardiocirculatory responses. Heterogeneous acute responses and training effects are explained by the nonuniform heart rate performance curve during incremental exercise which significantly alters the calculations of $\%HR_{max}$ and %HRR target HR data. Similar limitations hold true for using $\%VO_{2max}$ and $\%VO_2R$. The solution of these shortcomings is to strictly apply objective submaximal markers such as thresholds or turn points and to tailor exercise training within defined regions.

1. Introduction

Evidence regarding the health benefits of physical activity is overwhelming and there is no doubt about the impact of exercise training on health and fitness [1–3]. Exercise training improves exercise tolerance as well as symptoms of particular diseases and increases submaximal and maximal exercise capacity [2–5]. Furthermore, exercise training improves quality of life and reduces hospitalisation, morbidity, and mortality [6–10]. There is clear evidence that exercise training therapy positively affects chronic diseases in general [2, 5], and therefore exercise training is usually an integral part of secondary prevention and specifically of cardiac rehabilitation [11]. However, the applied exercise prescriptions in the underlying training interventions studies vary considerably. Corra et al. [11] suggested the usually applied exercise modalities to be safe, however, the question about the most effective training mode still remains to be answered.

As presented by the American College of Sports Medicine (ACSM) the essential components of a systematic individualized exercise prescription include the appropriate mode(s), intensity, duration, frequency, and progression of exercise training at which *exercise intensity* is considered as the most important of the primary variables [12]. With respect to exercise intensity, we may suggest that the optimal individually tailored exercise prescription for each single subject can only be determined from an objective evaluation of the individuals' response to exercise. This implies the standard use of cardiopulmonary exercise testing for the functional evaluation of healthy subjects and patients and the determination of individual reference points for every single subject [13–16]. It seems obvious that the relative but not the absolute intensity is the major impact for an exercise-induced increase in several mRNA [17] pointing to the importance of individual reference points for exercise prescription, independent of health and fitness status.

Health and fitness benefits associated with exercise training follow a dose-response relationship where the importance of optimal individual exercise intensity has been highlighted [5, 17]. That applies particularly to subjects with disease but also for apparently healthy subjects and athletes.

However, in the numerous studies available, various combinations of the above-mentioned components of exercise prescription were applied, and up to now there is

Table 1: Overview of recommendations for physical activity and public health in healthy adults and patients.

Recommendation	Intensity	Duration	Frequency
ACSM [18] resource manual for guidelines for exercise testing and prescription healthy individuals	moderate intensity 40%–59% HRR (VO_2R) vigorous intensity ≥ 60% HRR (VO_2R)	20–60 min·day^{-1} continuous or intermittent in bouts of at least 10 min 20–60 min·day^{-1} continuous or intermittent in bouts of at least 10 min	min. of 5 d·wk^{-1}min. 3 d·wk^{-1}
CAD + MI patients	40%–85% HRR (VO_2R)		
HF patients	40%–70% HRR (VO_2R)		
ACSM [19] guidelines for exercise testing and prescription	40%–85% HRR (VO_2R)	20–60 min·day^{-1}	3–5 d·wk^{-1}
ACSM/AHA [20] healthy adults 18–65 years of age	moderate intensity (between 3.0 and 6.0 METs) vigorous intensity (above 6.0 METs)	at least 30 min·day^{-1} continuous or intermittent in bouts of at least 10 min each at least 20 min·day^{-1} continuous activity	min. of 5 d·wk^{-1}min. of 3 d·wk^{-1}
ACSM/AHA [21] older adults aged >65 years	moderate intensity (5-6 on a 10-point scale)vigorous intensity (7-8 on a 10-point scale)	at least 30 min·day^{-1} continuous or intermittent (in bouts of at least 10 min each) activity at least 20 min·day^{-1} continuous activity	min. of 5 d·wk^{-1}min. of 3 d·wk^{-1}
AHA [22] coronary artery disease	moderate intensity (40%–60% of HRR) vigorous intensity as tolerated (60%–85 % of HRR)	at least 30 min·day^{-1}	min. of 3 d·wk^{-1}
ACSM [23] hypertension	moderate intensity (40%–60% of VO_2R) vigorous intensity acceptable for selected adults	30–60 min·day^{-1} continuous or intermittent (in bouts of at least 10 min each) activity	most, preferably all days per week
AHA [24] stroke	50%–80% of HR_{max}	20–60 min/session (or multiple 10 min sessions)	3–7 d·wk^{-1}
American Diabetes Association [21] type 2 diabetes	moderate intensity (50%–70% of HR_{max}) vigorous intensity (>70% of HR_{max})	at least 150 min·wk^{-1} moderate and/or at least 90 min·wk^{-1} vigorous activity	min. of 3 d·wk^{-1}, no more than 2 consecutive days without activity

HRR: heart rate reserve; VO_2R: oxygen consumption reserve.
CAD: coronary artery disease; MI: myocardial infarction; HF: heart failure.

no consistent model of exercise prescription fulfilling the optimal individual needs for training studies in healthy subjects and patients.

Guidelines for exercise testing and prescription have been established to provide optimal standards for exercise training in healthy subjects as well as for cardiac rehabilitation and secondary prevention programs [12, 14–16]. These standards give a broad spectrum of possibilities for the attending physician by defining safe and effective upper and lower limits in general terms. However, this wide range of intensities for the prescription of exercise recommended in these guidelines (Table 1) makes it rather difficult to make an appropriate choice of exercise intensity for a single individual. The application of various exercise intensities within this wide spectrum gives good reasons for differences in the training responses and the heterogeneity in outcome seen in all kinds of different exercise training intervention studies limiting the comparability of data [25, 26].

The questions to be answered are which optimal choice of intensity for an individual is safe (upper limit) and effective

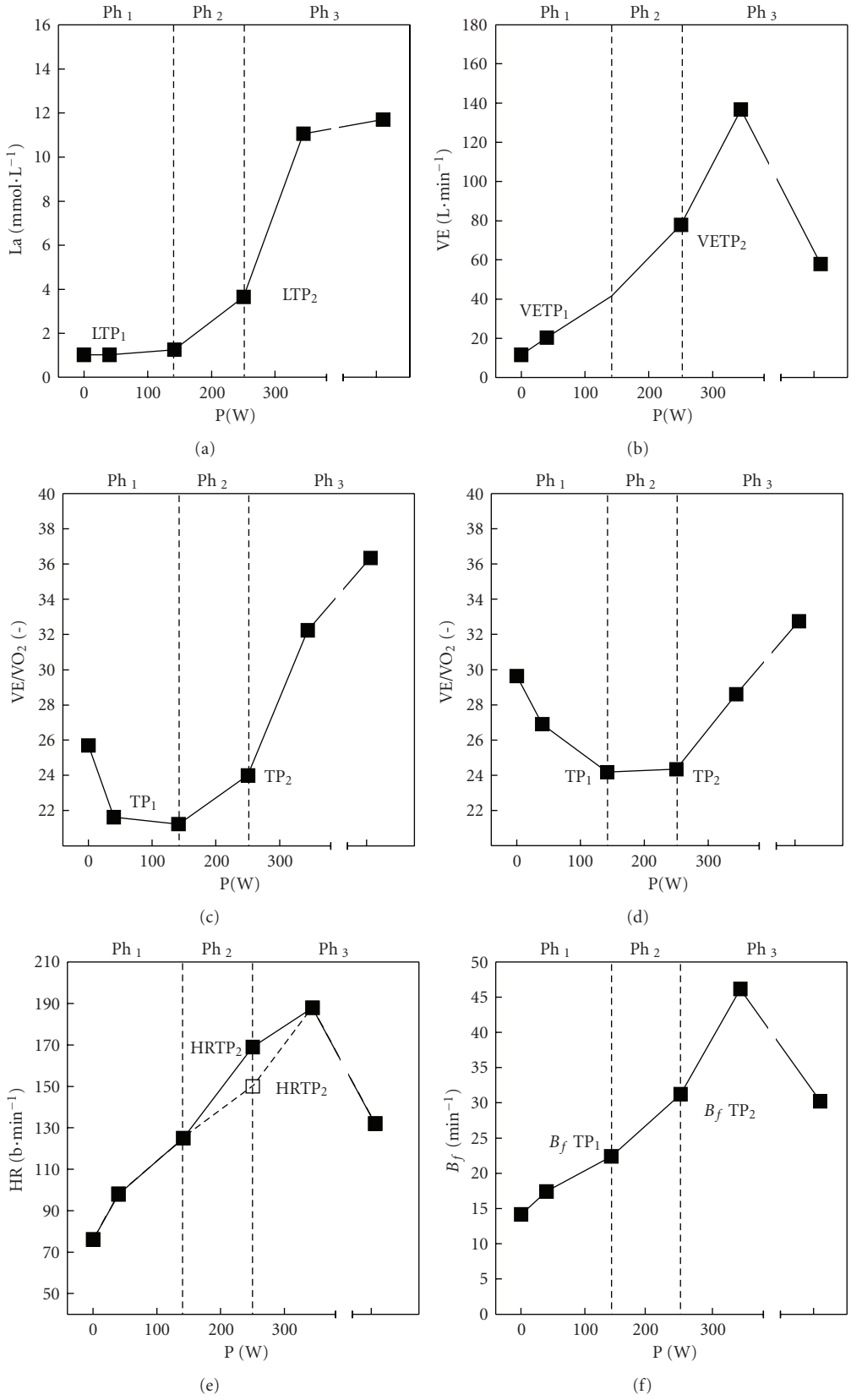


Figure 1: Schematic representation of first- and second- turn points of selected variables (La blood lactate concentration; VE: ventilation; VE/VO_2: equivalent for oxygen uptake; VE/VCO_2: equivalent for carbon dioxide output; HR: heart rate; B_f: breathing frequency) and distinct phases (Ph 1–3) of energy supply determined from young healthy male subjects. Ph 1: no increase of blood lactate concentration above baseline during constant load exercise. Ph 2: increased but steady state blood lactate concentration during constant load exercise. Ph 3: continuous increase of blood lactate concentration during constant load exercise leading to early termination of exercise.

(lower limit) and, even much more important, which is the optimal definition of exercise intensity for scientific investigations to evaluate training effects in healthy subjects and patients suffering from various chronic diseases [13, 27, 28].

As exercise intensity is suggested to be the leading component of exercise prescription we draw our attention especially to this specific component, although one should be aware of the fact that all components of exercise training and their combination are also substantial parts of the action of exercise training.

2. Exercise Intensity

It is suggested that physiological benefits gained from exercise training are primarily dependent on the intensity of the training stimulus [32]. The intensity should be above a minimal level required to induce a training effect which was shown to be at 40%–49% heart rate reserve (HRR) or 64%–70% maximal heart rate (HR_{max}) or even lower at 30% oxygen uptake reserve (VO_2R) in unfit subjects [19]. However, clearly defined standards for the lower limit of prescriptible aerobic training intensity have not been established yet, neither in healthy individuals nor in cardiac patients [27]. As it is well known in work physiology that staying below 33%–50% maximal oxygen uptake (VO_{2max}) is necessary to sustain eight-hour work shifts [33], we may assume this threshold to be a limit which has to be exceeded to gain training effects.

The upper limit of prescriptible aerobic training intensity is crucial for safety and control of exercise-related risks [27]. Therefore, exercise prescription should include individually prescribed upper limits for exercise intensities. Several studies showed that in general training using higher intensities gains significantly greater improvements than moderate or low intensity exercise training with the same volume of exercise [34–36] or similar energy expenditure [37]. These findings led to a revival of intense interval-type exercise training [38–42]. However, approaching the limits of tolerance requires more precise and sophisticated diagnostics and exercise intensity prescriptions particularly for patients.

3. Exercise Intensity Prescription by Means of HR_{max} and HRR

Standard variables used to prescribe exercise intensity are percentages of maximal heart rate (HR_{max}) and maximal oxygen uptake (VO_{2max}) as well as calculated subfractions of these variables such as HR reserve (HRR) and VO_2 reserve (VO_2R).

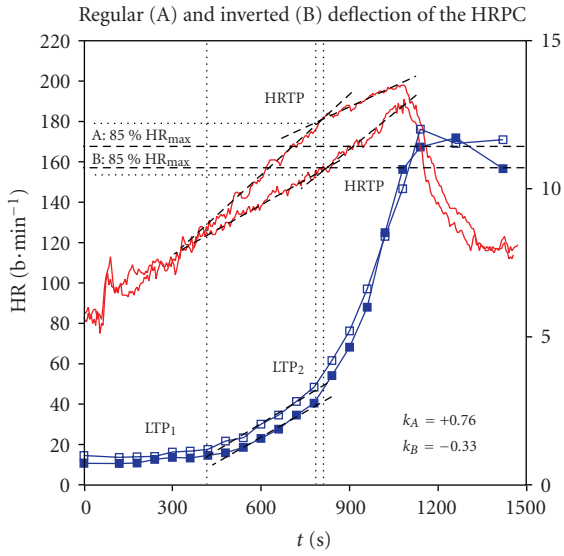
Heart rate is the most common parameter to determine target exercise training intensity. The usual recommendations are in a range between 64% and 70% to 94% of HR_{max} or between 40% and 50% to 85% of HRR (and VO_2R) [19] (Table 1). However, the HR response to incremental exercise was shown to be neither linear nor uniform [29, 30, 43] (Figure 2). Consequently, this heterogeneous character of the heart rate performance curve (HRPC) significantly alters the calculations of $\%HR_{max}$ and %HRR target training HR as shown previously [29, 44–47]. It is demonstrated in Figure 2 that two healthy young subjects with more or less identical maximal power output (P_{max}) and submaximal power output at the first lactate turn point (P LTP_1) and at the second lactate turn point (P LTP_2) vary considerably in their HR response, more precisely in their $\%HR_{max}$ at P LTP_2. So calculating the same target training upper limits by means of $\%HR_{max}$ or %HRR gives a completely different training load with respect to the reference turn points [13, 25, 29, 46, 47]. More importantly most patients with cardiovascular disease present an upward deflection of the heart rate performance curve [48] stressing the importance of this problem in this kind of population (Figure 2). Using $\%HR_{max}$ methods such as the common 85% HR_{max} model will lead to an overestimation of the individual training heart rate by at least 5%–10% and up to 40% in single cases [44]. Figure 3 shows the error of estimate caused by different $\%HR_{max}$ at P LTP_2 if fixed percentages of HR_{max} or HRR [29, 44] are applied. Similar results were also shown by Tabet et al. [46] and Wonisch et al. [47].

Additional concerns may be raised if true maximal HR or oxygen uptake values can be obtained in untrained subject and especially in patients [49, 50]. Because of local leg fatigue, tests may end prematurely before cardiopulmonary endpoints have been achieved [19].

4. Exercise Intensity Prescription by Means of VO_{2max} and VO_2R

Oxygen uptake-based prescriptions are frequently used for individual training but more often for exercise training studies since VO_{2max} is accepted as the criterion measure of cardiorespiratory fitness. Several studies [32, 51] indicated that among healthy adults, $\%VO_2R$ is more closely related to %HRR than it is to $\%VO_{2max}$, although there is a disparity of 10% between the two first methods mentioned above. It has also been shown that the disparity increases with age [32]. These findings, in addition to the disparity between %HRR and $\%VO_{2max}$ which is greater at low intensities and among low fit individuals, provoked the ACSM to adopt the use of $\%VO_2R$ in place of $\%VO_{2max}$ when prescribing exercise intensity among healthy adults and patients [51]. It is a common assumption that not only absolute oxygen uptake at the anaerobic threshold but also $\%VO_{2max}$ at this threshold is higher in trained subjects [52]. Similarly as shown for HR, exercise prescription based on fixed percentages of VO_{2max} will lead to an overestimation of target training intensity in patients with limited exercise tolerance and with a first lactate turn point appearing already at a very low power output [53]. In accordance with that, Scharhag-Rosenberger et al. [26] emphasized that applying the same fixed percentage of maximal oxygen uptake yields substantially variable acute metabolic responses across subjects (Figure 4) and that different training stimuli with respect to individual submaximal reference turn points (P LTP_1, P LTP_2) may be expected.

In addition, several studies have shown marked individual differences in responsiveness to exercise training



(a)

A	B
HR HRTP = 180 b.min^{-1}	HR HRTP = 157 b.min^{-1}
HR LTP$_2$ = 179 b.min^{-1}	HR LTP$_2$ = 155 b.min^{-1}
HR LTP$_1$ = 139 b.min^{-1}	HR LTP$_1$ = 127 b.min^{-1}
HR LTP$_2$ = 90.4%HR$_{max}$	HR LTP$_2$ = 83.4%HR$_{max}$
70% HR$_{max}$ = 139 b.min^{-1}	70% HR$_{max}$ = 130 b.min^{-1}
80% HR$_{max}$ = 158 b.min^{-1}	80% HR$_{max}$ = 148 b.min^{-1}
85% HR$_{max}$ = 168 b.min^{-1}	85% HR$_{max}$ = 157 b.min^{-1}
90% HR$_{max}$ = 178 b.min^{-1}	90% HR$_{max}$ = 167 b.min^{-1}
70% HRR = 163 b.min-1	70% HRR = 154 b.min-1
80% HRR = 174 b.min^{-1}	80% HRR = 164 b.min^{-1}
85% HRR = 180 b.min^{-1}	85% HRR = 170 b.min^{-1}
90% HRR = 186 b.min^{-1}	90% HRR = 175 b.min^{-1}

(b)

Figure 2: Accuracy of target training heart rate dependent on the time course of the Heart Rate Performance Curve. The same relative intensity of 85% HR$_{max}$ (usual upper limit) gives different work load related to the anaerobic threshold (LTP$_2$) [29]. Subject (A) 85% HR$_{max}$ is well below HR LTP$_2$; subject (B) 85% HR$_{max}$ is already above HR LTP$_2$.

interventions. For example, impacts of standardized training programs on VO_{2max} have ranged from almost no gain up to 100% increase in large groups of sedentary individuals [54–56]. Similar results have been reported by Hansen et al. [57] in cardiac patients. Data from the HERITAGE family study [56] showed that subjects who exercised at an HR associated with the same relative %VO_{2max} intensity vary substantially in their training response, in their rate of increase in power output over a 20-wk training program, and in their improvement of VO_{2max}. However, age, sex, race, and initial fitness had little impact on these individual differences [54, 56], and a genetic component to explain these differences was suggested [58, 59]. However, one may suggest also the mode of exercise prescription to be a possible factor of influence [25, 26, 28]. Furthermore, similar as discussed for HR_{max} we may critically argue if a true VO_{2max} can be obtained in untrained obese subjects [60] and patients [61].

Most of the prescription models used for exercise training interventions refer to maximal variables measured from incremental ergometer exercise giving a wide range of intensities (Table 1); however, given the aforementioned limitations of these models, the recommendations to use turn point models are increasing [13, 26, 62].

5. Exercise Intensity Prescription by Means of Submaximal Markers—The Turn Point Model

Scharhag-Rosenberger et al. [26] criticized the "traditional" concept to prescribe exercise intensity by means of maximal values, and they suggested that it might be more appropriate to consider the metabolic demand of exercise applying a threshold concept. Several authors [25, 46] have pointed out the shortcomings of training prescriptions without defining a threshold but applying fixed percentages of HR_{max} or HRR leading to differing levels of metabolic stress across subjects (see Figures 2 and 3). Recently Salvadego et al. [63] suggested that exercise prescription and evaluation should be made at workloads chosen with respect to submaximal markers from incremental exercise and not as percentages of VO_{2max}. Binder et al. [13] showed the advantage of applying a three phase model, using the first- and the second- turn point approach presented earlier by Davis et al. [64] and later on by our own working group [29, 30, 43, 65–67] and other authors [68]. This method, however, is surprisingly only marginally described in the current guidelines.

This concept is known as the three-phase-model presented already by Skinner and McLellan [69]. As there are numerous concepts to determine thresholds, this topic has been discussed extensively during the past decades. From all these concepts two different main approaches can be deduced:

(1) thresholds indicating the first increase in blood lactate concentration originally defined as the "anaerobic threshold" (AT) by Wasserman and McIlroy [70] and mostly described as the "aerobic threshold" equivalent to the first-turn point for lactate (La), ventilation (VE), and the oxygen equivalent (VE/VO_2), and breathing frequency (B_f) [13, 62],

(2) thresholds indicating the maximal lactate steady state which is significantly higher than the first-turn point and mostly described as the "anaerobic threshold" equivalent to the second-turn point for La, VE, B_f, VE/VO_2, and VE/VCO_2 [13, 29, 62, 65–67, 71] as well as to the heart rate turn point (HRTP) as earlier shown by our own working group [29, 30, 65].

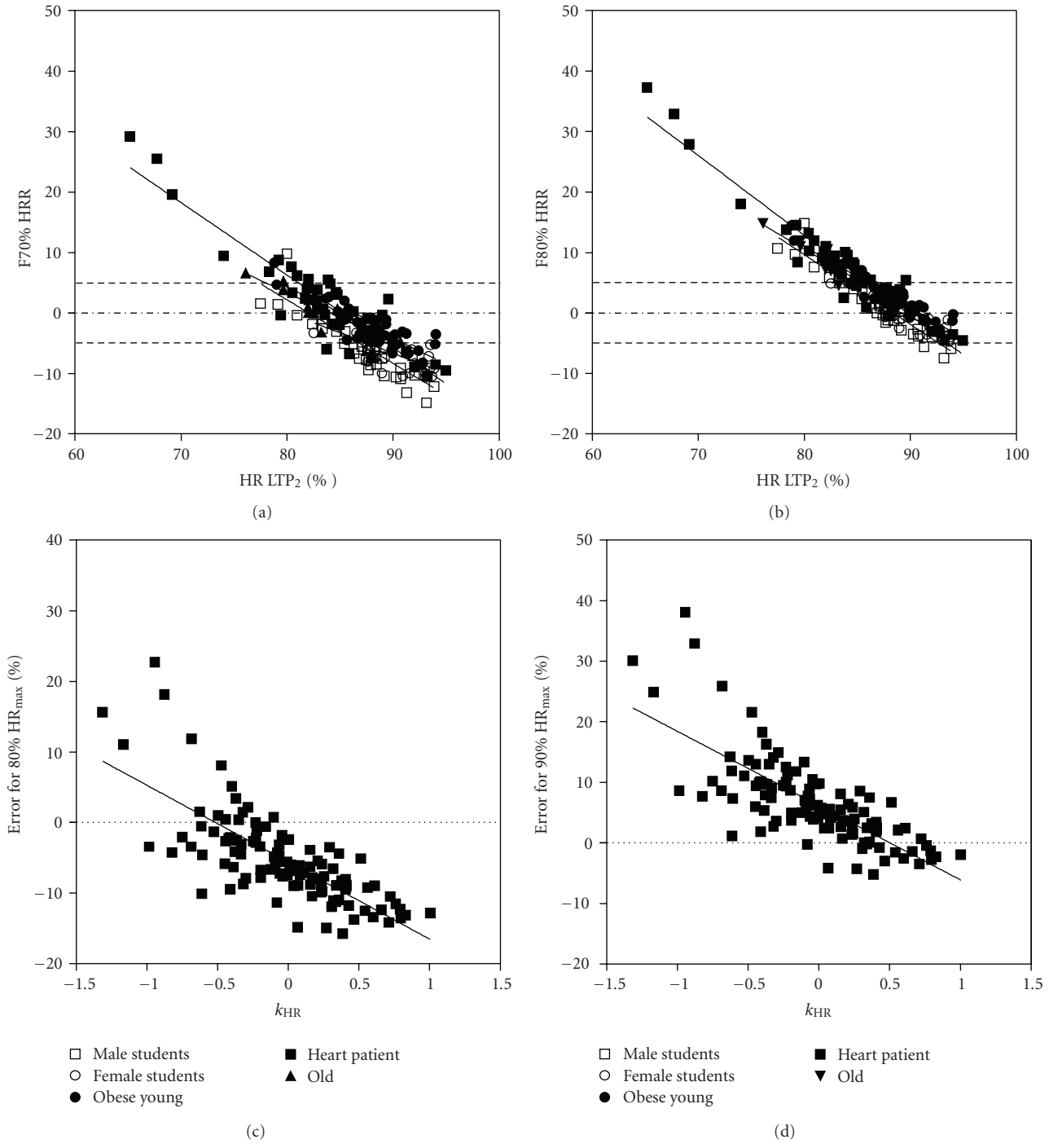


Figure 3: Error of estimate for percent heart rate reserve (HRR) compared to %HR at the second lactate turn point (LTP_2) as well as the error of estimate for percent HR_{max} related to the deflection of the heart rate performance curve (kHR) [29, 30] in healthy young male and female sports students, young obese subjects, older healthy subjects, and patients after myocardial infarction [31].

Numerous definitions and descriptions of these thresholds have been presented in the last decades [13].

To avoid any confusion, we therefore recommend to apply a nomenclature defining a first- (TP_1) and a second-turn point (TP_2) and denominate the turn points by the variable used to detect the turn point such as the first and the second turn points for lactate (LTP_1, LTP_2), heart rate ($HRTP_1$, $HRTP_2$) ventilation ($VETP_1$, $VETP_2$) or the oxygen equivalent (VE/VO_2TP_1, VE/VO_2TP_2) and the carbon dioxide equivalent (VE/VCO_2TP_1, VE/VCO_2TP_2).

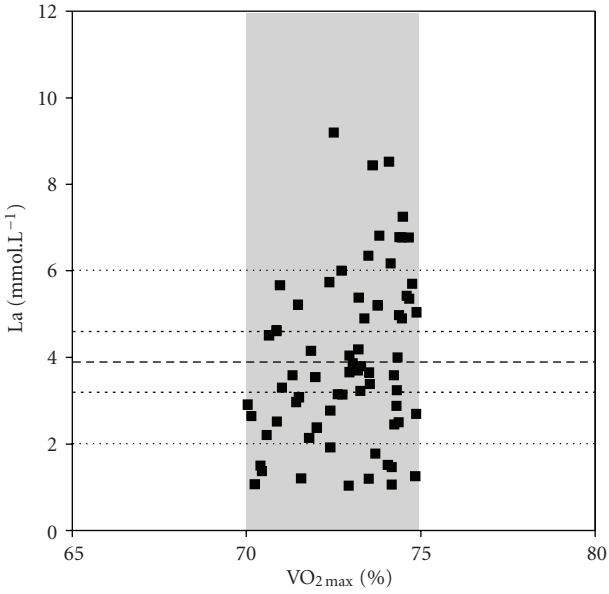


Figure 4: Mean blood lactate concentration (La) during constant load exercise in trained subjects applying controlled 70%–75% of VO_{2max} (unpublished results).

Figure 1 shows a schematic representation of the first and second turn points for these selected variables based on measures of 25 trained male subjects [31].

Using these objective individual turn points to prescribe exercise intensity allows for homogenous acute metabolic responses and uniform training stimuli across subjects yielding a reduction of health risk and enabling the comparison of results revealed by different training intervention studies.

The complex of problems associated with heterogeneous metabolic responses was pointed up by Hashimoto and Brooks [72] who argued that lactate is not only an oxidizable substrate and glucogenic precursor, but may also act as a pseudohormone called "lactormone" with a distinct signaling role. They nicely showed that lactate incubation upregulated hundreds of ROS-sensitive genes, suggesting the presence of a vast lactate-activated transcription network, a lactate transcriptome. This gives a good reason to postulate the use of exercise training regimes that induce similar metabolic responses across subjects. To ensure this demand, however, one has to respect the lactate shuttle theory [73] which implies a three-phase framework of the lactate performance curve with two distinct turn points [29–31] and three distinct phases of energy supply. Up to date there are no studies available applying such specifically tailored exercise protocols; however, some studies strongly support this assumption. Lamprecht et al. [74] showed that oxidative protein damage, as indicated by carbonyl protein oxidation, was significantly increased at intensities slightly above LTP_2 (VT_2) but was not at intensities below this turn point. Additionally, Jürimäe et al. [75] applied two constant workloads, one just below and one just above $HRTP_2$ (VT_2) in trained rowers. These authors showed that despite minimal heart rate differences of only 5 b·min^{-1} between two rowing exercise bouts just below or above VT_2, growth hormone response was almost doubled in exercise above the VT_2. Given these findings, the second turn point for La, HR, or VE [29, 30, 65, 71, 76], consistent with the maximal lactate steady state [67, 76], seems to be a criterion for the upper level of exercise prescription in healthy subjects and patients.

In addition, the prescription of exercise intensity by means of the turn point concept is successfully applicable not only for constant load exercise, but also for interval-type exercise as recently shown by Tschakert et al. [77].

However, there are still some controversies about the "correct" concept of AT-determination to apply. Standards have been set for ventilatory threshold [62]; however, standard lactate-derived thresholds are still missing.

6. Conclusions

Exercise intensity plays a pivotal role to gain a sufficient training response without harmful side effects in healthy subjects and patients. Higher exercise intensities seem to be more beneficial; however, approaching the upper limits of exercise tolerance demands a more precise determination of these limits. Fixed percentages of HR_{max} or VO_{2max} are not sufficient when approaching the upper limits and include some serious errors. For safety reasons, it may be concluded that the upper limit of target heart rate for exercise prescription should therefore *not* be assessed by means of a particular percentage of HR_{max}, HRR, VO_{2max}, or VO_2R, but by using intensities related to a certain threshold or turn point. The lactate turn point (LTP) concept gives a valid approach as it has a theoretical foundation and is consistent with other threshold determinations. As turn point concepts for lactate, heart rate, or ventilatory variables define these upper limits more precisely, this somewhat sophisticated approach is expected to be superior to the usual "art" of exercise prescription using fixed percentages and is therefore recommended by our working group especially for training studies. In addition, we ascertain that this definition of target training zones by means of turn points is necessary for trainings studies to obtain similar relative intensities and therefore comparable results for all study participants independent of their fitness level.

However, evidence regarding the most efficient training mode and intensity is still lacking. Further research is encouraged applying the turn point model describing distinct phases of energy supply to set exercise intensity standards for training intervention studies in patients.

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Research Article

Health-Adjusted Life Expectancy among Canadian Adults with and without Hypertension

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Hypertension can lead to cardiovascular diseases and other chronic conditions. While the impact of hypertension on premature death and life expectancy has been published, the impact on health-adjusted life expectancy has not, and constitutes the research objective of this study. Health-adjusted life expectancy (HALE) is the number of expected years of life equivalent to years lived in full health. Data were obtained from the Canadian Chronic Disease Surveillance System (mortality data 2004–2006) and the Canadian Community Health Survey (Health Utilities Index data 2000–2005) for people with and without hypertension. Life table analysis was applied to calculate life expectancy and health-adjusted life expectancy and their confidence intervals. Our results show that for Canadians 20 years of age, without hypertension, life expectancy is 65.4 years and 61.0 years, for females and males, respectively. HALE is 55.0 years and 52.8 years for the two sexes at age 20; and 24.7 years and 22.9 years at age 55. For Canadians with hypertension, HALE is only 48.9 years and 47.1 years for the two sexes at age 20; and 22.7 years and 20.2 years at age 55. Hypertension is associated with a significant loss in health-adjusted life expectancy compared to life expectancy.

1. Background

Hypertension or high blood pressure (HTN) is an important risk factor for cardiovascular disease. In 2002, the World Health Organization estimated that at least 50% of cases with cardiovascular disease and 75% of strokes were caused by elevated blood pressure [1]. Hypertension is considered to be one of the leading risk factors for death and disability worldwide.

The number of Canadians with hypertension is increasing in Canada. The first report on hypertension from the Canadian Chronic Disease Surveillance System published by Public Health Agency of Canada shows that the age-standardized prevalence of hypertension among the adult population increased by about 7% between 1998 and 2006 and is projected to increase by another 25% by the end of 2012 [2]. According to that report the crude prevalence of diagnosed hypertension among Canadian adults (20 years old and older) in 2006 was 22.7%. Similar estimates of the prevalence of hypertension are also reported by Statistics Canada based on results from the first cycle of Canadian Health Measure Survey [3]. In many cases, the presence of hypertension leads to premature death and therefore the reduction of life expectancy (LE) and health expectancy (healthy life expectancy). Because of high morbidity in the hypertensive population, the reporting of mortality or life expectancy which uses only mortality experience is not enough to fully describe the burden of the chronic condition in population.

This paper reports results on Health-Adjusted Life Expectancy (HALE). HALE is an indicator that can be used as a summary measure of population health. While LE is the average number of years a person is expected to live, HALE is life expectancy weighted or adjusted for the level of Health Related Quality of Life (HRQOL). It combines morbidity and mortality data in one single indicator of population health and indicates the average time that a person could expect to live in a healthy state. Comparison of disparities

in LE and HALE for a population of people with and without hypertension, and evaluation of loss in LE and the proportion of life lived in poor health for these cohorts can provide a comprehensive picture of how hypertension changes the lives of people.

There are few published studies which looked at the impact of hypertension on life expectancy [4, 5] and, to our knowledge, no previously published study has looked at high blood pressure and health expectancy. This is the first population-based Canadian study of life expectancy and health-adjusted life expectancy for people with and without diagnosed hypertension.

2. Data Sources and Methods

Health-adjusted life expectancy is a composite indicator that combines morbidity and mortality into a single statistic. Mortality data files from the Canadian Chronic Disease Surveillance System (CCDSS) were used for estimating age and sex-specific mortality rates. While mortality data and population counts are sufficient for calculating life expectancy, a measure of health-related quality of life is also needed to estimate health-adjusted life expectancy, its variance and corresponding 95% confidence intervals. The measure used in this analysis was the Health Utilities Index Mark 3 which was estimated from the Canadian Community Health Survey (CCHS).

2.1. Canadian Chronic Disease Surveillance System. The Canadian Chronic Disease Surveillance System is a collaborative network of provincial and territorial chronic disease surveillance systems, supported by the Public Health Agency of Canada [6]. It was created to improve the breadth of information about the burden of chronic diseases in Canada so that policy makers, researchers, health practitioners, and the general public could make better public and personal health decisions. CCDSS collects data from various sources on the prevalence, incidence, mortality, and utilization of health care services related to hypertension and other chronic conditions and diseases.

In each province and territory, the health insurance registry database is linked to the physician billing and hospitalization databases to generate summarized data for residents of Canada who have used the Canadian health care system. These summarized data are stored in the CCDSS for routine analysis. If there is sufficient evidence of use due to hypertension, it is assumed that a person had been diagnosed with hypertension. The minimum requirement was at least 1 hospitalization or 2 physician claims over a 2-year period with specific code(s) for hypertension from the International Classification of Diseases (ICD) (ICD-9 codes 401–405; ICD-10 codes I10– I13 and I15). With respect to hypertension, the CCDSS collects data for the adult population only, that is, 20 years old and older.

For Canadian adults with and without hypertension, age-specific mortality rates for all causes are included in the CCDSS. For this study, the age-specific mortality rates for persons with and without adult hypertension were used to calculate life expectancy and health-adjusted life expectancy. The study was limited to persons who are 20 years old and older.

2.2. Canadian Community Health Survey. The Canadian Community Health Survey is an ongoing cross-sectional national health survey, conducted by Statistics Canada [7–9], that collects information related to health status, health care utilization, and health determinants for the Canadian population. It includes a large sample of about 130,000 respondents and is designed to provide reliable estimates at the local health region level.

Prior to 2007, data collection occurred every 2 years for a 12-month period. After major changes to the survey design in 2007, data collection now occurs on an ongoing (monthly) basis with annual releases. Data are available for 2000/2001, 2003, 2005, 2007, 2008, and 2009.

The CCHS produces an annual microdata file and a file combining 2 years of data. The survey collection years can also be combined by users to examine subpopulations of rare characteristics. The respondents of the first three cycles of the survey were asked if they have any of 26–30 chronic conditions including hypertension. The survey data include information for persons aged 12 years and older. The survey does not include people who live in institutions or in remote areas. The household-level response rate in 2005 was 84.9%, and the person-level response rate was 92.5% [9].

As a measure of health-related quality of life, the Health Utilities Index Mark 3 from the following three CCHS data files was used for this study: (1) cycle 1.1 2000/2001 share file [7]; (2) cycle 2.1 2003 subsample 1 file [8]; and (3) cycle 3.1 2005 subsample 1 file [9].

2.3. Health Utilities Index Mark 3. HUI3 is a multiattribute utility measure that defines health states according to eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain), with five or six levels ranging from normal to severely limited functioning for each. Single attribute utility scores range from 0.0 (lowest level of functioning) to 1.0 (full functional capacity) [10]. The eight attributes are combined into a single score using the multiattribute utility function:

$$u = 1.371 * (b_1 * b_2 * b_3 * b_4 * b_5 * b_6 * b_7 * b_8) - 0.371, \quad (1)$$

where u is HUI3 and b_i is a single attribute utility score.

The overall scores on the HUI3 range from −0.36 (the worst possible HUI3 health state), through 0.0 (death), to 1.0 (perfect health). From a societal perspective, some health states are considered worse than dead, and consequently are assigned negative scores. Differences of 0.03 or more in overall HUI3 scores and 0.05 or more in single-attribute utility scores are considered to be clinically important [11].

Sex and age-specific HUI averages were estimated from a combined CCHS data file for persons with and without hypertension. The bootstrap methodology [12], recommended by Statistics Canada, was used to calculate the variance estimate. Both the point estimates and variance estimations were calculated using the BOOTVARE_V31 macro [13].

2.4. Survey Sample Sizes. All three cycles of the CCHS (cycle 1.1 share file, cycle 2.1 subsample, and cycle 3.1 subsample) were combined by the pooled method to increase the sample size and to decrease variation in the estimates [14]. The sample size for the combined file, which included people 20 years and older and spanned the years 2000 through 2005, was 173,567 (32,612 with hypertension; 140,955 without hypertension).

Mortality data for Quebec and Nunavut were unavailable from the CCDSS, and health utilities index data from the Northwest Territories and Nunavut were unavailable from the 2000/2001 CCHS (cycle 1.1) survey file. Therefore, these jurisdictions were excluded from all analyses.

2.5. Life Table Analysis. The Chiang method [15] was used to generate period (2004–2006) life tables by disease-specific/disease-deleted populations and by sex using the 14 standard age groups (20–24, 25–9, . . ., 80–85, 85+ years). The Gompertz function was used to provide an accurate estimate of life expectancy for the last open-ended 85+ age interval, in order to close the life table. This method was described by Hsieh [16]. The modified Sullivan method [17] was applied for the HALE calculation. According to this method the "life years lived" was adjusted by the HUI

$$L'_x = L_x * \mathrm{HUI}_x, \tag{2}$$

where L'_x is adjusted life years lived in age interval x, L_x is life years lived in age interval x, and HUI_x is Health Utilities index for people in age interval x.

The variance of LE was calculated by the Chiang method. The variance in HALE, for the population without hypertension, was calculated by the Bebbington method [18] taking into account just the variability of HUI. The sample size of the population without hypertension was large; therefore the variance of the life-table itself was close to zero and did not contribute much to the variance of HALE. However, the sample size of population with hypertension was relatively small and the life-table variance was quite noticeable and could not be ignored. Therefore the variance of HALE for the population with hypertension was calculated taking into account both the variability of the life table and the variability of HUI. This method was introduced by Mathers [19]. All calculations were performed using specially developed SAS macros. The 95% confidence intervals for LE and HALE were built based on the normality assumption. Z-tests were used to test the statistical significance of loss in life expectancy and the absolute difference in life expectancy. The absolute difference in life expectancy is defined as the difference between life expectancy and the health adjusted life expectancy (LE-HALE) for the same cohort.

3. Results

Figures 1 and 2 show age and sex-specific estimates of the total (LE) and the healthy (HALE) number of years of life remaining for adults without and with hypertension. As expected, higher values for both LE and HALE were obtained for people not diagnosed and who did not report hypertension. For 20-year-old females who were not diagnosed with hypertension, LE was estimated to be an additional 65.4 years and HALE was an additional 55 years (Figure 1). The corresponding LE and HALE for males were 61.0 and 52.8 years, respectively. Within the population of people with hypertension, the LE and HALE were, respectively, 62.1 and 48.9 years for females and 56.9 and 47.1 years for males (Figure 2).

Table 1: Difference in life expectancy (LE) and health-adjusted life expectancy (HALE) between females and males with and without hypertension (HTN) for selected ages, Canada, 2004 to 2006. (Dataset for this study excluded Quebec, Nunavut and Northwest Territories.)

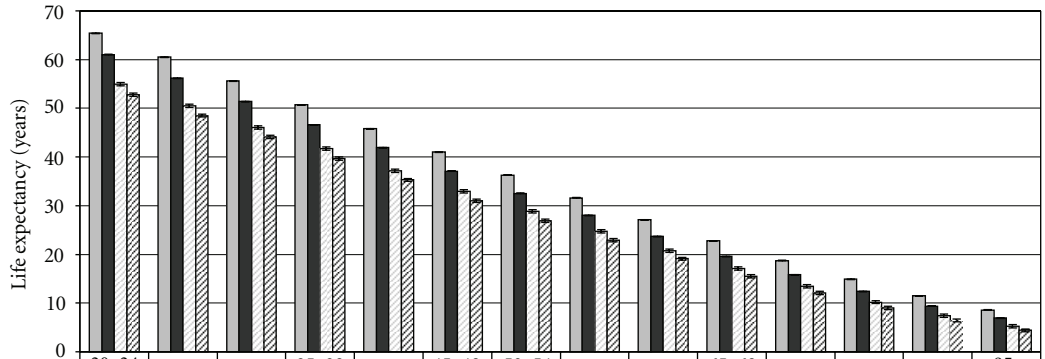
	LE(F)-LE(M)	HALE(F)-HALE(M)
At age of 20 years		
With HTN	5.2*	1.8**
Without HTN	4.4*	2.2*
At age of 55 years		
With HTN	4.2*	2.5*
Without HTN	3.6*	1.8*
At age of 85 years		
With HTN	2.0	0.9
Without HTN	1.7	0.8

*Statistically significant (P-value < .0001).
**Statistically significant (P-value < .05).

Figure 3 illustrates differences in age- and sex-specific average Health Utilities Index for persons with and without hypertension. HUI reported by men was higher than that reported by women for both populations. The index decreased with age and was lower for persons with disease.

The difference in LE between female and male populations with hypertension varies between 2.0 and 5.2 years across age groups, higher than that in the population without hypertension (Table 1). Differences in HALE between sexes were approximately half the difference in LE. HALE differences between females and males with hypertension were between 0.9 and 2.5 years. Similar patterns were observed for persons without hypertension. The narrower difference in HALE was a result of men reporting better health (higher HUI score) than women. Many LE and HALE differences reported in Table 1 were statistically significant.

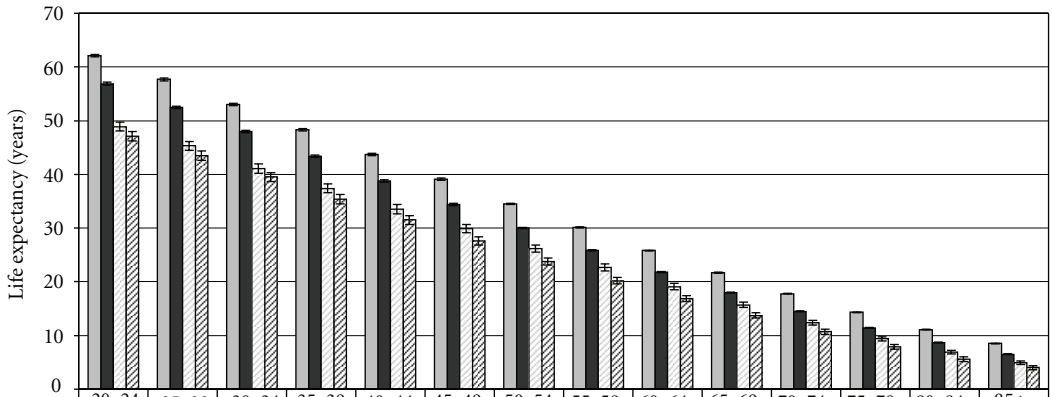
Table 2 illustrates absolute and relative measures of unhealthy years of life as well as the loss in LE and HALE associated with hypertension within age-sex grouping. The age groups selected for presentation were, the beginning of life table (age 20 years), the average age of hypertension incidence (55 years), and the last age interval of the life table (85 years). As age increases, the number of unhealthy years of life decreases while the proportion of unhealthy life years remaining increases. The unhealthy years of life for persons with hypertension varied between 13.2 years (at age 20) and 3.6 years (at age 85+) for females and between 9.8 years (at age 20) and 2.5 years (at age 85+) for males which was much higher than that for persons without hypertension. The corresponding number of unhealthy years for person



	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
LE, females	65.4	60.5	55.6	50.7	45.8	41	36.3	31.6	27.1	22.8	18.7	14.9	11.5	8.6
LE, males	61	56.2	51.4	46.6	41.9	37.1	32.5	28	23.7	19.6	15.8	12.4	9.4	6.9
HALE, females	55	50.5	46.1	41.7	37.2	32.9	28.8	24.7	20.8	17.1	13.5	10.2	7.4	5.2
HALE, males	52.8	48.5	44.1	39.7	35.3	31	26.9	22.9	19.1	15.5	12.1	9	6.4	4.4

Age (years)

Figure 1: Life expectancy (LE) and health adjusted life expectancy (HALE) for females and males, without hypertension, Canada, 2004 to 2006. (Data source: Canadian Community Health Survey Data Files (CCHS) from Statistics Canada, 2000–2005 and Canadian Chronic Disease Surveillance System Data Files (CCDSS) from Public Health Agency of Canada, 2004–2006. Data Files excluded Quebec, Nunavut and Northwest Territories.)



	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
LE, females	62.1	57.7	53	48.3	43.7	39.1	34.5	30.1	25.8	21.7	17.8	14.3	11.1	8.5
LE, males	56.9	52.5	48	43.4	38.8	34.4	30	25.9	21.8	18	14.5	11.4	8.7	6.5
HALE, females	48.9	45.3	41.1	37.4	33.5	29.9	26.2	22.7	19.1	15.7	12.4	9.4	6.9	4.9
HALE, males	47.1	43.5	39.5	35.4	31.5	27.6	23.8	20.2	16.9	13.7	10.7	7.9	5.6	4

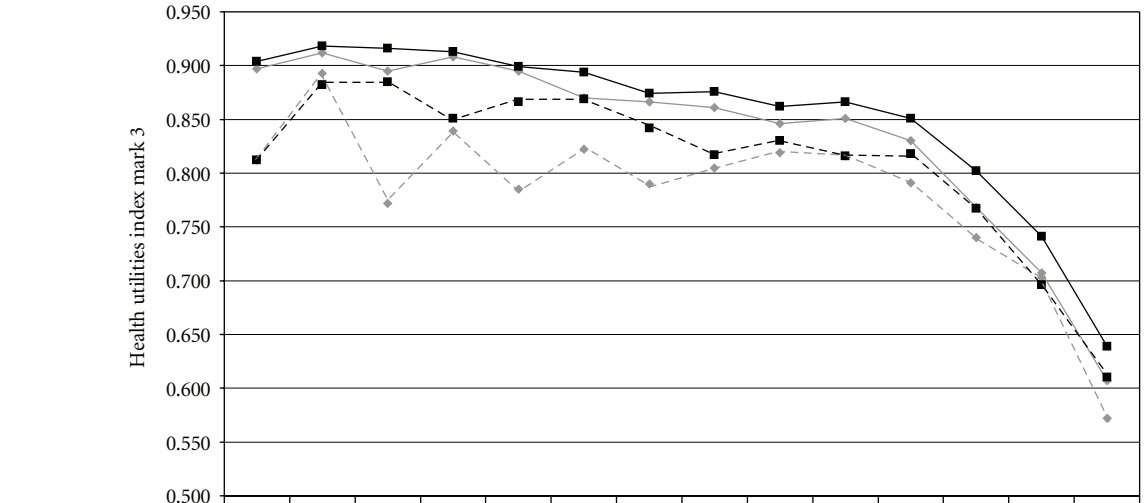
Age (years)

Figure 2: Life expectancy (LE) and health adjusted life expectancy (HALE) for females and males, with hypertension, Canada, 2004 to 2006. (Data source: Canadian community health survey data files (CCHS) from Statistics Canada, 2000–2005 and Canadian Chronic Disease Surveillance System Data Files (CCDSS) from Public Health Agency of Canada, 2004–2006. Data Files excluded Quebec, Nunavut and Northwest Territories.)

without hypertension was in a range 10.4–3.4 years for females and 8.2–2.5 years for males. When people without hypertension were compared to those with hypertension the loss in both LE and HALE decreased with increasing age for both women and men. The loss in LE decreased from 3.3 years at age 20 years down to 0.1 years at age 85 for women and from 4.1 down to 0.4 years for men. The loss in HALE decreases from 6.1 years at age 20 down to 0.3 years at age 85 for women and from 5.7 down to 0.4 years for men. All absolute differences were statistically significant (P-value $< .0001$) for all age groups except 85+ age group. (It was not possible to calculate the significance level for the 85+ age group.)

4. Discussion

In this study LE and HALE were estimated for Canadian adults (20 years old and older) with and without diagnosed hypertension by sex and fourteen 5-year age intervals. Our results show that life expectancy decreases with increasing age and that the decline is faster for LE than HALE (Figures 1 and 2). To explain this observation the age gradient in HUI



	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
without HBP, females	0.897	0.912	0.895	0.908	0.895	0.87	0.866	0.861	0.846	0.851	0.83	0.768	0.707	0.607
without HBP, males	0.904	0.918	0.916	0.913	0.899	0.894	0.874	0.876	0.862	0.866	0.851	0.802	0.741	0.639
with HBP, females	0.812	0.893	0.772	0.839	0.785	0.822	0.79	0.805	0.819	0.816	0.791	0.740	0.703	0.572
with HBP, males	0.812	0.882	0.885	0.851	0.866	0.869	0.842	0.817	0.83	0.816	0.818	0.767	0.696	0.61

Age (years)

Figure 3: Health utilities index (HUI) for females and males with and without hypertension (HTN), Canada, 2000 to 2005. (Data source: Canadian Community Health Survey Data Files (CCHS) from Statistics Canada, 2000–2005. Dataset for this study excluded Quebec, Nunavut and Northwest Territories.)

scores and mortality rates was compared, which revealed, as age increased, mortality rates increased faster than the HUI scores declined. Our results also confirm that, in Canada, the LE for females is higher than for males, a direct result of higher mortality among men. It is also true for the population of people with hypertension (Table 1).

It was observed that a greater number of years of life were lost in HALE than in LE especially at younger ages (Table 2). Hypertension impacts on health and body functions to a greater extent than it impacts on mortality among young people. Differences in LE and HALE for people who was aged 85 years or older were very small and similar for both men and women. Presence or absence of hypertension at this advanced age only slightly impacted longevity and the estimated loss in life was very small.

The results attribute significant loss of health expectancy to hypertension. In reality, hypertension is a convenient marker which functions as a surrogate for health risks not controlled for in the analysis. Future work should target controlling for risk factors concurrent with a diagnosis of hypertension. That kind of study could quantify the potential impact of prevention of obesity, smoking, physical inactivity, and other risk factors associated with population health. More detailed data would be required. For instance mortality rates by BMI class would be required to evaluate the effect obesity on population health. Work plans have been prepared to explore the feasibility of controlling for obesity in HALE estimation.

The absolute difference between LE and HALE represents the number of years a person spends in poor health. Relative differences between LE and HALE quantify the portion of life a person spends in poor health. That is, the ratio of unhealthy years to the life expectancy ((LE-HALE)/LE). These measures are only meaningful within the same population (i.e., for the population of people of the same age with or without hypertension). Both measures were greater for populations of people with hypertension than for people without the disease (Table 2). Women spent more years and a greater portion of life in poor health than did men. It was observed that the number of unhealthy years decreased and the portion of life a person spends in poor health increased with increasing age. This was true for both sexes and for both diseased and not diseased populations. For example, at age 20 years, women with hypertension spent 21% of their remaining lives in poor health and that percentage gradually increased to 42% by age 85. This age gradient in relative differences varied from 16% up to 40% for women without hypertension. The same pattern was observed for men as well but the proportions were smaller. Women with hypertension lived shorter lives and spend an even greater portion of their lives in poor health than did women without hypertension.

Differences in LE associated with hypertension were estimated for people in eastern Finland using a baseline age of 25 years by Kiiskinen et al. [4]. The loss in LE of 2.7 years for men and 2.2 years for women were reported. These estimates were lower than our estimates (3.7 men, 2.8 women, derived from Figures 1 and 2), but consistent in that the loss in life was larger for males than for females. Direct comparability with our results was hampered by differences in methodology, data used, reporting year, and characteristics of the populations studied. Our literature search did not identify any publication quantifying differences in HALE associated with hypertension.

Table 2: Life expectancy (LE), health-adjusted life expectancy (HALE) (With 95% Confidence Intervals), and Loss of LE and HALE at selected ages, by hypertension (HTN) status and sex, Canada, 2004 to 2006. (Dataset for this study excluded Quebec, Nunavut and Northwest Territories.)

Sex	Life expectancy measure	Without HTN (I)	With HTN (II)	Loss of life expectancy associated with HTN (I-II)
		At age 20 years		
Females	LE	65.4 (65.3-65.4)	62.1 (61.9–62.4)	3.3*
	HALE	55.0 (54.6–55.3)	48.9 (48.1–49.7)	6.1*
	LE-HALE	10.4*	13.2*	
	(LE-HALE)/LE	0.16	0.21	
Males	LE	61.0 (61.0-61.0)	56.9 (56.7–57.2)	4.1*
	HALE	52.8 (52.5–53.1)	47.1 (46.3–47.8)	5.7*
	LE-HALE	8.2*	9.8*	
	(LE-HALE)/LE	0.13	0.17	
		At age 55 years		
Females	LE	31.6 (31.6-31.7)	30.1 (30.1-30.2)	1.5*
	HALE	24.7 (24.4–25.1)	22.7 (22.3–23.0)	2.0*
	LE-HALE	6.9*	7.4*	
	(LE-HALE)/LE	0.22	0.25	
Males	LE	28.0 (28.0-28.1)	25.9 (25.8-25.9)	2.1*
	HALE	22.9 (22.6–23.2)	20.2 (19.8–20.6)	2.7*
	LE-HALE	5.1*	5.7*	
	(LE-HALE)/LE	0.18	0.22	
		At age 85 years		
Females	LE	8.6	8.5	0.1
	HALE	5.2	4.9	0.3
	LE-HALE	3.4	3.6	
	(LE-HALE)/LE	0.40	0.42	
Males	LE	6.9	6.5	0.4
	HALE	4.4	4.0	0.4
	LE-HALE	2.5	2.5	
	(LE-HALE)/LE	0.36	0.38	

∗Statistically significant at .05.

A limitation of our study was that data for residents of long-term care facilities were not available for calculation of our estimates of life expectancy and health-adjusted life expectancy. As a result, the true values for the entire population would be somewhat lower than what we reported. It is also important to note that misclassification of hypertension status is present in both the survey data and the surveillance system data we used. In the Canadian Community Health Survey, misclassification can be due to self-reporting bias, a tendency to underreport the true disease status. In the Canadian Chronic Disease Surveillance System, misclassification can be present in geographic areas where complete data are not available. Areas with a larger proportion of salaried physicians provide the least complete data, which results in identifying fewer individuals with disease. Consequently, the disease status concordance between the two data sources varies by province and territory [20–22]. Future linkage of these two data sources (CCDSS and CCHS) would reduce self-reporting bias and misclassification error. The estimates of LE and HALE presented in this paper are based on mortality and morbidity experience of people with and without hypertension for the period of 2004–2006. They should be treated as descriptive cross-sectional statistics based on past experience rather than predictive, as the mortality and morbidity experience will change with time.

This paper described the method used by the Public Health Agency of Canada to calculate life expectancy and health-adjusted life expectancy among Canadian adults with and without hypertension, based on mortality data for 2004 to 2006 and morbidity data for 2000 to 2005. Our work shows that it is possible to calculate health-adjusted life expectancy for all Canadians and for subpopulations

with this particular chronic condition. Our method can be adapted for calculations for other chronic conditions and diseases to provide useful information for public health researchers and policy makers.

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