Behavioural Neurology

Prevention and Rehabilitation for Dementia

Lead Guest Editor: Shinichiro Maeshima
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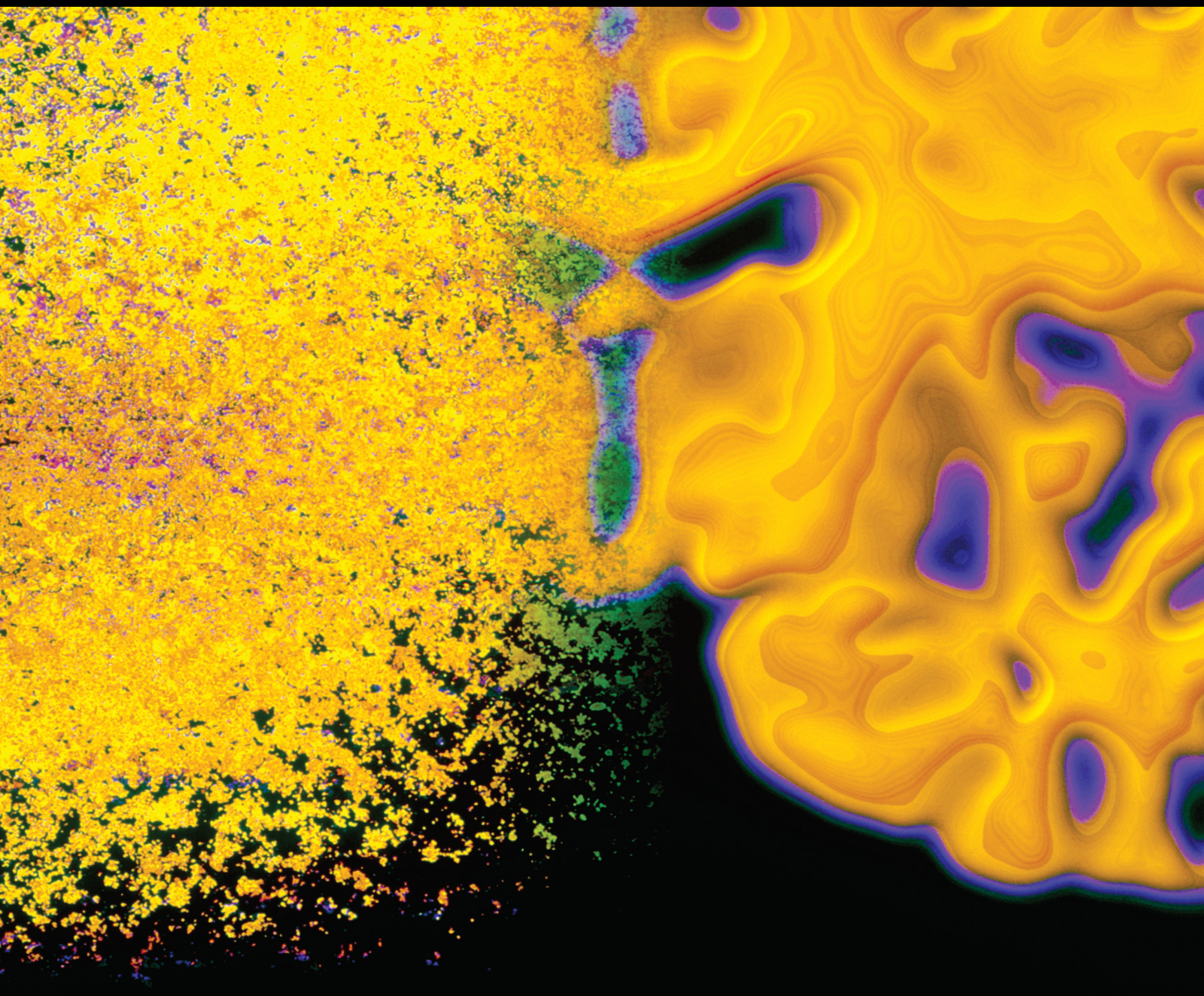

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Review Article

Potential Benefits of Physical Activity in MCI and Dementia

Hallie Nuzum[1,2] **Ariana Stickel**[1,3] **Maria Corona**[1] **Michelle Zeller**[1] **Rebecca J. Melrose**[1,4] **and Stacy Schantz Wilkins**[1,4]

[1]*VA Greater Los Angeles Medical Center, Los Angeles, CA, USA*
[2]*Department of Psychology, University of Notre Dame, Notre Dame, IN, USA*
[3]*Department of Psychology, University of Arizona, Tucson, AZ, USA*
[4]*David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*

Correspondence should be addressed to Hallie Nuzum; hallie.a.nuzum@gmail.com

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Physical activity improves overall health and reduces the risk of many negative health outcomes and may be effective in improving cognition, independent functioning, and psychological health in older adults. Given the evidence linking physical activity with improvements in various aspects of health and functioning, interventions exploring pathways for decreasing risk of dementia in those with mild cognitive impairment (MCI) and improving outcomes for those with dementia are of critical importance. The present review highlights the work examining physical activity interventions in order to achieve a comprehensive understanding of the potential benefits of physical activity for individuals experiencing cognitive decline. The primary focus is on aerobic exercise as this is the main intervention in the literature. Our review supports the thesis that physical activity can promote healthy aging in terms of cognition, independent functioning, and psychological health for individuals experiencing cognitive decline. Specifically, physical activity improves cognition, especially executive functioning and memory in MCI, independent functioning in MCI and dementia, and psychological health in dementia. Given that benefits of physical activity have been observed across these domains, such interventions provide an avenue for preventing decline and/or mitigating impairment across several domains of functioning in older adults with MCI or dementia and may be recommended (and adjusted) for patients across a range of settings, including medical and mental health settings. Further implications for clinical intervention and future directions for research are discussed.

1. Introduction

The existing literature on physical activity in patients with MCI and dementia highlights improvements in physical health, especially aerobic health/fitness, as a crucial factor in improving brain health ([1]; for a review, see [2]). Physical activity improves overall health and reduces the risk of many negative health outcomes, including coronary heart disease, stroke, certain cancers, type 2 diabetes, obesity, hypertension, osteoporosis, falls, and mortality [3–6]. Although older adults (typically defined as age ≥ 65 years old) have the highest rates of the illnesses mentioned above, they are the least physically active age group and spend a significant proportion of their day being sedentary [6]. Physical activity also may be effective in improving cognition, independent functioning, and psychological health [4, 7, 8]. As such, randomized controlled trials (RCTs) have been conducted in order to carefully test the impact of physical health on cognitive, daily, and psychological functioning. The majority of research on physical activity in older adults has focused on healthy, community-dwelling individuals, yet there is promising evidence emerging regarding the benefits of physical activity even for frail and/or cognitively impaired older adults [9]. Therefore, physical activity should be explored as a potential pathway for decreasing risk of dementia in those with mild cognitive

impairment (MCI)—individuals at increased risk for developing dementia—and improving outcomes for those already diagnosed with dementia.

Previous studies investigating the effects of physical activity among those with MCI or dementia have generally focused on outcomes in specific domains of functioning, such as cognition [10] or independent functioning [11]. Such domains are often distinct but interrelated [12], and there is some evidence that physical activity can support several domains of functioning concurrently, including cognition, independence in daily activities, and psychological health/-quality of life [13]. Hence, the present review is aimed at highlighting the work in each of these areas in order to support a more comprehensive understanding of how physical activity may benefit individuals experiencing cognitive decline. Physical activity interventions targeting older adults have included a wide variety of programs, including aerobic exercise (e.g., walking), resistance training, yoga, and tai chi, and there is some support for each of these forms of activity having a positive impact on healthy aging (e.g., [14–16]). We decided to use the more inclusive term, physical activity, given the diversity of interventions included in the literature; however, the most common intervention type was aerobic exercise. Thus, the goal of this literature review is to characterize the utility of physical activity, especially aerobic exercise, in preventing or lessening the impact of declines in cognition, daily functioning, and psychological health among individuals with MCI and dementia. To this end, we searched online repositories (i.e., PubMed, PsycINFO) using the following primary search terms: ("mild cognitive impairment" or "neurocognitive disorder" or "dementia") and ("physical activity" or "exercise"), combined with terms related to cognitive/neuropsychological assessment, brain imaging, ADLs/IADLs/independent functioning, and mental health/quality of life/social connectedness. The present review focused on meta-analyses, particularly those published within the past 10 years, whenever available. As an aside, due to changes in the criteria for MCI, the following literature review uses the term MCI to refer to all four subgroups of MCI now diagnosed. Most of the literature reviewed was done in accord with previous criteria [17, 18] and as such is reflective of amnestic MCI patients, both single and multiple domains. When studies distinguished between amnestic and nonamnestic MCI, we have indicated this; however, such instances were rare. Moreover, most studies did not incorporate biomarkers into the diagnostic procedures, and thus, specification of MCI due to AD was not used.

2. Cognition in Older Adults

Better physical health, especially cardiovascular health, contributes to individual differences in cognitive functioning in several cognitive domains, including executive functioning and memory in general populations of older adults [19]. Executive functions are sets of cognitive processes used in complex tasks, such as planning, strategizing, decision-making, updating working memory, inhibition of irrelevant information, and switching flexibly between two tasks [20, 21]. Cross-sectional and prospective studies have demonstrated that individuals who are more physically active show improvements in neurocognitive functioning compared to more sedentary individuals [22, 23]. However, two observational, prospective studies in a sample of older adults, Verghese et al. [24, 25], did not find associations between physical leisure activity and lower risk of developing either amnestic or nonamnestic MCI, respectively. This null finding may be at least partially explained by the forms of physical activity included, such as tennis, golf, climbing more than 2 flights of stairs, and babysitting, given evidence of a dose response with higher intensity of physical activity being associated with better cognitive functioning in older adults [26]. Further, there is evidence from longitudinal studies that physical activity may prevent cognitive decline and dementia and that people with higher levels of physical activity are at reduced risk compared to those with lower levels [27].

2.1. Physical Activity Interventions and Cognition among Those with MCI. Intervention efforts, such as those aimed at reducing cardiovascular risk factors and preventing stroke by increasing physical activity, have been proposed as effective methods for preventing further cognitive decline among those with MCI [28]. For example, in a sample of older adults with cognitive impairment but no diagnosis of dementia, Blumenthal et al. [29] observed modest, yet significant, cognitive gains in global cognitive functioning ($d = .36$) and executive function ($d = .32$) following participation in physical activity intervention, but no significant gains were observed for memory ($d = .19$) or language ($d = .12$). Similarly, Lautenschlager et al. [30] found that a 6-month physical activity intervention led to significant, yet modest, improvement across cognitive domains for older adults at risk for Alzheimer's disease. A meta-analysis of aerobic exercise intervention studies, which attempted to address shortcomings of individual studies (i.e., small sample sizes and effect sizes), demonstrated that improved fitness also improves cognitive function, especially in the domain of executive functioning [4]. More recently, a systematic review of RCTs spanning the adult lifespan revealed modest improvements in the domains of attention and processing speed, executive functioning, and memory following aerobic exercise interventions [10]. Importantly, those with MCI had smaller benefits (albeit benefits) in the domain of executive functioning but had somewhat larger gains in memory than cognitively healthy individuals. Regarding working memory, older samples, but not younger samples, benefitted from physical activity; the authors were unable to test for differences based on MCI status. Finally, physical activity benefitted attention and processing speed in a uniform manner that did not differ based on sample ages or MCI status.

A systematic review of RCTs specific to cognitively impaired individuals found that participants with MCI demonstrated improved global cognition, executive functioning, attention, and memory with increased physical activity [31]. Most studies included in Öhman et al. [31] did not distinguish between MCI subtypes (i.e., amnestic versus nonamnestic). One exception was Suzuki et al.'s [32] physical activity randomized control intervention, which included groups of both amnestic and nonamnestic MCI subtypes.

These authors found that across MCI subtypes, their physical activity intervention was not associated with better maintenance of cognitive functions relative to controls. However, when examining the amnestic MCI group in isolation, those who participated in the physical activity intervention had improved immediate memory from baseline to end of intervention at 6 months compared to controls. Further, within the amnestic MCI group, controls showed declines in global cognition and had significant whole-brain cortical atrophy over the 6-month period whereas those who participated in the intervention did not evidence such negative outcomes over time. Taken together, Suzuki et al.'s [32] findings suggest that those with amnestic subtype MCI may uniquely benefit from physical activity interventions.

2.2. Physical Activity Interventions and Cognition among Those with Dementia. Regarding those already diagnosed with dementia, there is mixed evidence of physical activity improving cognition. One of the most cited meta-analyses on the topic [33] found that those enrolled in physical activity interventions showed greater improvements in cognition relative to controls. However, more recent meta-analyses have found lesser or no benefits. For example, Forbes et al. [34] reported a questionable benefit of physical activity intervention on cognition among those with dementia, which was qualified due to sizable heterogeneity between studies. Further, in Forbes et al.'s [35] most recent meta-analysis, they failed to detect a benefit of physical activity intervention on cognitive functioning across nine randomized clinical trials with over 400 participants. Similarly, Öhman et al.'s [31] review determined that physical activity interventions did not evidence clear overarching benefits on cognition, which the authors suggest may be due to methodological issues (e.g., poorly defined criteria for determining dementia status). Alternatively, for those with dementia, overall lifestyle may be more predictive of cognitive gains than a time-limited physical activity intervention [36]. Perhaps the level of neurodegeneration in dementia makes cognitive gains more difficult to achieve, and other outcomes (e.g., increases in independent functioning and psychological health) should be targeted in physical activity interventions. More research is needed to examine how to maximize the benefits of physical activity across varying levels of cognitive functioning.

2.3. Possible Mechanisms. Across individuals of varying cognitive functioning, the benefits of physical activity on cognition are thought to be mediated by various brain mechanisms [37]. One pathway by which physical activity impacts the brain is via the prevention or better management of cardiovascular risk factors (e.g., diabetes, hypertension, hyperlipidemia, and obesity). In fact, among those with MCI, presence of cardiovascular risk factors is associated with increased likelihood of progression to dementia [38]. Cardiovascular risk factors are associated with various changes to brain health. For example, hypertension is associated with hardening of the blood vessels to the brain, which increases risk for stroke [39], and can lead to small vessel damage in the form of white matter hyperintensities seen on magnetic resonance imaging [40, 41]. Obesity is associated with increased inflammation to the brain [42, 43] and has been associated with reduced cerebral blood flow [44, 45]. In addition to improving brain health by reducing cardiovascular risk factor burden, physical activity is thought to improve brain health by increasing neurogenesis and synaptic plasticity (for a review, see [37]). Physical activity, especially aerobic exercise, is associated with increases in brain-derived neurotrophic factor (BDNF), a serum that stimulates cell growth and maintains neurons [46]. Even acutely, physical activity is associated with increases in BDNF (measured in the periphery), though these immediate effects may be specific to males, not females [47]. Of note, physical activity is better at immediately increasing BDNF serum levels compared to cognitive training and meditation [48], evidencing a distinct mechanism by which physical activity enhances brain function. Further, the benefits of physical activity interventions on executive functioning may be mediated by increases in BDNF, especially among older adults [49].

Cognitive neuroscience studies employing neuroimaging techniques provide additional evidence for the impact of physical activity on brain function and structure. Functional connectivity, the extent to which different regions of the brain activate in sync with one another either during a task or when one is not directed toward a specific task (also known as resting state), is one measure of brain function. Increased functional connectivity in the default mode network (DMN), a commonly studied activation network that is hypothesized to be important for introspection and memory retrieval [50], during resting state was observed in older adults with MCI following 12 weeks of aerobic physical activity [51]. Changes to DMN connectivity are found in many diseases of aging [52–54]. Functional connectivity changes have also been observed in different brain networks following other forms of physical activity training [55, 56], suggesting specificity of effects dependent on the form of physical activity training. Somewhat surprisingly, among women with MCI who completed a resistance training, and not those who completed an aerobic exercise intervention, increased region-specific brain activity during an associative memory task was linked to better performance on the task.

In addition to using neuroimaging metrics to understand functional brain changes that occur following interventions, researchers have examined general relations between physical activity and brain structure. Physical activity may be a good predictor of long-term changes to brain structure, such as brain volumes, and in-turn risk for dementia, especially for those who average more physical activity than their peers [57]. Regarding training, participation in an aerobic exercise intervention was found to have increased BDNF serum levels and increased volume of the anterior hippocampus, and this was associated with improvements in spatial memory among older adults without cognitive impairment [58]. With regard to physical activity interventions, better aerobic health/fitness was associated with better white matter integrity (a measure of the health of white matter microstructure) only among those who completed aerobic exercises but not among those who completed stretching exercises [59]. Although better white matter integrity is typically associated with better cognitive functioning, the authors did not detect such relationships [59].

There is growing evidence suggesting that physical activity helps maintain brain health among those at risk for Alzheimer's disease. Specifically, among at-risk individuals, greater physical activity is associated with fewer changes to the brain that indicate preclinical Alzheimer's disease (e.g., reduction in hippocampal volumes and increased β-amyloid burden; [60]). Further, among cognitively healthy late-middle-aged adults with family history of and/or genetic risk for Alzheimer's disease, moderate, rather than light or vigorous, physical activity may be most beneficial to maintaining brain function as measured by glucose metabolism [61]. Although there is evidence for physical activity improving and maintaining brain health among cognitively healthy older adults and those with MCI, which may then confer benefits on cognition, these relations are not well understood among those with established dementia.

3. Independent Function

The impact of physical activity interventions on functional independence largely seems to be beneficial. In a national longitudinal study that included Americans across the age span, Cotter and Lachman [62] found that several factors, including greater physical activity, were associated with better self-rated physical health and less physical disability 9 years later. Moreover, greater physical activity and smaller waist circumference attenuated age-related increases in physical disability. Likewise, an observational study of community-dwelling older adults with functional limitations found that health behaviors, particularly physical activity, contributed to functional independence [63]. In contrast, Gu and Conn's [11] meta-analysis of physical activity interventions in older adults did not reveal benefits on participants' activities of daily living, but the authors found that physical activity interventions improved functional performance across a variety of tasks that were designed to simulate activities of daily living. In their 12-year longitudinal study of older adults without baseline activity limitations, Rist et al. [64] demonstrated that among individuals with high and low probability of dementia, physical activity was associated with decreased odds of developing limitations to instrumental activities of daily living (everyday activities that are more cognitively involved than basic activities of daily living). In contrast, physical activity did not appear to be protective of basic activities of daily living [65], suggesting that physical activity may have specific protections for maintenance of more cognitively demanding tasks.

3.1. Physical Activity Interventions and Functioning among Those with Dementia. In McLaren et al.'s [66] systematic review of nonpharmacological RCTs for community-dwelling individuals with dementia, all six RCTs that examined physical activity reported statistically significant improvement in functional ability among those in the physical activity intervention groups. Forbes et al. [34, 35] have consistently detected benefits of physical activity on daily functioning though they note that there is significant heterogeneity between randomized control trials. Blankevoort et al.'s [67] review provided evidence that compared to resistance training alone, multicomponent physical activity interventions benefitted physical functioning and functional independence in all stages of dementia. Further, the greater the physical activity volume during the intervention (as measured by number of sessions and time per session), the greater the functional improvements [67]. Zeng et al. [68] also found that physical activity improved physical functions such as reach, balance, and mobility, which are core parts of basic activities of daily living (e.g., toileting).

Physical activity interventions in long-term care settings also have varied effects. For example, in a study of patients with mild-to-moderate dementia who were living in residential care facilities, a high-intensity physical activity program slowed decline in functional independence and improved balance, but only in patients with non-Alzheimer's-type dementia [69]. Another physical activity intervention for patients in an acute psychiatric ward, on the other hand, delayed loss of mobility in patients with moderate-to-severe dementia but did not significantly impact other forms of daily living [70]. Thus, more research is needed to clarify the extent to which physical activity may affect functioning in patients who are institutionalized.

3.2. Additional Considerations. It is important to consider the role of cognition when measuring functional independence outcomes. Cognition and functional independence impact one another with declines in one often predicting declines in the other; most often, cognitive declines precede and predict functional declines [12]. Given this relationship, it is crucial to understand how to promote independence in older adults experiencing cognitive decline. Oftentimes, approaches like Poulos et al.'s [71] comprehensive "reablement" approach for those with mild-to-moderate dementia include both pharmacological and nonpharmacological approaches to support daily functioning, such as goal-based cognitive rehabilitation and physical activity, targeted rehabilitation following acute illness/injury, and caregiver education and support. Consistent with this model, health behaviors, especially physical activity, have been implicated in older adults' abilities to maintain functional independence [62, 63]. Thom and Clare [72] highlighted evidence that physical activity and cognitive rehabilitation, independently, have been shown to improve functioning in older adults and, to some degree, those diagnosed with dementia. Further, they suggested that the combination of these types of interventions may enhance improvements in functional independence in those with dementia because they could target both physical and cognitive deficits relevant to preventing functional dependence, including, for example, cardiovascular risk and risk of falls with physical activity, and behavioral and problem-solving strategies with cognitive rehabilitation, thereby maximizing efficacy of intervention efforts above and beyond the effects of a single-domain intervention [72]. Others posit that physical activity may impact functional independence by improving cognitive domains that may be especially crucial to maintaining independence, such as executive functioning [73].

Another important consideration to these relationships, especially in individuals with dementia, is involvement of families, friends, and other social supports, particularly those

with caregiving responsibilities. The availability of caregivers provides greater opportunity for the person with dementia to remain more functional and engaged in meaningful activities in their communities [74]. However, caregiver burden, stress, depression, anxiety, poor health, social isolation, and financial hardship all can negatively affect caregivers and, indirectly, the person with dementia as well [75]. In addition to promoting the functional independence of people with dementia, supporting caregivers directly, especially targeting their psychological well-being and providing information, can benefit both the caregiver and the person with dementia [75, 76]. Often, resources such as time and transportation limit the accessibility of interventions. Working with caregivers, Vreugdenhil et al. [77] implemented a community-based home physical activity program that involved patients with Alzheimer's disease walking under the supervision of their informal caregivers. The intervention was effective at improving patients' cognition, mobility, and instrumental activities of daily living, highlighting the potential gains of working with caregivers; of note, however, is that no caregiver outcomes were included in this study. When informal caregivers are unable to provide support for a person with dementia, long-term care placement becomes an alternative solution. In a meta-analysis of nursing home placements of older adults with dementia, impairments in functional independence, poorer cognition, and behavioral/psychological dysfunction were significant risk factors for placement in long-term care [78]. These authors also found an association between caregiver burden and risk of institutionalization and recommended caregiver education and support to delay placement in nursing homes. Therefore, it is vital to identify ways to maintain independence among those with cognitive decline.

4. Psychological Health

Research on the effects of increased physical activity on emotional and social functioning also has been an important area of study. Meta-analyses have demonstrated that physical activity interventions reduce symptoms of depression and anxiety in healthy adults, including older adults [79, 80]. Physical health is linked to decreased depression and loneliness and improved mood and life satisfaction [81].

4.1. Physical Activity Interventions and Psychological Health among Those with Dementia. Among older adults with dementia, physical activity interventions improved general psychological well-being across a variety of neuropsychiatric symptoms (for a meta-analysis, see [68]). Meta-analytic studies have also found that physical activity is associated with improved mood and well-being [8, 82]. However, Forbes et al.'s [34, 35] meta-analyses examining the impact of physical activity interventions on depression among those with dementia did not find a benefit of intervention. Forbes et al. [34, 35] were also interested in examining quality of life outcomes but were unable to do so due to lack of information on the outcome in the studies they investigated. Older adults with dementia report lower quality of life, and there is preliminary evidence that certain interventions mitigate this effect [83]. For example, in a systematic review of different types of nonpharmacological interventions, Cooper et al. [83] noted that factors, such as improved caregiver coping and whether someone lives at home versus in a nursing facility, may influence the impact of interventions on improving quality of life for people with dementia. Taken together, this emphasizes the need for more research regarding mediators, moderators, and individual differences in interventions aimed at improving quality of life. Regarding physical activity interventions, increased physical activity was found to improve quality of life indirectly, by first reducing distress among older adults [84]. It is unclear if such a relationship would differ in those with MCI or dementia. Interestingly, brain integrity, which tends to be poorer in those with cognitive impairment, may be a good predictor of mental health improvements following physical activity. In a large sample of older adults, larger amygdala volumes predicted greater decreases in loneliness following physical activity intervention [85]. In addition, larger prefrontal cortex volume predicted greater reductions in stress following physical activity. Regarding mechanisms, BDNF (a promoter of neuronal health and function) levels are lower in individuals with psychological dysfunction (e.g., in depression), and increases in BDNF via physical activity may improve functioning in brain regions/circuits key in maintaining psychological well-being (e.g., in the frontal cortex and hippocampus; [86]).

Alternatively, psychosocial health may impact physical activity. Social connectedness, or the degree to which an individual engages in social interactions and activities of societal value, is an additional construct that is relevant to older adults' health and well-being. Levels of social connectedness have been associated with better health and successful aging [87, 88]. However, the study of this construct in relation to physical activity is less prominent in the literature, and there are conflicting findings in the few studies that do include measures of this construct. Some studies have demonstrated that people with more active social lives have better quality of life and physical/health function [87, 89]. However, the patterns by which all three components—physical activity, social connectedness, and cognitive functioning—interrelate are unclear [90, 91]. Participants in physical activity programs also have identified social connectedness as an attraction to engaging in such interventions [92]. However, a large, longitudinal study found no evidence of an association between social connectedness and successful aging [93]. These authors suggested that social connection may be related to self-perceptions of successful aging but does not actually lead to improved outcomes in the aging process. It will be important to continue studying the interrelations between physical activity and psychological functioning, particularly in the context of cognitive decline and functional dependence, as this literature has not yet clarified such pathways. The interrelations among these domains are key when determining how to optimally approach rehabilitation for adults with MCI and dementia.

5. Conclusions

While promotion of physical activity is encouraged throughout the lifespan, it can have particularly important

effects on older adults, especially those experiencing cognitive impairment. In this review, we described the benefits that physical activity can have on individuals' functioning across several domains, including cognition, functional independence, and psychological health. Specifically, physical activity improves cognition, especially executive functioning and memory in MCI, independent functioning in MCI and dementia, and psychological health in dementia. Often, the effect of physical activity on each of these functional domains has been studied separately and in diverse samples at various points in aging or cognitive/functional decline. Considering these findings all together, it becomes clear that increased physical activity has the potential to improve functioning across several important domains in older adults at risk for or diagnosed with MCI or dementia. Therefore, future research clarifying the effects of exercise on these domains concurrently, as well as the interrelations among these constructs, is likely to provide useful information regarding optimal approaches toward prevention and/or rehabilitation efforts for older adults with MCI or dementia.

Clinically, physical activity may be considered an important part of health promotion in medical settings, when not contraindicated for a given patient. This is true even in frail older adults and/or individuals with cognitive impairment. Given that benefits of physical activity have been observed across domains of cognition, independent functioning, and psychological health, such interventions may be recommended (and adjusted) for patients across a range of settings, including medical and mental health settings. Much of the existing literature has supported aerobic exercise interventions as promoting cardiovascular and brain health, as well as other forms of healthy aging. However, few studies have directly compared the effects of different forms of physical activity (e.g., aerobic exercise vs. resistance training, aerobic exercise vs. yoga, and aerobic exercise vs. balance training) on multiple domains of aging, and this will be an important area for future research to explore. The ideal format or amount of physical activity in order to maximize efficacy is unclear. The "amount" (e.g., frequency, duration) of physical activity varies considerably across studies, and future research will need to determine the optimal amount (or ideal range) of physical activity to maximize benefits in a given population. The World Health Organization recommends that older adults complete a minimum of 150 minutes of moderate-intensity aerobic physical activity, 75 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity each week [94]. While these recommendations are based on research, more structured protocols should be developed and examined in order to determine the optimal amount of physical activity for older adults.

There are several knowledge gaps in the literature that represent important limitations of the present review and suggest potential avenues for future research. First, as mentioned previously, the current state of the literature generally includes studies with small sample sizes. Larger sample sizes are needed to determine the effect sizes of various results. Moreover, when examining effects on multiple cognitive domains, parts of the brain, and/or symptoms and behaviors, larger sample sizes are needed to determine who benefit most from what exact interventions. In addition, there are varied protocols with different forms of physical activity of varying frequency and duration, and therefore, it is difficult to compare or consolidate results from individual studies. Meta-analyses, which were the focus of this review, when available, counteract some of these shortcomings (e.g., small sample sizes, small effect sizes), but they cannot tease apart the effects that such characteristics pose. In addition, the vast majority of the research on physical activity in older adults with cognitive impairment involves individuals diagnosed with MCI and Alzheimer's disease, with fewer studies focused on other forms of dementia, such as cerebrovascular or Lewy body dementias. We also did not find many studies that mention the issue of behavioral disturbance in dementia, as this factor is generally not mentioned or may even be an exclusionary criterion. In our literature review, we decided not to include studies specifically studying individuals with Parkinson's disease, which has a large separate literature on physical activity of its own.

Additional limitations of the literature, and therefore, our review, are lack of information on intrapersonal and extrapersonal mediators between physical activity and cognition, functional independence, and psychological health. Studies that are sufficiently powered to examine longitudinal interactions and mechanisms are required. In addition, it is important that future studies include measures from multiple domains concurrently, including physical, cognitive, neuroimaging, functional, and psychological outcomes, following physical activity interventions. These effects will be particularly important to examine longitudinally and in relation to one another so that the specific course and therefore mechanisms may be illuminated. One final point is that cost-effectiveness should be considered in future research so as to determine the optimal and most efficient interventions in the promotion of healthy aging and specifically prevention and rehabilitation of MCI and dementia.

Overall, the present review summarizes the current state of the literature that exists on the effects of physical activity on cognition, independent functioning, and psychological health, all of which are important aspects of healthy aging. We found strong evidence that physical activity interventions provide an avenue for preventing decline and/or mitigating impairment across several domains of functioning in older adults with MCI or dementia.

Disclosure

The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Social Aspects of Dementia Prevention from a Worldwide to National Perspective: A Review on the International Situation and the Example of Italy

Giovanna Ricci

School of Law, University of Camerino, Camerino, Italy

Correspondence should be addressed to Giovanna Ricci; giovanna.ricci@unicam.it

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At the moment, dementia is affecting around 47 million people worldwide, with a forecast amount of 135 million affected people in 2050. Dementia is a growing health concern worldwide with no treatment currently available, but only symptomatic medication. Effective interventions in the prevention and management of dementia are urgently needed to contain direct and indirect costs of this disease. Indeed, the economic impact of dementia is a vast and continually growing figure, but it is still difficult to quantify. Due to an increase in both the disease spreading and its direct and indirect costs, national and international action plans have to be implemented. As a virtuous example, the Italian national plan for dementia has been summarized. Faced with an increasingly less sustainable disease impact at national and international levels, the plan suggests that it is certainly the entire welfare model that should be rethought, strengthening the network of services and providing interventions to support affected people and their caregivers. Alongside this synergistic approach, scientific research could play a crucial role for pharmacological and nonpharmacological treatments capable of delaying the state of loss of self-sufficiency of the patient, with a significant impact on social and health costs.

1. Introduction

More than 47 million people are affected worldwide by dementia, and the majority of them are over 65 years old. For this reason, this phenomenon is considered a growing health concern, given the increased longevity of the world population (especially in developed countries) combined with the absence of a treatment capable of modifying the disease [1]. This occurrence creates an urgent need for effective interventions with respect to prevention and disease management.

Priorities on the dementia phenomena are comprehension of the pathology in terms of cellular, molecular, and genetic processes and early diagnosis through the use of cognitive tests and clinical trials, but mainly the understanding of social aspects including social programs and technology to benefit medical care and programs to contain the costs of the disease.

The most common forms of dementia are the vascular and the Alzheimer variations, differentiable by measuring specific biomarkers in biological fluids, particularly in the cerebrospinal fluid (CSF), and by imaging these biomarkers. Both approaches are of extreme importance in optimizing a precise early clinical diagnosis and predicting the outcome in particular settings [2, 3].

The chronically degenerative process inducted by dementia includes a set of conditions such as functional and behavioural alterations, dynamic progression of cognitive disabilities, loss of self-sufficiency, and increasing dependence on caregivers. In this sense, the disease starts interfering with working abilities and social interactions and ends with more or less total dependency on others, and the damage done by the disease is irreversible.

Mild cognitive impairment is considered the early stage of any form of dementia and is characterized by a light cognitive decrease in comparison to a previous level of capability. This decrease poorly interferes with the normal activities of the patient during the daily life, and this condition is mainly identified in specialized centres. This

impairment is present in about 19% of people over 65. The conversion rate in dementia is 46% in three years [4]. Considering that many patients do not have a direct diagnosis of dementia at its early stages, it can be stated that the former data underestimates the problem. At the same time, it cannot be ignored that there are also rates of reversion to normal cognition varying from 29 to 55% in population-based cohort studies and from 4 to 15% in clinical settings [5].

The two screening tools currently used for diagnosis are the General Practitioner Assessment of Cognition (GPCog) and the clock-drawing test, both used to screen cognitive impairment and dementia and as measures of spatial dysfunction and neglect. The GPCog consists of a four-component patient assessment and a brief informant interview (six questions) [6], whereas in the clock-drawing test, the subject is simply asked to draw a clock from memory [7]. Besides these two principal methods to screen dementia, there are several other tools including the Montreal Cognitive Assessment, the Mini-Mental State Examination, and memory- and executive function-specific measures [8, 9].

Patients with signs of cognitive decline could then be referred to specialized structures, to undergo deeper investigation.

In reversible forms of dementia, whose prevalence is highly variable (8-40%, with an approximate general value of 12% in patients presenting themselves at services with symptoms) depending on the clinical evaluation and the sociodemographic features of patients [10], the deficits are secondary and, if timely and appropriately cared for, the deterioration can regress and the patient returns to their standard level of capability [2].

Irreversible dementias can be distinguished into a primary and a secondary form. In the primary form, the disease is degenerative and includes Alzheimer's disease, frontotemporal dementia, and dementia with Lewy bodies. In secondary dementia, the vascular variation is predominant [2].

At initial and intermediate stages, symptomatic characteristics of all forms of irreversible dementia are quite distinguishable from each other; this difference in fact decreases and disappears completely with the progress of the degeneration [2].

"Major neurocognitive disorders" are the current formal identification of dementia, according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) 5 [11], characterizing them as illnesses where the neural substrate anomaly is demonstrable, together with a cognitive deficiency, in patients with previous normal brain capability [12].

More specifically, in 2011, the National Institute on Aging and the Alzheimer's Association (NIA/AA) in the United States published new diagnostic guidelines for Alzheimer's disease focusing on three stages of the disorder: dementia due to Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and preclinical (presymptomatic) Alzheimer's disease [13–15].

In dementia due to Alzheimer's disease, impairments in memory, thinking, and behaviour reduce the ability to autonomously operate in everyday life. In mild cognitive impairment due to Alzheimer's disease, mild changes in memory and thinking are noticeable and measurable with mental status tests but are not severe enough to disrupt a person's day-to-day life. Differently, preclinical Alzheimer's disease is a newly defined stage of the disease where measureable biomarker changes in the brain may occur years before symptoms affecting memory, thinking, or behaviour can be detected. In all these three stages, additional research is advocated to explore if biomarkers exist to detect each of the stages and "which biomarkers may best confirm that Alzheimer's-related changes are underway and how best to measure them" [13–15].

1.1. Epidemiology. Dementia hits an increasingly high number of people: in 2015, about 47 million people were affected and in 2050, 135 million patients are expected, with a prevalence of about 8% people over 65 years old in industrialized countries, rising to more than 20% in eight years. Due to these numbers, the World Health Organization (WHO) and Alzheimer's Disease International (ADI) have defined dementia as a world health priority [1].

According to the World Alzheimer Report [1], in 2015, the world regional distribution of new dementia cases was 4.9 million (49% of the total) in Asia, 2.5 million (25%) in Europe, 1.7 million (18%) in the Americas, and 0.8 million (8%) in Africa. Compared to the previous 2012 estimates, these values represent an increased proportion of new cases arising in Asia, the Americas, and Africa, while the proportion arising in Europe has dropped [12].

The evolution of dementia epidemiology is nonhomogeneous: according to international studies [16–18], countries like Sweden, Canada, the UK, the Netherlands, and the USA experienced a decrease in dementia prevalence or incidence, with a stable situation in Nigeria [19] and an increase in incidence in China [20] and in prevalence in Japan [21]. Despite the general increase in the absolute population, two recent studies showed a decrease in prevalence for age-specific segments [18, 22].

Over the next 20 years, an important increase in cases of dementia is expected in China, India, and sub-Saharan Africa [23]. Italy ranks second for the world's oldest population behind Japan and before Germany and Portugal: 21.4% people are over 65 and 6.4% are over 80 [1]. In the next 20 years or so, Chile, China, Iran, and Russia are expected to have a proportion of elderly population similar to Japan. By 2050, most people over 60 years old—120 million—will live in China, while 434 million will live in the rest of the world.

1.2. Dementia in Sub-Saharan Africa and Other Developing Countries: Increasing Evidence Highlighting the Current and Future Burden. About 4 million people with dementia were living in Africa in 2015, with over 27 million people living in other developing countries [1].

In 1990, Nigeria started the investigation on dementia prevalence in sub-Saharan countries, with an epidemiological study (Ibadan-Indianapolis Dementia Project). In that concern, community-based researches were indicating that the disease (Alzheimer dementia) was uncommon. After twenty years, sub-Saharan Africa is still poorly covered by studies

(only nine studies identified the diseases thus far, carried in Tanzania, Benin, Central African Republic, Nigeria, and the Republic of Congo), but there is improving evidence of dementia prevalence.

According to the World Alzheimer Report 2015 [1], in this region of the world, there may be a 63% increase by 2030 in the population living with dementia, with a further increase of 257% by 2050.

Conversely, no information is currently available concerning any variation in the epidemiology of dementia in EU countries and particularly in Italy due to recent immigration flows from Africa. Indeed, it has to be considered that immigration from Africa is still a rising phenomenon involving very young people, so that it is not possible to predict the disease's prevalence in EU.

1.3. Effects of Potentially Modifiable Risk Factors on the Brain. There is a combination of nine risk factors for dementia in about 35% cases: education limited to the age of 12, midlife obesity and hypertension, late-life depression, loss of hearing, smoking, diabetes, poor physical activity, and social isolation [24].

On the other hand, it has been demonstrated that the complete elimination of the apolipoprotein E (ApoE) $\varepsilon 4$ allele, which represents the major genetic risk, can lead to a 7% decrease in disease incidence [25].

According to the current international studies, it is observed that several dementia manifestations can now be managed, and even if the illness per se is not curable, the evolution may be modified with proper dementia care.

The following is a list of modifiable risk factors for dementia:

(i) Vascular brain damage, which increases the risk of macrovascular and microvascular lesions, atrophy, and neurodegeneration [26]

(ii) Inflammation and oxidative stress, which are associated with deposition of amyloid beta peptide [27]

(iii) Metabolic syndrome and diabetes, which are associated with pathologies like atherosclerosis or brain infarction and glucose-mediated toxicity responsible for microvascular abnormalities and neurodegeneration [28]

There is also evidence of impaired insulin receptor activation in Alzheimer's disease [29], suggesting that it might represent a brain state that is insulin-resistant [30].

1.4. Pharmacological Treatments in Dementias. Starting from 1998, only four of the 100 drugs tested against dementia have been authorized for use worldwide. In few cases, they can help manage several symptoms, but most people cannot access them. In addition, although many dementia manifestations are now manageable, the underlying illness is generally not curable, even if modifiable with good dementia care. Currently, even if a number of studies are trying to find effective treatment for dementias, only symptomatic treatments are available in practice. Two types of drugs are mainly accessible: The cholinesterase inhibitors—galantamine, rivastigmine, and above all donepezil [31]—which prevent the acetylcholinesterase enzyme from breaking down acetylcholine, and the neurotransmitter that connects nerve cells and keeps memory functioning. The other type of drug is memantine, an NMDA receptor antagonist that improves memory by restoring homeostasis in the glutamatergic system. Memantine blocks the effects of glutamate, which is released in excessive amounts in the brain of people affected by Alzheimer's disease.

Since it has been shown that Alzheimer's disease causes an imbalance between overproduction and inadequate clearance of the amyloid beta peptide that accumulates in the brain in plaques, drugs have been developed with the aim of stopping this phenomenon. One of these drugs is crenezumab consisting of monoclonal antibodies targeting beta-amyloid, and the other is gantenerumab, a human IgG1 antibody centrally acting to disassemble and degrade amyloid plaques [32].

In addition, a cholesterol-controlling drug, gemfibrozil, has been found to reduce amyloid levels and brain inflammation, at least in an animal model in mice and another humanized IgG1 version of the mouse monoclonal antibody mAb158, and BAN2401 has been found to reduce the amyloid beta peptide in the brain of 81% patients and slow cognitive decline in the brain by 30% [33].

In Italy, the only approved drugs to treat Alzheimer dementia are memantine and reversible acetylcholinesterase inhibitors: donepezil, rivastigmine, and galantamine.

These treatments are all regulated and prescribed by the Italian Drug Agency (AIFA) in charge of drug regulation and prescription [34]. To treat typical and atypical behavioural disorders in dementia, AIFA recommends the use of antipsychotic drugs.

1.5. Nonpharmacological Treatments. For the prevention of dementia or as support for other treatments, nonpharmacological treatments are crucial. There are two classes of prevention strategies: lifestyle-associated and diet-associated interventions.

1.5.1. Lifestyle Strategies. Lifestyle strategies include caloric restriction, cognitive stimulation, socialization, and physical activity [35].

According to several studies [36, 37], physical activity is associated with the reduction of Alzheimer dementia prevalence [38]. Physical activity is associated with an improvement of hippocampal neurogenesis [38] and learning capability, as demonstrated in rodents [39].

Two explanations of the neuroprotective effect of physical activity were proposed:

(1) Release of various neurotrophic factors (e.g., BDNF, IGF-1, NGF, and VEGF), stimulating the transcription factor (CREB) and activating the neurogenesis and the synaptic neuronal plasticity [39]

(2) Reduction of free radicals in the hippocampus and a concurrent increase in superoxide dismutase and nitric oxide endothelial synthase [40]

Although there are studies showing that mental stimulation could protect against Alzheimer's disease and cognitive decline, they are more debatable [41]. There is evidence showing that cognitive stimulation can induce an increase in neuronal density [42].

1.5.2. Food Supplements and Dementias. In recent years, many studies were aimed at confirming the preventive effect of food supplements, such as vitamins B6 and B12, folate, and vitamins E, C, and D [43].

Researches on vitamin B have achieved inconsistent findings. For example, a two-year treatment in 271 patients with vitamins B12 and B6 and homocysteine showed a significant difference in cerebral atrophy indexes, compared to placebo [44], while other reports indicate opposite results [45].

It has been shown that folic acid provides neuroprotective activity through an epigenetic mechanism, inhibiting the accumulation of the beta-amyloid peptide [46]. Conversely, a three-year treatment with vitamin E did not produce any protective effect, even when adding vitamin C to the treatment [47, 48]. Trials with vitamin D are also not definitive [49].

Finally, an absence of reduction in Alzheimer dementia and cognitive decline incidence after 6 years of *Ginkgo biloba* treatment has been demonstrated in high-quality trials [50–52].

2. Social Aspects of Dementia: From Caregivers to Related Costs

There are two main social aspects of dementia: The first point concerns the evidence that the Alzheimer's disease prevalence is likely to increase [1]. A second aspect pertains to people professionally involved in the assistance of the patients (caregivers) and the workload and costs that this assistance imposes to the family members [53]. For example, developed countries face increasing health expenses, both in absolute terms and as a percentage of the gross domestic product [54]. Since neurological and psychiatric diseases in Europe afflict more than 14% of the population, representing about 20% of health expenditure, this implies a segment of considerable public spending [55].

2.1. Caregiver Interventions and Family Engagement in Dementia. The term "caregiver" is used more in the United States, Canada, and China, while "carer" or "caretaker" is more common in the United Kingdom [56].

In any case, we can consider the following:

(i) Informal or primary caregivers, who play the role of caring for a family member

(ii) Formal caregivers who carry out the role of assistance (doctor, nurse, social worker, etc.)

A management strategy is required to assess the cost/-benefit ratio of treatments, and the expansion of the number of patients with dementia disease requires an acceleration of efforts in these fields. This explains why international research has developed considerably on this point. Chronic diseases have led to financial difficulties in public health systems. Hence, the role of informal caregivers is also important in evaluating economic and health analyses [57].

During preclinical dementia, when the disease appears and develops until its terminal phase, the patient poses complex health issues to social workers and family caregivers, who cannot always find the correct answer from the health and welfare services. These services, however, have not always reached a widespread and effective organizational model that can take into account the complexity of needs of the elderly [57].

Indirect costs account for about 75% of total cost of dementia, the most in the overall expenditure of the disease. They mainly consist of a loss of productivity, on individuals, families, and society. This very high impact is due to the loss of autonomy of patients and to the resistance of family members to take care of them, with consequences on health and welfare costs [58]. To the cost of diagnosis, the cost of home care and support for families must also be added: shortly after the first symptoms of the disease, a patient with Alzheimer dementia will need intensive assistance, even for 24 hours a day.

A percentage over 80% Alzheimer's patients is assisted at home, but during the evolution of the disease, two-thirds of the patients incur very serious behavioural problems that lead to stress issues for family caregivers, as well as causing an increase in the demand for professional care, with proportional greater economic commitment [57, 58].

Family members usually provide assistance to patients with dementia: professional support is required in the most serious cases. From the point of view of state balance, care provided by family members is considered to be free of charge. The assistance provided by the caregiver, on the other hand, is a real consumption of resources and a social cost. Consequently, a link can be established between the informal cost of assisting the patient and the social cost of the illness. In addition to the costs mentioned above, there are also intangible costs, i.e., the impact due to the physical and psychological suffering of the patient and relevant family members, which have social and human importance. Only towards the end of the last century, social policies and services have identified caring as a theme to pay attention to.

Patients living in caring structures usually have a lesser quality of life than those at home. Nevertheless, along the evolution of dementia, it may happen that the informal caregiver starts lacking the strength to assist the patient. Therefore, in this situation, a possible solution is the institutionalization by a private structure or the identification of a professional figure who will assist the patient at home [57, 58].

The advances in the technology of healthcare devices, including electronic health records, portal technologies, and wireless communications [59, 60], will probably have a key role in future dementia care. For example, tools for remote surveillance are very important and they give an important contribution to improving and making safer the environment in which patients and families live [59, 60].

There are also a few European experiences about neighbourhoods inhabited by patients and caregivers.

The city of Hogewey (Netherlands) [61] has been a European example of this since 1993, while in Rome, Italy, there is the Alzheimer's Village of the Fondazione Roma, in the Bufalotta district [62], where 100 patients are hosted free of charge in 14 houses, gathered around a square, and connected to everyday services, including a bar and a minimarket.

Also in the Lombardy region, there have been active interventions of this type, such as "Paese Ritrovato" (retrieved village) [63], launched a few months ago by the Cooperativa La Meridiana of Monza. It includes an area of 14,000 square meters, where 64 patients are housed, living in 8 apartments, with single rooms, assisted bathrooms, living areas, and a common kitchen; here, the hosted patients can keep external contacts and implement forms of sociality. The place is self-sufficient and, thanks to the presence of shops, allows patients to move in a protected yet autonomous way.

Another fundamental service for people living with dementia is represented by the role of Diagnostic Therapeutic Care Pathways (DTCP). The DTCP is an organization that covers both clinical and care aspects and is concerned in addressing them with the required harmonization [64].

They are the bodies that support the patient and his family in a straightforward way along the course of the disease, helping recognize and properly interface the different parts of the disease support system. The governance of the process should be shared, with different roles and responsibilities, between the general practitioner and the cognitive deterioration and dementia centres.

2.2. Costs Related to Dementia. The economic impact of dementia is a vast and continually growing figure, but it is still difficult to quantify [54]. The patients, their families, and carers suffer economically and in terms of quality of life [55]. Cost of dementia on the society is the sum of all expenses concerning goods and services used to prevent, diagnose, treat, and cope with the disease [65]. Per capita costs are divided into three subcategories: direct medical costs (e.g., drugs, medical and social services, hospital resources, and professional caregivers), direct social care costs (paid and professional home care and residential and nursing home care), and costs of informal (unpaid) care. Informal care is valued using an opportunity cost approach, valuing hours of informal care by the average wage for each country. In addition, indirect costs have to be taken into consideration such as the loss of income by the patient and possibly by family members or careers. Among the studies that have evaluated the costs of dementia [66, 67], some have focused on the relationship between costs and severity of the disease. Mean cost increases with the progress of the disease for patients in community dwellings, with variations across countries. Generally speaking, cost estimates have increased for all world regions, with the greatest relative increases occurring in African and Eastern Asia regions (largely driven by the upward revision of prevalence estimates for these regions) [68]. Distribution of costs between the three major subcategories (direct medical, social care, and informal care) has not changed substantially. As reported in 2010 [1], direct medical care costs are modest and account for roughly 20% of global dementia costs, while direct social sector costs and informal care costs each account for roughly 40%. As the country income level increases, the relative contribution of direct social care sector costs increases and the relative contribution of informal care costs decreases [69]. The relative contribution of informal care is greatest in African regions and lowest in North America, Western Europe, and several South American regions, while the reverse is true for social sector costs [69].

Other studies focused on the economic impact of drug therapies, concluding that cholinesterase inhibitors may be cost-effective in a short-term perspective [70]. The neuropsychiatric disorders and behavioural and psychological symptoms of dementia (BPSD) significantly contribute to the overall costs of dementia care. Interventions targeted at BPSD may help to reduce the staggering societal costs of this illness [71, 72]. Finally, the functional dependency grade of patients and comorbid medical conditions also affect the disease cost [73, 74]. With respect to direct medical care costs, they account for about 20% global dementia costs, with a further 80% divided among direct social sector and informal care costs. The upward revision of dementia prevalence in the African regions drove one of the greatest relative increases in costs compared to the previous estimates in 2010 and showed also a greater contribution of informal care to the costs [75].

In Italy, the direct costs of the assistance sum up to over 11 billion euros: 73% of the cost is charged to families, and the average annual cost per patient is 70,587 euros, including costs for the National Health Service [76].

Due to the expected increases in the number of people with dementia in the next future [77], the cost of the resources needed to support patients with dementia will significantly increase. To address these concerns, many countries are actively developing action plans for dementia at a national level. These plans are generally informed by a scientific approach to determine the type of care to be provided, where it is best to provide it, and the skill required of the personnel in charge of delivering it [78].

Nevertheless, many of the economic analyses reported above do not take into account the likely decline in age-specific dementia incidence that has been mentioned earlier [18, 22]: if this is true, then some of the reported costs could be considered overestimates.

2.3. Dementia as a Public Health Priority at the International Level. With respect to dementia awareness, there is an increasing involvement of international organizations, such as the WHO, the Organisation for Economic Cooperation and Development (OECD), and the EU.

During the 9th session of the Conference of the Member States on the "Convention on the Rights of Persons with Disabilities (CRPD)" [79], the United Nations (UN) dedicated a slot to dementia reaffirming the importance of the recognition and respect of the rights of all persons with mental and intellectual disabilities. Other initiatives have been deployed in recent years to promote and support collaboration with countries at international, regional, and national levels, in response to dementia.

The WHO hosted in March 2015 the first Ministerial Conference on Global Action Against Dementia, to discuss the global challenges posed by dementia, which brought together ministers, researchers, experts, clinicians, and nongovernmental organizations (NGOs) from around the world. The goal was to pay attention to the socioeconomic burden associated with dementias and how it could be reduced, raising it at the top of the global public health agenda. As a first result, there was the drafting of the "Global Action Plan (GPA) on the Public Health Response to Dementia 2017-2025," which was later adopted by WHO member states at the 70th World Health Assembly in May 2017 [80].

The primary goal of the GPA is to improve the quality of life of people (patients and caregivers) living with dementia, to promote respect for their situation, and to reduce the negative impact on communities and states. To that effect, a series of actions were promoted in the following areas:

(1) Improving awareness on dementia; increasing public knowledge, acceptance, and understanding of the illness; and adapting the societal environment to this disease. This is considered a key point to enable people with dementia to improve their social participation, give a contribution in the community, and maximize their autonomy. It is expected that 100% of countries will have one or more working public awareness campaigns on dementia and that 50% of countries will have one or more dementia-friendly initiatives, to foster a more inclusive dementia society by 2025

(2) Reducing the risk of dementia, by increasing the capacity of health and social care professionals to provide appropriate interventions to the population and to educate about modifiable risk factors for dementia. Managing them proactively can reduce the risk of developing dementia, and its progression can be delayed

(3) Ensuring diagnosis, treatment, and care to patients, granting that the needs and preferences of people with dementia can be met and their autonomy respected. This result can be achieved through integrated, appropriate, community-based health, psychosocial, and long-term care and support focused on the patient and, where appropriate, on families and carers. It is expected that in at least half of countries, 50% of the estimated number of people with dementia will be diagnosed by 2025

(4) Supporting family members and caregivers so that the implementation of solutions to deliver multisectoral care, support, and services for caregivers will help to meet their needs and will prevent a decline in their physical and mental health and social well-being. It is expected that, by 2025, 75% of countries will provide support and training programmes for caregivers and families of patients with dementia

(5) Working on information systems for dementias, in order to start a systematic monitoring and evaluation process of the usage of health and social care systems. This action can provide the best evidence for policy development and service delivery and can improve the prevention, the accessibility, and the coordination of care for patients with dementia, from risk reduction to the end of life. It is expected that, by 2025, half of countries routinely will collect a core set of dementia indicators, through their national health and social information systems, with a period of two years

(6) Promoting research and technological innovation, in order to increase the probability of effective progress towards better prevention, diagnosis, treatment, and care for patients with dementia. It is expected that, between 2017 and 2025, the output of global research on dementia will double

As a consequence of the adoption of the plan, the WHO launched a "Global Dementia Observatory," oriented to the description and worldwide monitoring of the characteristics of dementia and the relevant public health responses, provided by different countries. For the setup of this observatory, Italy was invited to collaborate as a pilot country in order to test the feasibility of data collection and provide suggestions for the selection of key parameters and indicators.

2.4. Dementia as a Public Health Priority at the European Union (EU) Level. In recent years, the "Joint Action on Dementia (JA)" and the "Joint Programming Research Initiative" were the main tools that the EU used to leverage and translate into action the official documents that have been produced by the commission and the council in the field of dementias. The first of those initiatives, in which Italy has actively participated, is called "ALCOVE" and sees the majority of EU member states involved in research activities, using a common scientific approach and sharing experiences.

ALCOVE, which stands for Alzheimer Cooperative Valuation in Europe, ended in 2013: in this project, Italy coordinated the epidemiological section [81].

The participation of Italy in the second JA, which started in 2016 and is expected to last 3 years, has the main objective of translating the recommendations of ALCOVE into working implementations. The goal of the Act on Dementia Joint Action is to promote collaborative actions among member states, to increase the quality level of the lives of patients and families living with dementia. It will provide a practical pattern for policymakers developing and implementing their national dementia plans and strategies. The JA is aimed at providing practical and cost-effective examples of the core elements of good dementia diagnosis, care, and support [82].

In addition, Alzheimer Europe, the organization that brings together European associations concerned with the disease, recently presented the assessment called "European Dementia Monitor" [83], which covered almost all member states of the EU (with the exception of Estonia) plus non-EU member countries like Albania, Bosnia and Herzegovina, Jersey, Monaco, Norway, Switzerland, Turkey, and Israel,

which even if outside the EU territory are officially associated with the EU. The analysis was developed on the basis of ten different categories, which included the availability and accessibility of care services, the reimbursement of medicines, and the deployment of initiatives in favour of patients living with dementia. The investigation showed significant differences between the 36 participating countries with no country scoring full points in all ten categories. Finland had the best ranking with an overall score of 75.2%, followed by England (72.4%), the Netherlands (71.2%), Germany (69.4%), Scotland (68.8%), and Italy (52.9%).

Finland had the highest score in terms of availability and accessibility of care services and, together with the Netherlands and England, also scored best on initiatives on inclusion and dementia-friendly community. Belgium, England, Ireland, Scotland, and Sweden ranked first in terms of reimbursement policies of drugs.

In these countries, in fact, all antidementia treatments are fully reimbursed by the health service, and there is in force a limit against the inappropriate use of antipsychotics. France, Germany, and Spain scored highest in the category of clinical trials, while Ireland and Norway were the first to recognize dementia as a national research and policy priority.

England, France, Germany, Israel, the Netherlands, Scotland, and Slovenia were distinguished by following Alzheimer Europe's recommendations on respect for the legal rights of patients with dementia and their families; Ireland ranked first in terms of recognized care and work rights, while Finland and Norway already ratified international and European human rights conventions.

Although Italy is the most committed and active country in European research collaborations, it only ranks halfway through the general ranking because of a lack of availability of and accessibility to care services, in addition to a low recognition of dementia as a public health priority [83].

2.4.1. National Dementia Plan of Italy. In October 2014, Italy (one of the countries with the oldest people, as reported above) approved the National Dementia Plan (NDP) that was later presented at an international conference as part of the initiatives of the Italian Presidency of the EU; it is recognized that the plan contributed to strengthening the quality of cooperation within the European Commission [84].

The plan was approved as an agreement between the Unified Conference with local administrations, the government, the regions, and the autonomous provinces redacting the document "National Dementia Plan - Strategies for the Promotion and Improvement of the Quality and Appropriateness of Welfare Interventions in the Dementia Sector."

This plan was aimed at promoting and improving interventions on specialist therapeutic aspects of dementia and at supporting patients and their families throughout the care process. Furthermore, it provided strategic indications for the promotion and improvement of new strategies "starting from the assumption that, as in all chronic degenerative pathologies in which the pharmacological approach is not decisive in modifying its natural history, it is necessary to provide an articulated and organic set of care pathways, according to a philosophy of integrated management of the disease." Since its launch, the NDP has represented the most important national public health goal that aligns Italy with the dementia policies carried out by other Western countries. The awareness of the complexity of the dementia phenomenon, with all its implications on the social fabric, requires an extraordinary commitment by the central and regional institutions in close collaboration with the associations of family members and patients. This commitment has to be directed towards the development of governance ability for complex phenomena, an indispensable tool for facing this social and health emergency [85].

It has been established that the implementation of the plan has to be monitored through the "Monitoring Table of the Implementation of the National Plan for Dementia (NDP)," coordinated by the Ministry of Health, which is aimed at reverting into concrete actions the objectives of the plan itself.

The main objectives of the document are as follows:

Objective 1. The identification of interventions and measures in the field of health and social-health policy, with the aim of increasing the awareness of the general population, of people with dementias and their families and professionals, each for its own level of competence and involvement; prevention, early diagnosis, treatment, and care of people with dementia, also with attention to early-onset forms; achieving, through research support, improvement in caring for and improving the quality of life of patients with dementia and their caregivers. A further goal is to organize and implement an epidemiological survey, focused on planning and improving care, for effective and efficient management of the disease

Objective 2. The creation of an integrated network on dementias and the deployment of integrated management actions to promote prevention, early diagnosis, and appropriate intersectional policies, also with a view to reducing discrimination. A further objective is to converge to a common and homogeneous assistance process, paying particular attention to social inequalities and to conditions of fragility and social and health vulnerability

Objective 3. The implementation of strategies and interventions to increase the quality of caring, improving the ability of the NHS to deliver and monitor effective services, through actions such as rationalization of the supply and the use of working methods based primarily on the appropriateness of the provided services. Furthermore, promoting strategies to improve the quality of care to patients with dementia at home, in residential and semiresidential facilities, and during the entire evolution of illness; eventually

developing the appropriateness of the use of drugs, technologies, and psychosocial interventions

Objective 4. The increased awareness and reduction of stigma, for the improved quality of life of patients living with dementia and their families, through correct information on the disease and the available services; the objective here is to facilitate the access to them as early as possible

Objective 5. The improvement of the quality of life and care and the promotion of a full social integration for patients with dementias, also through strategies of personal and family involvement

Objective 6. The promotion of any form of participation, in particular through the involvement of families and associations

After its emanation, the plan implementation was monitored at the regional and national levels by evaluating the activities of permanent confrontation and monitoring as reported in Objective 1.

Besides the monitoring activity, the future objectives reported in the NDP are aimed at the following:

(i) Identification of quality standards and measures for monitoring plan activities

(ii) Elaboration of guidelines concerning crucial aspects linked to the disease such as diagnosis communication, informed consent, and use of legal options

(iii) Discussion on ethical issues such as advance directives and accessibility to palliative care

(iv) Formulation of guidelines dedicated to patients developing dementia in working age and focused on early-onset dementias [86]

For the achievement of these goals, the NDP required the activation of a permanent steering group on dementias in order to monitor the transposition and implementation of the NDP.

After the approval of the NDP, many activities were carried out to monitor the state of transposition and implementation of the NDP at the regional level with the establishment of two working groups to formulate the technical documents "Diagnostic Therapeutic Care Pathways" and "System and Information Flows," and two national guidelines have been drawn up to better achieve the objectives of the NDP [85].

As reported in the Ministry of Health's document "General Directive for Administrative Activity and Management," approved in March 2019 [87], the monitoring of the NDP is being carried out at the central level together with the 21 Italian regions and, in particular, after the approval of the two above-reported technical documents during the Regional Unified Conference in 2017; the formulation of a further document on ethical issues will be completed.

Furthermore, the mental health working group created in January 2019 by the Minister of Health will proceed to

(a) verify the implementation of the scientific guidelines, including the agreements established in the State-Regions Conference and Unified Conference as a commitment of the National Action Plan for Mental Health

(b) verify the appropriateness of the treatment and rehabilitation courses provided by the territorial health services and by the psychiatric diagnosis and treatment services

(c) explore the existence of any eventual critical issues in the territorial health services and elaborate proposals for their solution and for optimizing the network of services, through their strengthening

(d) propose operational and regulatory actions to facilitate the implementation of the most appropriate models of intervention for the psychosocial diagnosis, treatment, and rehabilitation of people with mental illness, aimed at reducing compulsory and voluntary mental health treatments and mechanical and pharmacological restraints [87]

Nevertheless, several relevant issues still negatively affect the management of the phenomenon of dementia in Italy. In particular, there are many disparities of resources and services across the different regions which demonstrate the lack of national standards. The different aspects of dementia management (i.e., diagnosis, assistance, and rehabilitation) are still addressed in separate moments and processes in different parts of the nation, severely limiting the possibility of actually implementing an integrated approach to dementia [86].

In addition, so far the National Dementia Plan has not been financially supported and there are numerous activities aimed at raising the awareness of the competent authorities to identify funds for the implementation of the projects and services established by the plan.

In conclusion, even in the presence of several unsolved situations, it can be said that to date, Italy is improving the management of the dementia problem both nationally and in Europe, to develop and optimize new health and social strategies for improving the quality of life of the people affected by dementia and for greater appropriateness of care interventions.

3. Conclusions

We aimed to review the most important social aspects of dementia, briefly reminding the current epidemiology of the disease, with a special attention to the situation in developing countries and sub-Saharan Africa. We concisely listed the modifiable risk factors for dementia and the pharmacological and nonpharmacological treatments including lifestyle strategies. Then, we focused on the caregivers' interventions and the costs related to dementia.

They can be useful to allow policymakers to define their choices according to the economic and social situations of their countries [53]. This is of particular importance for developing countries, where dementia prevalence is expected to increase in the next decades, so that programs focused on pharmacological but above all nonpharmacological treatments (i.e., lifestyles) should be taken as soon as possible. Conversely, in the US and Europe, where life expectancy is already high, different strategies should be considered, taking into account the cost of these interdisciplinary efforts including, as previously reported [53], physicians, neuropsychologists, and economists.

Conflicts of Interest

The author declares that she has no conflicts of interest.

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