

Physical Activity and Alzheimer's Disease: From Prevention to Therapeutic Perspectives

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A number of factors, including physical activity, may contribute to prevention of cognitive decline and delay the onset of dementia. In addition to its convincing multiple benefits, an increasing body of evidence suggests that an active life has a protective effect on brain functioning in elders. Physical activity may also slow down the course of Alzheimer's disease. These hypotheses have led to increasing research in this specific area during the past decade. This review systematically analyzes the current literature on Alzheimer's disease and the effect of physical activity. Epidemiological studies, short-term randomized controlled trials (RCTs) in nondemented participants, and biological research suggest that physical activity improves cognitive function in older subjects. The limitations of these works

are discussed. No RCTs have yet demonstrated that regular physical activity prevents dementia. Additional challenging clinical interventional studies are needed to demonstrate this relationship, but accumulating evidence from biological research is available. Defining the optimal preventive and therapeutic strategies in terms of type, duration, and intensity of physical activity remain an open question. In the future, the prevention of Alzheimer's disease may be based on rules governing lifestyle habits such as diet, cognitive activity, and physical activity. (*J Am Med Dir Assoc* 2008; 9: 390–405)

Keywords: Alzheimer; physical activity; prevention; cognitive decline

During the past 2 decades, epidemiological research has emphasized that modifiable lifestyle factors such as inactivity may affect the development and progression of Alzheimer's disease (AD). Research in this specific area has therefore intensified. At the present time, evidence suggests that potential preventive strategies such as a physically active lifestyle may help to delay the onset of cognitive decline and slow down disease progression. During AD, physical activity may also prevent various devastating and frequent complications of the disease such as falls, behavior disturbances, mobility disability, or weight loss. Such a nonpharmacological therapeutic approach may be an appealing low-cost, low-risk alternative treatment for this major public health priority. In 2007, more than 5 million people in the United States suffered from Alzheimer's disease and there is still no pharmacological treatment. Even a modest effect on the disease would thus result in a significant impact on social and economic cost. In addition to the multiple reasons for engaging in physical activity,

preserving brain health could be a strong and convincing argument to promote activity in the population and one that could have a major impact on medical practice and public health education. The risk of numerous chronic diseases such as congestive heart disease¹ or cancer of the breast² or colon³ can be reduced by increased physical activity. In the future, prevention of Alzheimer's disease may target multiple aspects of lifestyle habits such as diet, cognitive activity, and physical activity.

Our purpose is to review the literature concerning the association between physical activity and its potential impact on the risk of Alzheimer's disease. This review focuses on the epidemiological data and fundamental hypotheses currently debated. The limitations of these works will be discussed. In addition, it examines the potential benefits of physical activities in Alzheimer's disease patients. Finally, we will try, based on the current scientific literature, to make practical recommendations regarding physical activities to prevent cognitive decline or the disease in healthy subjects, and to slow down disease progression and prevent its complications in patients who already have AD.

METHODS

This review was conducted by identifying the relevant articles published between January 1966 and October 2007 and referenced in PubMed, Medline, and BIOSIS, using the following key words: Alzheimer, cognitive decline, dementia, physical activity, and exercise. Manual research and cross-referencing from previous literature, reviews, and original

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articles were also performed. Retrospective studies, such as case-control studies,^{4,5} are only briefly cited here because they are subject to important methodological drawbacks such as survival bias and recall bias, especially in demented populations. Articles in languages other than English were excluded from the review.

RESULTS

Physical Activity and the Prevention of Dementia, Alzheimer's Disease, or Cognitive Decline

All evidence related to the prevention of dementia or Alzheimer's disease by means of physical activity is derived from case-control studies and cross-sectional and longitudinal epidemiological studies. We found 24 longitudinal epidemiological studies that evaluated the possible impact of physical activity on cognitive decline, dementia, and/or Alzheimer's disease. There is currently no evidence based on RCTs relating to the efficacy of physical activity in preventing or delaying the onset of dementia or Alzheimer's disease.

Longitudinal Epidemiological Studies

Since 1991, and the first report by Li et al,⁶ the results of these studies have been inconsistent. However, 20 of the 24 longitudinal epidemiological studies (Table 1) analyzed in our systematic review suggested a significant and independent preventive effect of physical activity on cognitive decline or dementia. All these results were adjusted for various confounders (Table 2). On the other hand, only 3 longitudinal epidemiological studies have failed to find any association between physical activity and cognitive decline.^{11,15,20} All 24 studies are summarized in Table 1. Most investigated the relationship between physical activity and the risk of dementia or Alzheimer's disease in particular. Others examined the relationship between physical activity and risk of cognitive decline. Despite similar outcomes, these longitudinal epidemiological studies differ in many respects.

Case-Control Studies

Case-control studies also suggest that mentally demanding occupations or physical activities may have a direct influence on the neuropathology of Alzheimer's disease.^{30,31} In 1990, Broe et al⁴ reported that a low level of physical activity in both the recent and the distant past was associated with AD. Others have reported that Alzheimer's patients were less active during their adulthood than nondemented subjects.³²⁻³⁷ These case-control studies are subject to important methodological bias; however, they all found that elderly participants who performed better on cognitive testing self-reported higher levels of physical activities in their past.

Randomized Controlled Trials

The beneficial effects of physical exercise on the cognitive performances of nondemented participants have also been reported in several randomized trials³⁸⁻⁴² while others found no cognitive improvement in physically active groups.^{33,43-45} These RCTs were all based on small samples of young-old participants, and were short-term trials, none of which were

designed to assess incidence of Alzheimer's disease or dementia as the main outcome. Most of these RCTs concluded that compared with controls, individuals assigned to a physical exercise program improved^{40,43-48} or maintained⁴⁹ their cognitive function. In a young-old population, Molloy et al⁵⁰ also suggested that the acute effects of an exercise program on neuropsychological function were not long lasting.

Other small RCTs, in community-dwelling elderly or nursing-home residents, have failed to demonstrate any improvement of cognitive function.^{39,47,49,51-56} One explanation may be that most exercise programs last a few months, whereas physical activity may protect cognitive function in the long term.

Colcombe and Kramer⁵⁷ in 2003 carried out a meta-analysis of 18 interventional studies published between 1966 and 2001 and reported a significant but selective effect of fitness training on cognitive function, with the main benefits occurring in executive-control processes. In 2006, Colcombe et al⁵⁸ reported a significant increase in brain volume in volunteers aged 60 to 79 years who participated in a 6-month aerobic program.⁵⁸ Their findings provide convincing support for the hypothesis that physical activity prevents age-related cognitive decline.

Other Epidemiological Arguments

It has been suggested that physical activity reduces the risk of cognitive decline and dementia in the elderly. Epidemiological studies have reported that low physical performances⁵⁹⁻⁶¹ are associated with higher rates of cognitive decline and dementia. Low physical activity is one of the main factors of poor physical performance. A poor score on tests such as walking speed⁵⁹⁻⁶¹ or poor results on the timed chair-stand test, standing balance, or grip strength tests⁶¹ are associated with higher rates of cognitive decline and dementia. In cross-sectional studies, cardiovascular fitness was associated with attention and executive function^{62,63} or visuospatial function.⁶⁴ In the Sydney Older Person Study, participants with both cognitive impairment and slow gait speed were most likely to progress to dementia during a 6-year period.⁶⁵ On the other hand, during the 7-year follow-up of the Hispanic Established Population for the Epidemiological Study of the Elderly (EPESE), participants with poor cognition had a steeper decline in physical performance than those with good cognition.⁶⁶ These results reinforced the growing evidence of the links between physical performance and cognition.

Basic Research

Numerous studies on rodents suggest that exercise improves acquisition and retention in memory-dependent tasks such as the radial arm maze,⁶⁷ the Morris water maze,^{68,69} passive avoidance,⁷⁰ and object recognition.⁷¹ There is no clear explanation for this relation between physical activity and brain function. However, numerous hypotheses have been put forward and growing evidence from animal research suggests that physical activity may directly modulate the formation of beta-amyloid protein through several biological mechanisms. A review published in 2007 by Cotman et al⁷² examined the multiple underlying mechanisms promoted by physical activ-

Table 1. *Observational Studies of Physical Activity and Risk of Alzheimer's Disease or Dementia*

Author and Study Name	Year of Publication	Longitudinal Nondemented Population-based Study	Maximal Follow-up Period	Assessment of Physical Activity	Outcome Measure	Summary of Major Findings (Adjusted for Confounders)
Li et al ⁶	1991	1090 individuals aged 60 years or over	3 years	Self-reported questionnaire (no details)	Dementia	Individuals with limited physical activity had a higher risk for developing dementia
Stern et al ⁷	1994	593 individuals aged 60 years or over	4 years	Questionnaire of occupational attainment	Dementia and AD	Individuals with low lifetime occupational attainment had a higher risk for developing dementia. RR 2.25, 95% CI 1.32–3.84
Yoshitake et al ⁸ Hisayama Study	1995	828 individuals aged 65 years or over	7 years	Active group: daily exercise during the leisure period or moderate to severe physical activity at work.	Dementia and AD	Physical activity was a significant preventive factor for AD
Albert et al ⁹ MacArthur Study	1995	1192 individuals aged 70 to 79 years	2.5 years	Questionnaire including frequency and level	Cognitive decline	Strenuous physical activity but not moderate physical activity was associated with a reduced risk of cognitive decline
Fabrigoule et al ¹⁰ Paquid study	1995	2040 individuals aged 65 years or over	3 years	10 social and leisure activities Physical activity: yes/no	Dementia	Physically active individuals had a lower risk of dementia RR 0.33, 95% CI 0.10–1.04 (gardening only = RR 0.53, 95% CI 0.23–0.99)
Broe et al ¹¹ Sydney Older Persons Study	1998	327 individuals aged 75 years or over	3 years	Self-reported questionnaire (no details)	Cognitive decline, dementia and AD	No association
Schuit et al ¹²	2001	347 individuals aged 65 years or over	3 years	“Maximal 1 hour per day” versus “more than 1 hour per day”	Cognitive decline	Low physical activity group a two-fold risk of cognitive decline OR 2.0, 95% CI 0.9–4.8 especially for ApoE4 carriers OR 3.7, 95% CI 1.1–12.6
Laurin et al ¹³ Canadian Study of Health and Aging	2001	6434 individuals aged 65 years or over	5 years	Score based on frequency, and intensity High level of activity = ≥ 3 time/week at an intensity greater than walking.	Cognitive impairment and dementia	High levels of physical activity were associated with reduced risks of cognitive impairment, OR 0.58, 95% CI 0.41–0.83, Alzheimer disease, OR 0.50, 95% CI 0.28–0.90 dementia of any type, OR 0.63, 95% CI 0.40–0.98
Scarmeas et al ¹⁴ Health Care Financing Administration Study	2001	1772 individuals aged 65 years or over	7 years	13 leisure activities including walking for pleasure, physical conditioning	Dementia and AD	Subjects with high leisure activities (>6/monthly) RR 0.62, 95% CI 0.46–0.83 Walking for pleasure or going for an excursion RR 0.73, 95% CI 0.55–0.98

Table 1. *Continued*

Author and Study Name	Year of Publication	Longitudinal Nondemented Population-based Study	Maximal Follow-up Period	Assessment of Physical Activity	Outcome Measure	Summary of Major Findings (Adjusted for Confounders)
Ho et al ¹⁵	2001	2030 individuals aged 70 years or over	3 years	Questionnaire (no details)	Cognitive impairment	No exercise was associated with an increased risk of cognitive impairment
Yaffe et al ¹⁶ Study of Osteoporotic Fractures	2001	5925 individuals aged 65 years or over	8 years	Self reported blocks Active, 1 block = 160 meters walked/week	Cognitive decline	Highest quartile compared with the lowest quartile of blocks walked: OR 0.66 (0.54–0.82) Total energy: OR 0.74 (0.60–0.90)
Lindsay et al ¹⁷ Canadian Study of Health and Aging	2002	6434 individuals aged 65 years or over.	5 years	Participants were asked whether they engaged in regular exercise (yes/no), but “regular” was not explicitly defined	AD	Regular physical activity was associated with a reduced risk of AD, OR 0.69, 95% CI 0.5–0.96
Pignatti et al ¹⁸ Brescia Study	2002	364 individuals aged 70–85 years	12 years	Active = walking at least 2 km	Cognitive decline	Inactivity was associated with a higher risk of cognitive decline RR 3.7, 95% CI 1.2–11.1
Wang et al ¹⁹ Kungsholmen Project	2002	776 individuals aged 75 years or over	9 years	Frequency (daily, weekly, monthly, annual) of swimming, walking, or gymnastics	Dementia	Less than daily physical activity RR 0.97, 95% CI 0.42–2.22 Daily physical activity RR 0.41, 95% CI 0.13–1.31
Yamada et al ²⁰ Radiation Effect Research Foundation Adult Health Study	2003	1774 individuals	30 years	Self-assessment of physical activity	AD and vascular dementia	No effect of physical activity on the risk of dementia
Verghese et al ²¹ Bronx Aging Study	2003	469 individuals aged 75 years or over	21 years	Score based on frequency of 6 cognitive activities and 11 physical activities	Dementia and AD, vascular dementia, mixed and other types	Leisure cognitive activities were associated with a reduced risk of dementia but physical activity was not Dancing was the only physical activity associated with a lower risk of dementia HR 0.24, 95% CI 0.06–0.99
Dik et al ²²	2003	1241 individuals aged 62 to 85 years	Retro-spective	Physical activity from 15 to 25 years old	Processing speed	Active men at low or moderate level displayed faster processing speed
Barnes et al ²³ Sonoma study	2003	349 individuals aged 55 years or over	6 years	Peak oxygen consumption	Cognitive decline (mean MMSE decline)	Lowest VO ₂ tertile = –0.5 (–0.8–0.3) Middle VO ₂ tertile = –0.2 (–0.5–0.0) Highest VO ₂ tertile = 0.0 (–0.3–0.2) <i>P</i> = .002 for trend over tertiles
Lytle et al ²⁴ Monongahela Valley Independent Elders Survey (MoVIES)	2004	1146 individuals aged 65 years or over	2 years	“High exercisers” = aerobic exercise of ≥30 min, ≥3 times/week or number of training per week	Cognitive decline	“High exercise” OR 0.39, 95% CI 0.19–0.78. Threshold = 5 times per week

Table 1. *Continued*

Author and Study Name	Year of Publication	Longitudinal Nondemented Population-based Study	Maximal Follow-up Period	Assessment of Physical Activity	Outcome Measure	Summary of Major Findings (Adjusted for Confounders)
Abbott et al ²⁵ Honolulu-Asia Aging Study	2004	2257 men aged 71–93 years	8 years	Average distance walked per day	Dementia and AD, vascular dementia and other types	Men who walked <0.25 mile/day experienced a 1.8-fold excess risk of dementia compared with those who walked more than 2 mile/day; RR 1.77, 95% CI 1.04–3.01.
Weuve et al ²⁶ Nurses' Health Study	2004	18,766 women aged 70 to 81 years	15 years	Estimated energy expenditure in leisure-time physical activities/week during the past year.	Cognitive decline	Women in the highest quintile of activity had lower cognitive decline OR 0.80, 95% CI 0.67–0.95. Walking at least 1.5 hours/week at a pace of 21–30 min/mile was associated with a significantly higher cognitive score
Podewils et al ²⁷ Cardiovascular Health Cognitive Study	2005	3375 individuals aged 65 years or over	8 years	Leisure-time energy expenditure based on the modified Minnesota Leisure Time Activity and number of different physical activities based on the Index of Physical Activity	Dementia	Individuals in the highest quartile of physical energy expenditure had lower risk of dementia, RR 0.85, 95% CI 0.61–1.19 compared with those in the lowest quartile, individuals engaging in >4 activities had lower risk of dementia, RR 0.51, 95% CI 0.33–0.79 compared with those engaging in 0–1 activity
Rovio et al ²⁸ Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE)	2005	1449 individuals aged 65 to 79 years	21 years	"How often do you participate in leisure-time physical activity that lasts at least 20–30 min and causes breathlessness and sweating?" at midlife	Dementia	Leisure-time physical activity, at least twice a week, was associated with a reduced risk of dementia and AD, OR 0.48, 95% CI 0.25–0.91 and 0.38 (0.17–0.85), respectively
Larson et al ²⁹ Adult Change in Thought	2006	1740 individuals aged 65 years or over	10 years	Number of days/week subjects did aerobic activities for ≥15 minutes at a time during the past year	Dementia, AD, vascular disease other types	Active (>3 times/week) compared with <3 times/week: HR 0.68, 95% CI 0.48–0.96 for dementia and 0.69, 95% CI 0.45–1.05 for AD

AD, Alzheimer's disease; 95% CI, 95% confidence interval; HR, hazard ratio; MMSE, mini-mental status; OR, odds ratio; RR, relative risk; VO₂, maximal oxygen consumption.

Table 2. Some Potential Confounding Factors between Physical Activity and Cognition

Age	Health Condition
Gender	Diabetes
Ethnicity	Depression
Education	Hypertension
Spouse's education	Cholesterol
Family history of dementia	Congestive heart failure
Physical functioning	COPD
Physical activity decline since mid-adulthood	Parkinson's disease
Balance	Heart attack
Visual or hearing impairment	Angina pectoris
Pain	Stroke
Baseline cognitive function	BMI
Lifestyle	Osteoarthritis
Income	Fatigue
Marital status	Hypothyroidism
Smoking	Kidney disease
Alcohol	Hip fracture
Social network and productive activities	Cancer
Diet	Body composition (lean mass, fat mass)
Stress	ApoE4 allele carriers
Medication (NSAI or other treatments)	Brain white matter grade
Postmenopausal hormone therapy	Carotid thickness

ity to ensure brain health. The common pathway of these mechanisms may be a preventive effect of physical activity on the inflammatory pathway and its deleterious consequences on growth factor signaling. The major findings of basic research on physical activity in healthy animals or models of AD are shown in Table 3. This evidence suggests that the brain retains the capacity to regenerate new connections and new neurons. An external stimulus such as physical activity may influence the age-related neurological process or the neuropathological AD processes. Participation in physical activity may thus lower the risk of cognitive decline and dementia by improving cognitive reserve.^{10,13,14,19,42,120}

Physical Activity for Alzheimer's Disease Patients

Falls,¹²¹ malnutrition,¹²² behavioral disturbances,¹²³ and depression¹²⁴ are some of the multiple devastating complications that often develop during the course of AD. They result in a high rate of hospitalization, disability, institutionalization, and death. Some RCTs suggest that physical activity may be a key component in the prevention and management of AD complications. In addition to the well-known benefits of physical activity on health and quality of life, preventing the complications of the disease may also be a realistic approach to delay cognitive decline. Depression, poor physical performance, malnutrition, and behavior disturbances are all linked to faster cognitive decline.¹²⁵ RCTs on physical activity in AD patients are scarce, but most report significant improvement in psychological and/or physical performance as

well as in mobility, balance, strength, gait speed, sleep, agitation, mood, and cognitive function (Table 4). Interactions between these factors are difficult to assess in AD patients. It is however quite conceivable that higher levels of physical activity have an orexigenic effect, improve bowel movement, increase energy expenditure, facilitate access to nutriment or to human relationships, and may result in increased food intake, less fatigue, and better sleep, mood, and quality of life and finally better cognitive functioning. A meta-analysis performed in 2004 by Heyn et al¹⁴⁵ has shown that even in people with cognitive impairment or dementia, exercise training improved behavior disturbances, physical function, and cognitive function. The mean time required to achieve these results was short. Most training programs lasted less than 4 months. It is very unlikely that physical activity reverses the pathophysiological process of dementia during this lapse of time. A program including even a small amount of physical activity may improve cognitive reserve in AD patients. These reports also highlight the sedentary way of life of the elderly, especially in institutions. In nursing homes, residents are frequently physically inactive.¹⁴⁶ In institutions, demented residents spent only 12 minutes a day in any constructive activity other than watching television. Even modest physical training can effect a radical change in life. Most evidence relies on studies of small sample size, nursing home residents, participants with moderate to severe AD, and frail or dependent demented residents. However, these trials highlighted the benefits of nonpharmacological approaches such as physical activities in the management of AD patients.¹⁴⁷

DISCUSSION

Physical Activity and Prevention of Alzheimer's Disease

This review suggested that physical activity could result in better brain health, prevent cognitive decline, and reduce the incidence of AD. Physical activity could protect against cognitive decline and dementia through a reduction of various cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia, and obesity. However, most of the epidemiological studies reported a protective effect after adjustment for these cardiovascular risk factors, suggesting that physical activity has an independent preventive role. Higher cognitive reserve may help the subject engaged in regular physical activity to cope with the first cognitive symptoms of AD. This effect may delay the onset of the clinical manifestations of the disease, which may become apparent only later. Although most evidence on the effect of physical activity on cognitive decline is based on human epidemiological studies, recent basic research has yielded convincing arguments that physical activity acts as a stimulus of neurogenesis, enhances the brain cytoarchitecture and electrophysiological properties, and may influence neuropathological processes such as the formation of beta-amyloid protein during AD.

With a view to preventing cognitive decline, dementia, and AD, it remains to be assessed how much physical activity, of what type and at what time of life, is optimally effective in preventing cognitive decline and dementia. Although con-

Table 3. Major Findings in Biological Research on Enriched Environment (including Physical Activity) in Animals, including Models of Alzheimer's Disease*

	References
Reduction of general risk factors	
Decreased cardiovascular risk factors: hypertension, glucose tolerance, insulin resistance, lipid profile, overweight	74–78
Reduced risk of stroke	79
Improved cerebral blood flow and oxygen delivery	42, 80
Promotion of endothelial nitric oxide production	81
Reduction of inflammation	82
Decreased accumulation of radical oxidative proteins	83
Promotion of brain plasticity	84, 85
Increased cognitive reserve	45, 84, 86, 87
Greater social activity	88
Enhanced brain cytoarchitecture	
Increased dendritic length, neural progenitor proliferation, dendritic complexity	89
Growth of blood vessels in the hippocampus	68
Growth of blood vessels in the cortex	90
Growth of blood vessels in the cerebellum	91
Increased microglia proliferation	92
Enhanced short- and long-term potentialization in the dentate gyrus	93
Increased cerebral capillary density	91
Promotion of expansion of neural fibers	80, 94
Proliferation of microglia in the cortex	92
Increased neurogenesis and proliferation	95
Reduced loss of hippocampal brain tissue	58
Increased number of differentiating neurons	96
Enhanced electrophysiological properties	
Enhanced potentialization in response to high-frequency stimulation	71, 97
Increased synapsin and synaptotrophin level	98
Increased glutamate receptors (NR2b and GluR5)	93
Increased brain growth factors	
Increased brain-derived neurotrophic factor (BDNF)	73, 99–102
Down-regulation of hippocampal neurotrophin (NT3), BDNF and hippocampal neurogenesis*	103
Increased insulin-like growth factor-1 (IGF-1)	104, 105
Increased vascular endothelial-derived growth factor (VEGF)	106
Increased serotonin	107
Increased acetylcholine	108
Inducing fibroblast growth factor	109
Impact on amyloid loading*	
Reduced amyloid burden	110, 111
Stabilized amyloid burden	112
Enhanced hippocampal functioning despite elevated APP level	113
Higher amyloid burden	114
Other mechanisms	
Higher expression of hippocampal enzymes involved in glucose use	115
Change in gene transcript	73, 116–118
Increased level of calcium in the central nervous system	119

clusive evidence is lacking to answer these questions, current epidemiological and animal studies suggest under what conditions physical activity (intensity, type, frequency, and duration) may reduce the risk of dementia.

Intensity and Frequency

In most longitudinal studies, arbitrary approaches are used to distinguish exercisers from nonexercisers. A relevant measure of intensity and duration or a standardized physical activity assessment scale is generally lacking. These epidemiological studies (Table 1) have not been designed to determine a threshold of physical activity that starts to protect against cognitive decline or AD. Although some studies have based their cut-off on

previous recommendations for health-promoting physical activity,²⁸ an optimal dose-response effect of regular physical activity can only be suggested from these reports.

Whether low-intensity physical activity, such as walking, cycling, or swimming, or high-intensity activity, such as weight bearing, protects brain function is an important practical question. High-intensity activity such as resistance training may be difficult to organize in the community and has less appeal for sedentary elders in the long term than low-intensity aerobic training. Albert et al⁹ reported that strenuous, but not moderate, physical activity was associated with less cognitive decline in a prospective study. However, in frail elderly people, organizing high-intensity activity may be challenging.

Table 4. *Randomized Controlled Trials on Physical Activity in Demented Populations*

Author (Reference)	Year	Participants	Intervention	Main Outcome Measures	Summary of Major Findings
Molloy et al ⁵¹	1988	15 NH residents Mean MMSE = 24/30	Two groups: Light aerobic training or no intervention 45 min once a week over 2 weeks	Neuropsychological performances	No significant improvement except for word fluency
Friedman et al ¹³⁰	1991	30 NH residents Moderate to severe AD	Two groups: Walking or conversation, 30 min 3 times/week over 10 weeks	Communication performances	Improvement of communication performances
Mulrow et al ¹³¹	1994	194 dependent NH residents Mean MMSE = 21/30	Two groups: Physical therapy including strength, balance, transfer, mobility exercise, or friendly visit 45 min 3 times/week over 16 weeks	Disability, self-perceived health, ADL, falls	Modest mobility benefits: 15.5% improvement in the mobility subscale of the PDI
Fiatarone et al ¹³²	1994	100 NH residents Mean MMSE = 22/30	Four groups: Resistance training or nutritional supplementation or both or neither, 45 min 3 times/week over 10 weeks	Gait speed, stair climbing power, muscle mass	Improved physical performance and muscle mass in the exercise groups
Tappen ¹³³	1994	42 demented NH residents Mean MMSE = 6/30	Three groups: Skill training, traditional stimulation approach or no intervention 150 min 5 times/week over 20 weeks	Performance Test of ADL	Greatest functional improvement in the skill training group and modest improvement in the traditional stimulation group
Alessi et al ¹³⁴	1995	65 NH residents Mean MMSE = 14/30	Two groups: Sit-to-stand, walking, and transferring exercise 120 min 5 times/week or rowing and walking 60 min 3 times/week over 9 weeks	Endurance, physical activity, nighttime sleep, daytime sleep	Improved mobility, no improvement in night or day sleep disruption
McMurdo et al ¹³⁵	1995	55 dependent NH residents Mean MMSE = 15/30	Two groups: Seated exercise or reminiscence exercise 45 min, 2 times/week over 6 months	Quadriceps strength, climbing stairs, cognitive function	Improved quadriceps strength, no change in cognitive function
Schnelle et al ¹³⁶	1995	76 incontinent NH residents Mean MMSE = 12/30	Two groups: Functional Incidental Training (FIT) or prompted voiding 30–55 min 5 times/week over 8 weeks	Endurance, physical activity, agitation	Reduced agitation in both groups Improved endurance and physical activity
MacRae et al ¹³⁷	1996	37 NH residents Mean MMSE = 20/30	Two groups: Walking program or social visit 30 min 5 times/week over 12 weeks	Walking distance and speed, timed up and go, mobility, quality of life	Improved endurance and walking distance per day
Schnelle et al ¹³⁷	1996	97 NH residents Mean MMSE = 10/30	Two groups: Walking or wheelchair movement or no exercise 20–35 min 3 times/week over 9 weeks	Endurance, speed, strength	Low compliance, improved endurance, strength for those who completed the exercise
Pomeroy et al ¹³⁸	1999	81 hospitalized demented patients MMSE/NA	Two groups: 30 min 5 times/week over 2 weeks	Southampton Mobility Assessment Test, 2-minute walk test	No significant improvement

Table 4. *Continued*

Author (Reference)	Year	Participants	Intervention	Main Outcome Measures	Summary of Major Findings
Lazowski et al ¹³⁹	1999	68 NH residents with mild dementia MMSE/NA	Two groups: Seated ROM exercises or Functional for Long Term Care (FFLTC) program 45 min 3 times/week over 4 months	Mobility, balance, flexibility, lower extremities strength	Improved mobility, balance, flexibility, lower extremities strength in the FFLTC group
Alessi et al ¹⁴⁰	1999	29 NH residents Mean MMSE = 13/30	Two groups: Daytime aerobic exercise plus nighttime intervention to decrease noise or nighttime intervention only over 14 weeks	Daytime physical activity, physical function, sleep	Improved sleep and decreased agitation
Tappen et al ¹²⁷	2000	65 AD NH residents Mean MMSE = 11/30	Three groups: Walking or walking + conversation or conversation only 30 min 3 times/week over 16 weeks	Modified 6-minute walk test	More compliance and less functional mobility decline in the walking + conversation group
Schnelle et al ¹⁴¹	2002	256 incontinent NH residents Mean MMSE = 12/30	Two groups: Incontinence care and exercise every 2 hours 60 min 5 times/week over 8 months or no intervention	Distance walked per day, continence, strength	Improved continence and physical performance
Cott et al ³²	2002	74 AD NH residents Mean MMSE = 6/30	Three groups: Walk and talk or talk only or no intervention 30 min 5 times/week over 16 weeks	Communication skills, 2-minute walk test, London Psychogeriatric Rating Scale	No significant improvement
Teri et al ¹²⁶	2003	153 community-dwelling AD participant Mean MMSE = 17/30	Two groups: Exercise and caregiver training program or routine medical care 30 min 2 to 4 times/week over 12 weeks	Physical and functional health, depression, mobility	Fewer days of restricted activity, improved physical function, less depression
Baum et al ¹²²	2003	20 NH and LTC residents Mean MMSE = 21/30	Two groups: Seated range of motion (ROM) and strength training or recreational therapy 60 min 3 times/week over 6 months	Cognition, timed get-up and go, Berg Balance Scale, Physical Performance Test (PPT)	Improved physical performances and MMSE
Van de Winckel et al ¹⁴²	2004	15 demented women Mean MMSE = 13/30	Physical activity + music or daily conversation 30 min/day over 3 months	Cognition, behavior	Improved MMSE, no effect on behavior
McCurry et al ¹²⁹	2005	36 community-dwelling AD patients Mean MMSE = 12/30	Specific recommendations about sleep hygiene including daily walk or no intervention over 6 months	Sleep	Improved sleep
Stevens et al ¹⁴³	2006	75 NH residents with mild dementia MMSE = 9–23/30	Three groups: Physical activity, social visit or no intervention 30 min 3 times/week over 12 weeks	Clock drawing test, Revised Elderly Persons Disabilities Scale	Slower cognitive and disability decline in the physical activity group

Table 4. Continued

Author (Reference)	Year	Participants	Intervention	Main Outcome Measures	Summary of Major Findings
Williams et al ¹⁴⁴	2007	90 AD NH residents Mean MMSE = 10/30	Three groups: Supervised walking or walking plus strength, balance, flexibility exercises or social conversation 30 min 5 times/week over 16 weeks	Mood	The whole-body exercise program had a positive effect on mood
Rolland et al ¹²⁸	2007	134 AD NH residents Mean MMSE = 9/30	Two groups: Usual care or collective exercise (walk, strength, balance, and flexibility) 60 min 2 times/week over 12 months	ADL, balance, 4-meter walk test, behavior disturbances, depression, MNA	Slower disability decline, increased gait speed

AD, Alzheimer's disease; NPI, Neuro-Psychiatric Inventory; PDI, Physical Disability Index; ADL, Activities of Daily Living; ADQRL, Alzheimer Disease-Related Quality of Life; CRAI, Copper Ridge Activity Index; MMSE, Mini-Mental Status Examination; MNA, mini-nutritional assessment; ROM, range of motion; SF-36, 36-item Short-Form Health Survey; NH, nursing home; LTC, long-term care; NA, not applicable.

Recommendations on physical activity have to be easily adopted by the population to be pertinent.

Most data suggest, however, that the intensity threshold of physical activity required for a clinically relevant impact on cognitive decline or dementia prevention is low. Moderate physical activity such as playing golf, walking 1.6 km per day, or playing tennis twice a week was associated with a reduced risk of cognitive decline in the Study of Osteoporotic Fractures.¹⁶ Schuit et al¹² reported that compared with the elderly who did less than 1 hour of physical activity per week, the risk of cognitive decline was decreased twofold in those who did more than 1 hour daily. Scarmeas et al¹⁴ have shown that physical activity, mainly assessed on the basis of walking activities, was associated with a reduced risk of dementia. Yaffe et al¹⁶ also reported in a large cohort of women that those who walked were less likely to develop cognitive decline over a 6- to 8-year follow-up. According to the Adult Changes in Thought (ACT) data, subjects who exercised at least 3 times per week had a lower risk of dementia than the less active subjects.²⁹ In the Nurses' Health Study, walking at least 1.5 hours a week at a pace of 21 to 30 minutes per mile was associated with higher cognitive score.²⁶ Doing at least 15 minutes of activity at a time, 3 times a week, and per year among the physical activities of walking, hiking, bicycling, aerobics or calisthenics, swimming, water aerobics, weight training or stretching, or other exercise was associated with a significantly lower risk of dementia in the ACT study.²⁹ In this study, being active (at least 3 activities per week) seemed sufficient to reduce the risk by 32%. In RCTs, improved cognitive performances followed even a small increase in aerobic fitness.⁴⁵ Colcombe et al⁵⁸ also reported that a 1-hour aerobic exercise training session (40% to 50% heart rate [HR] reserve increasing to 60% to 70% HR reserve over the course of the trial) 3 times per week over 6 months increased brain volume. In this study, no dose-related response between physical activity and prevention of cognitive decline was found.²⁹

Other authors reported significant trends for increased protection with greater intensity of physical activity. In the Canadian Study of Health and Aging, regular physical activity was associated with lower risk of AD than no activity. In addition, an increasing level of physical activity was associated with a decreasing risk of cognitive impairment and dementia.¹³ In this cohort, risk of AD was reduced by half in subjects with higher levels of physical activity (odds ratio [OR] = 0.5, 95% confidence interval [CI] 0.28–0.98).¹³

These results all suggest that the threshold of intensity that reduces the risk of cognitive decline and dementia is probably low. Previous studies have suggested that moderate activity could reduce dramatically the risk of other chronic diseases such as coronary heart disease.¹⁴⁸ The same appears to be true for brain health. However, the optimal intensity of physical activity required to maximize the slowing of cognitive decline and reduce the risk of dementia remains unclear.

Type of Activity

The American College of Sports Medicine (ACSM) and the Centers for Disease Control and Prevention (CDC) suggest that the benefit of physical activity is related to the

amount of activity per day (energy expenditure), rather than to the type and modality of activity. Most epidemiological studies have investigated the role of physical activity on cognition using a composite score. Other studies have also combined leisure time and occupational physical activity.²⁰ None of these approaches make it possible to assess the influence of any specific activity on cognition.

Yet, in addition to the increased energy expenditure, some specific physical activities may result in better brain functioning through social interaction and cognitive training. The beneficial effects of social, cognitive, and physical activities on cognitive decline and the prevention of dementia seem to have common pathways.¹⁴⁹ The psychological dimension of physical activity appears an important issue. In rodents, voluntary exercises benefit more than forced exercises.⁷² Engagement in various physical activities, but not total energy expenditure, was significantly associated with the risk of dementia²⁷ in the Cardiovascular Health Cognition Study (CHCS). Compared with participants engaged in 1 or no activity, risk of dementia decreased by half in those engaged in 4 or more different activities, even after adjustment for energy expenditure.²⁷ In the Bronx Aging study, dancing was the only physical activity that significantly reduced the risk of dementia.¹⁵⁰ Among the 13 different leisure activities of the Health Care Financing Administration (HCFA) study, walking for pleasure or going for an excursion was one of the activities most strongly associated with a reduced risk of incident dementia.¹⁴ These results reinforce the hypothesis that physical activity may affect cognition through its social interactions or cognitive training during the activity.

However, other studies also suggested that simple tasks of a physical activity program such as walking prevent cognitive decline. Barnes et al²³ reported that peak VO₂, a value that corresponds to the ability of an individual to perform aerobic exercise, was associated with reduced risk of cognitive decline in a 6-year follow-up. Results from the Nurses' Health Study suggest that benefits from physical activities are not restricted to vigorous activities.²⁶ Among nurses who were not engaged in vigorous physical activity, women who walked at an easy pace had higher cognitive scores than those who walked less.²⁶

Duration

Most studies assessed physical activity at baseline but did not assess subjects' life-long involvement. Currently, we do not know at what period of life physical activity may have the most benefit on the risk of dementia. However, the pathophysiological process of AD begins long before cognitive decline is evident and the diagnosis established. It is probably necessary to begin being physically active early in life. Most authors suggest that the protective effect is not a short-term but a long-term one, such as those reported in cardiovascular or cerebrovascular disease.⁷² According to the cognitive reserve hypothesis, physical activity performed across the whole lifespan may contribute to maintain cognitive function in old age.¹⁴⁹ However, results from epidemiological studies also suggest that even in late life, involvement in physical activity is of benefit in brain functioning.

Other Considerations

Apo E4. Several studies have suggested that ApoE4 may modify the association between physical activity and the risk of dementia. Schuit et al¹² found that the risk of cognitive decline was higher in participants who reported less than 1 hour of physical activity daily and were also Apo E4 carriers. In the CAIDE study, the association between midlife leisure-time physical activity and reduced risk of dementia was also more pronounced in ApoE4 carriers.²⁸ Subjects with E4, a high AD risk genotype, may have less effective neuronal protection mechanisms and so may be more dependent on lifestyle-related factors.²⁸ On the other hand, the association between dementia risk and physical activity was significant in ApoE4 noncarriers but absent in carriers in the Cardiovascular Health Cognition Study.²⁷ Previous studies have reported less benefit from physical activity in ApoE4 carriers than in noncarriers in terms of lipid pattern and blood pressure.^{151–153}

Gender. In the Canadian Study of Health and Aging, physical activity was found to have a greater protective effect against dementia in women than in men.¹³ Interactions between hormones and physical activity in women have been suggested to explain a greater enhancement of cognitive tests in women.^{57,73,154} Estrogen replacement, like physical activity, increased levels of brain-derived neurotrophic factor (BDNF), a molecule involved in neurogenesis and neuroprotection. Estrogens and physical activity may have a synergic effect on brain functioning. However, these results may also be related to the smaller number of men studied and thus the lower statistical power of these epidemiological analyses. Moreover, Barnes et al²³ reported that men were more protected than women.

Limitations

Current clinical evidence of the benefits of physical activity on the prevention of AD relies on epidemiological studies. These approaches are exposed to many sources of bias. First, in most studies, the reliability of the physical activity assessment is questionable. Assessment relies on one single question, a composite score based on physical activity during leisure and at work, and estimated average energy expenditure. Very few research protocols have used validated standardized physical activity scales. The collection of self-reported activities introduces reporting bias. The exact type, frequency, and duration of activity are usually not quantified. Physical activity is assessed at study baseline but this assessment may not correspond to a mean stable regular activity in the long term and even less to activity over the subject's past lifetime. The time elapsing between physical activity assessment and the onset of dementia or cognitive decline is variable. Mean follow-up between physical activity assessment and cognitive assessment varies from 2.5 to 21 years. Second, one important limitation of these epidemiological studies is that initial cognitive decline is associated with functional decline.^{155–157} In fact, inactivity may be a manifestation of the early phase of dementia rather than a risk factor. Most epidemiological studies have tried to reduce this potential effect of behavior

changes on physical activity in the early phase of Alzheimer's disease by excluding subjects with low cognitive function at baseline or those who converted to AD in the early phases of follow-up. However, behavior disturbances such as depression, not assessed at baseline, usually precede Alzheimer's disease and result in low physical activity. Third, the mean follow-up is relatively short (3 to 7 years) compared with the decade before pathophysiological changes begin to be symptomatic and enable the diagnosis of dementia to be confirmed. Only one study investigated the long-term association between midlife physical activity and the risk of dementia or AD.²⁸ Fourth, another main limitation in interpreting these epidemiological studies is that despite adjustment for several potential confounders, sedentary participants differ from exercisers in many ways. There exist numerous other potential confounders that may influence the relationship between exercise and risk of dementia (Table 2). Fifth, physical activity involves cognitive functions (in addition to energy expenditure and mobility) that may enhance cognitive performances. Physical, social, and cognitive activities usually overlap. It is thus difficult to ascertain the specific and individual impact of each component on brain functioning.

Physical Activity in AD Populations

Current research on Alzheimer's disease and physical activity has demonstrated the feasibility of physical training even in severely demented nursing home patients (Table 4). Most RCTs reported promising benefits in terms of cognitive function or prevention of various complications. However, these RCTs are few, are short-duration trials with small samples of participants, and leave many questions unresolved. They need to be replicated in large future RCTs. Moreover, in most of these trials, physical activity was part of a combined intervention such as physical activity plus sensory environmental stimulation,¹⁵⁸ behavior management,¹²⁶ or social interaction.¹²⁷ The impact of physical training on improved physical health, mood, or functional mobility is then impossible to ascertain.

The physical activity training ranges from 150 minutes 5 times per week to 20 minutes 3 times per week. Population-based studies differ in terms of age, cognitive impairment severity or type of dementia, and outcomes of the trial. Most studies have been organized in nursing home facilities, and few in the community (Table 4). It is thus difficult to propose, on the basis of the literature, a specific kind of physical program for AD patients. However, intensive exercise programs may not be practical in some nursing home settings in the long term. Simple programs such as an aerobic exercise, twice a week, have been reported to slow disease progression in nursing home residents.¹²⁸ Most RCTs suggest that aerobic exercise such as walking may promote cognitive and functional capacities in people with AD.

Compliance is another key issue for physical activity programs. In this population, compliance seems to be a major limitation, more than cognitive status. The physical program has to be enjoyable and accessible.¹²⁹ Individualized exercises, based on the participant's behavioral readiness for the proposed training, and music during the session¹⁵⁹ seem to in-

crease compliance. Successful and safe interventions including strength, flexibility, and balance training have been reported in this frail and cognitively impaired population.^{126,128,160} Compliance with the physical activity program appeared better when the staff assigned to this task communicated with the resident at the same time.¹²⁷

CONCLUSION

Regular physical activity is a key component of successful aging. In addition to its convincing multiple benefits, increasing evidence suggests that an active life has a protective effect on brain functioning in the elderly population. Physical activity may also slow down the course of AD.

Epidemiological studies, short-term RCTs in nondemented participants, and biological research suggest that physical activity improves cognitive functioning in older subjects. However, no RCTs have yet demonstrated that regular physical activity prevents dementia. Additional interventional studies are needed to examine this relationship. Moreover, type, duration, and intensity of physical exercise need to be determined in challenging RCTs, as well as its precise impact on the different aspects of cognitive function. Future research should focus on developing specific exercise programs that will best postpone or reduce the risk of dementia, or slow down disease progression. In the coming decade, large on-going RCTs will probably provide some of the answers to these questions. Preventive approaches to dementia could then be the basis of recommendations in the community. The main problem, however, is how to change lifestyle habits and promote physical activity in the older population in the long term. Yet, in primary care, prevention of many diseases should already rely on a healthy diet and lifestyle, control of cardiovascular risk factors, on-going learning experiences, and regular physical activity. Prevention of cognitive decline and dementia could well be a decisive argument to convince our patients and modify public health policy.

REFERENCES

1. Physical activity and cardiovascular health. NIH Consensus Development Panel on Physical Activity and Cardiovascular Health. *JAMA* 1996;276:241–246.
2. Brody JG, Rudel RA, Michels KB, et al. Environmental pollutants, diet, physical activity, body size, and breast cancer: Where do we stand in research to identify opportunities for prevention? *Cancer* 2007;109:2627–2634.
3. Thune I, Furberg AS. Physical activity and cancer risk: Dose-response and cancer, all sites and site-specific. *Med Sci Sports Exerc* 2001;33:S530–50; discussion S609–610.
4. Broe GA, Henderson AS, Creasey H, et al. A case-control study of Alzheimer's disease in Australia. *Neurology* 1990;40:1698–1707.
5. Kondo K, Niino M, Shido K. A case-control study of Alzheimer's disease in Japan—significance of life-styles. *Dementia* 1994;5:314–326.
6. Li G, Shen YC, Chen CH, Zhou YW, Li SR, Lu M. A three-year follow-up study of age-related dementia in an urban area of Beijing. *Acta Psychiatr Scand* 1991;83:99–104.
7. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 1994;271:1004–1010.
8. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: The Hisayama Study. *Neurology* 1995;45:1161–1168.

9. Albert MS, Jones K, Savage CR, et al. Predictors of cognitive change in older persons: MacArthur studies of successful aging. *Psychol Aging* 1995;10:578–589.
10. Fabrigoule C, Letenneur L, Dartigues JF, Zarrouk M, Commenges D, Barberger-Gateau P. Social and leisure activities and risk of dementia: A prospective longitudinal study. *J Am Geriatr Soc* 1995;43:485–490.
11. Broe GA, Creasey H, Jorm AF, et al. Health habits and risk of cognitive impairment and dementia in old age: A prospective study on the effects of exercise, smoking and alcohol consumption. *Aust N Z J Public Health* 1998;22:621–623.
12. Schuit AJ, Feskens EJ, Launer LJ, Kromhout D. Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. *Med Sci Sports Exerc* 2001;33:772–777.
13. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* 2001;58:498–504.
14. Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology* 2001;57:2236–2242.
15. Ho SC, Woo J, Sham A, Chan SG, Yu AL. A 3-year follow-up study of social, lifestyle and health predictors of cognitive impairment in a Chinese older cohort. *Int J Epidemiol* 2001;30:1389–1396.
16. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: Women who walk. *Arch Intern Med* 2001;161:1703–1708.
17. Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* 2002;156:445–453.
18. Pignatti F, Rozzini R, Trabucchi M. Physical activity and cognitive decline in elderly persons. *Arch Intern Med* 2002;162:361–362.
19. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: A longitudinal study from the Kungsholmen project. *Am J Epidemiol* 2002;155:1081–1087.
20. Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G. Association between dementia and midlife risk factors: The Radiation Effects Research Foundation Adult Health Study. *J Am Geriatr Soc* 2003;51:410–414.
21. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med* 2003;348:2508–2516.
22. Dik M, Deeg DJ, Visser M, Jonker C. Early life physical activity and cognition at old age. *J Clin Exp Neuropsychol* 2003;25:643–653.
23. Barnes DE, Yaffe K, Satariano WA, Tager IB. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *J Am Geriatr Soc* 2003;51:459–465.
24. Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M. Exercise level and cognitive decline: The MoVIES project. *Alzheimer Dis Assoc Disord* 2004;18:57–64.
25. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. *JAMA* 2004;292:1447–1453.
26. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *JAMA* 2004;292:1454–1461.
27. Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: Findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol* 2005;161:639–651.
28. Rovio S, Kareholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol* 2005;4:705–711.
29. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med* 2006;144:73–81.
30. Smyth KA, Fritsch T, Cook TB, McClendon MJ, Santillan CE, Friedland RP. Worker functions and traits associated with occupations and the development of AD. *Neurology* 2004;63:498–503.
31. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944.
32. Christensen H, Korten A, Jorm AF, Henderson AS, Scott R, Mackinnon AJ. Activity levels and cognitive functioning in an elderly community sample. *Age Ageing* 1996;25:72–80.
33. Emery CF, Schein RL, Hauck ER, MacIntyre NR. Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. *Health Psychol* 1998;17:232–240.
34. Clarkson-Smith L, Hartley AA. Relationships between physical exercise and cognitive abilities in older adults. *Psychol Aging* 1989;4:183–189.
35. Carmelli D, Swan GE, LaRue A, Eslinger PJ. Correlates of change in cognitive function in survivors from the Western Collaborative Group Study. *Neuroepidemiology* 1997;16:285–295.
36. Friedland RP, Fritsch T, Smyth KA, et al. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc Natl Acad Sci U S A* 2001;98:3440–3445.
37. Hulstsch DF, Hammer M, Small BJ. Age differences in cognitive performance in later life: Relationships to self-reported health and activity life style. *J Gerontol* 1993;48:1–11.
38. Pierce TW, Madden DJ, Siegel WC, Blumenthal JA. Effects of aerobic exercise on cognitive and psychosocial functioning in patients with mild hypertension. *Health Psychol* 1993;12:286–291.
39. Madden DJ, Blumenthal JA, Allen PA, Emery CF. Improving aerobic capacity in healthy older adults does not necessarily lead to improved cognitive performance. *Psychol Aging* 1989;4:307–320.
40. Blumenthal JA, Emery CF, Madden DJ, et al. Long-term effects of exercise on psychological functioning in older men and women. *J Gerontol* 1991;46:352–361.
41. Emery CF, Huppert FA, Schein RL. Relationships among age, exercise, health, and cognitive function in a British sample. *Gerontologist* 1995;35:378–385.
42. Rogers RL, Meyer JS, Mortel KF. After reaching retirement age physical activity sustains cerebral perfusion and cognition. *J Am Geriatr Soc* 1990;38:123–128.
43. Dustman RE, Ruhling RO, Russell EM, et al. Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiol Aging* 1984;5:35–42.
44. Williams P, Lord SR. Effects of group exercise on cognitive functioning and mood in older women. *Aust N Z J Public Health* 1997;21:45–52.
45. Kramer AF, Hahn S, Cohen NJ, et al. Ageing, fitness and neurocognitive function. *Nature* 1999;400:418–419.
46. Hassmen P, Koivula N. Mood, physical working capacity and cognitive performance in the elderly as related to physical activity. *Aging (Milano)* 1997;9:136–142.
47. Emery CF, Gatz M. Psychological and cognitive effects of an exercise program for community-residing older adults. *Gerontologist* 1990;30:184–188.
48. Fabre C, Chamari K, Mucci P, Masse-Biron J, Prefaut C. Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. *Int J Sports Med* 2002;23:415–421.
49. Hill RD, Storandt M, Malley M. The impact of long-term exercise training on psychological function in older adults. *J Gerontol* 1993;48:12–17.
50. Molloy DW, Beerschoten DA, Borrie MJ, Crilly RG, Cape RD. Acute effects of exercise on neuropsychological function in elderly subjects. *J Am Geriatr Soc* 1988;36:29–33.
51. Molloy DW, Richardson LD, Crilly RG. The effects of a three-month exercise programme on neuropsychological function in elderly institutionalized women: A randomized controlled trial. *Age Ageing* 1988;17:303–310.
52. Thompson RF, Crist DM, Marsh M, Rosenthal M. Effects of physical exercise for elderly patients with physical impairments. *J Am Geriatr Soc* 1988;36:130–135.

53. Barry AJ, Steinmetz JR, Page HF, Rodahl K. The effects of physical conditioning on older individuals. II. Motor performance and cognitive function. *J Gerontol* 1966;21:192–199.
54. Blumenthal JA, Emery CF, Madden DJ, et al. Cardiovascular and behavioral effects of aerobic exercise training in healthy older men and women. *J Gerontol* 1989;44:M147–157.
55. Okumiya K, Matsubayashi K, Wada T, Kimura S, Doi Y, Ozawa T. Effects of exercise on neurobehavioral function in community-dwelling older people more than 75 years of age. *J Am Geriatr Soc* 1996;44:569–572.
56. Stevenson JS, Topp R. Effects of moderate and low intensity long-term exercise by older adults. *Res Nurs Health* 1990;13:209–218.
57. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci* 2003;14:125–130.
58. Colcombe SJ, Erickson KI, Scaif PE, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* 2006;61:1166–1170.
59. Camicioli R, Howieson D, Oken B, Sexton G, Kaye J. Motor slowing precedes cognitive impairment in the oldest old. *Neurology* 1998;50:1496–1498.
60. Marquis S, Moore MM, Howieson DB, et al. Independent predictors of cognitive decline in healthy elderly persons. *Arch Neurol* 2002;59:601–606.
61. Wang L, Larson EB, Bowen JD, van Belle G. Performance-based physical function and future dementia in older people. *Arch Intern Med* 2006;166:1115–1120.
62. Dustman RE, Emmerson RY, Ruhling RO, et al. Age and fitness effects on EEG, ERPs, visual sensitivity, and cognition. *Neurobiol Aging* 1990;11:193–200.
63. van Boxtel MP, Paas FG, Houx PJ, Adam JJ, Teeken JC, Jolles J. Aerobic capacity and cognitive performance in a cross-sectional aging study. *Med Sci Sports Exerc* 1997;29:1357–1365.
64. Shay KA, Roth DL. Association between aerobic fitness and visuospatial performance in healthy older adults. *Psychol Aging* 1992;7:15–24.
65. Waite LM, Grayson DA, Piguet O, Creasey H, Bennett HP, Broe GA. Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study. *J Neurol Sci* 2005;229–230:89–93.
66. Raji MA, Kuo YF, Snih SA, Markides KS, Peek MK, Ottenbacher KJ. Cognitive status, muscle strength, and subsequent disability in older Mexican Americans. *J Am Geriatr Soc* 2005;53:1462–1468.
67. Schweitzer NB, Alessio HM, Berry SD, Roeske K, Hagerman AE. Exercise-induced changes in cardiac gene expression and its relation to spatial maze performance. *Neurochem Int* 2006;48:9–16.
68. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci* 2005;25:8680–8685.
69. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci* 2004;20:2580–2590.
70. Radak Z, Toldy A, Szabo Z, et al. The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. *Neurochem Int* 2006;49:387–392.
71. O'Callaghan RM, Ohle R, Kelly AM. The effects of forced exercise on hippocampal plasticity in the rat: A comparison of LTP, spatial- and non-spatial learning. *Behav Brain Res* 2007;176:362–366.
72. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends Neurosci* 2007;30:464–472.
73. Cotman CW, Engesser-Cesar C. Exercise enhances and protects brain function. *Exerc Sport Sci Rev* 2002;30:75–79.
74. Wareham NJ, Wong MY, Day NE. Glucose intolerance and physical inactivity: The relative importance of low habitual energy expenditure and cardiorespiratory fitness. *Am J Epidemiol* 2000;152:132–139.
75. Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L. The acute versus the chronic response to exercise. *Med Sci Sports Exerc* 2001;33:S438–445.
76. Van Dam RM, Schuit AJ, Feskens EJ, Seidell JC, Kromhout D. Physical activity and glucose tolerance in elderly men: The Zutphen Elderly study. *Med Sci Sports Exerc* 2002;34:1132–1136.
77. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001;322:1447–1451.
78. Launer LJ. Demonstrating the case that AD is a vascular disease: Epidemiologic evidence. *Ageing Res Rev* 2002;1:61–77.
79. Evenson KR, Rosamond WD, Cai J, et al. Physical activity and ischemic stroke risk. The atherosclerosis risk in communities study. *Stroke* 1999;30:1333–1339.
80. Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer AF, Greenough WT. Exercise, experience and the aging brain. *Neurobiol Aging* 2002;23:941–955.
81. Taddei S, Galetta F, Virdis A, et al. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. *Circulation* 2000;101:2896–2901.
82. Pedersen BK. The anti-inflammatory effect of exercise: Its role in diabetes and cardiovascular disease control. *Essays Biochem* 2006;42:105–117.
83. Radak Z, Taylor AW, Ohno H, Goto S. Adaptation to exercise-induced oxidative stress: From muscle to brain. *Exerc Immunol Rev* 2001;7:90–107.
84. Cotman CW, Berchtold NC. Exercise: A behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 2002;25:295–301.
85. Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* 2004;101:3316–3321.
86. Scarmeas N, Stern Y. Cognitive reserve and lifestyle. *J Clin Exp Neuropsychol* 2003;25:625–633.
87. Scarmeas N, Zarahn E, Anderson KE, et al. Association of life activities with cerebral blood flow in Alzheimer disease: Implications for the cognitive reserve hypothesis. *Arch Neurol* 2003;60:359–365.
88. Seeman TE, Crimmins E. Social environment effects on health and aging: Integrating epidemiologic and demographic approaches and perspectives. *Ann N Y Acad Sci* 2001;954:88–117.
89. Eadie BD, Redila VA, Christie BR. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J Comp Neurol* 2005;486:39–47.
90. Ding YH, Li J, Zhou Y, Rafols JA, Clark JC, Ding Y. Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. *Curr Neurovasc Res* 2006;3:15–23.
91. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc Natl Acad Sci U S A* 1990;87:5568–5572.
92. Ehninger D, Kempermann G. Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. *Cereb Cortex* 2003;13:845–851.
93. Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* 2004;124:71–79.
94. Chodzko-Zajko WJ, Moore KA. Physical fitness and cognitive functioning in aging. *Exerc Sport Sci Rev* 1994;22:195–220.
95. Brandt MD, Jessberger S, Steiner B, et al. Transient calretinin expression defines early postmitotic step of neuronal differentiation in adult hippocampal neurogenesis of mice. *Mol Cell Neurosci* 2003;24:603–613.
96. Llorens-Martin M, Torres-Aleman I, Trejo JL. Pronounced individual variation in the response to the stimulatory action of exercise on immature hippocampal neurons. *Hippocampus* 2006;16:480–490.
97. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A* 1999;96:13427–13431.
98. Vaynman SS, Ying Z, Yin D, Gomez-Pinilla F. Exercise differentially regulates synaptic proteins associated to the function of BDNF. *Brain Res* 2006;1070:124–130.

99. Berchtold NC, Chinn G, Chou M, Kesslak JP, Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience* 2005;133:853–861.
100. Molteni R, Ying Z, Gomez-Pinilla F. Differential effects of acute and chronic exercise on plasticity-related genes in the rat hippocampus revealed by microarray. *Eur J Neurosci* 2002;16:1107–1116.
101. Kuipers SD, Bramham CR. Brain-derived neurotrophic factor mechanisms and function in adult synaptic plasticity: New insights and implications for therapy. *Curr Opin Drug Discov Devel* 2006;9:580–586.
102. Gomez-Pinilla F, Dao L, So V. Physical exercise induces FGF-2 and its mRNA in the hippocampus. *Brain Res* 1997;764:1–8.
103. Wolf SA, Kronenberg G, Lehmann K, et al. Cognitive and physical activity differently modulate disease progression in the amyloid precursor protein (APP)-23 model of Alzheimer's disease. *Biol Psychiatry* 2006;60:1314–1323.
104. Ding Q, Vaynman S, Akhavan M, Ying Z, Gomez-Pinilla F. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience* 2006;140:823–833.
105. Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci* 2001;21:1628–1634.
106. Fabel K, Fabel K, Tam B, et al. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci* 2003;18:2803–2812.
107. Blomstrand E, Perrett D, Parry-Billings M, Newsholme EA. Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions in the rat. *Acta Physiol Scand* 1989;136:473–481.
108. Fordyce DE, Farrar RP. Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning. *Behav Brain Res* 1991;46:123–133.
109. Gomez-Pinilla F, So V, Kesslak JP. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: Neural substrates for increased cognition associated with exercise. *Neuroscience* 1998;85:53–61.
110. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *J Neurosci* 2005;25:4217–4221.
111. Lazarov O, Robinson J, Tang YP, et al. Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell* 2005;120:701–713.
112. Arendash GW, Garcia MF, Costa DA, Cracchiolo JR, Wefes IM, Potter H. Environmental enrichment improves cognition in aged Alzheimer's transgenic mice despite stable beta-amyloid deposition. *Neuroreport* 2004;15:1751–1754.
113. Teather LA, Magnusson JE, Chow CM, Wurtman RJ. Environmental conditions influence hippocampus-dependent behaviours and brain levels of amyloid precursor protein in rats. *Eur J Neurosci* 2002;16:2405–2415.
114. Jankowsky JL, Xu G, Fromholt D, Gonzales V, Borchelt DR. Environmental enrichment exacerbates amyloid plaque formation in a transgenic mouse model of Alzheimer disease. *J Neuropathol Exp Neurol* 2003;62:1220–1227.
115. Ding Q, Vaynman S, Souda P, Whitelegge JP, Gomez-Pinilla F. Exercise affects energy metabolism and neural plasticity-related proteins in the hippocampus as revealed by proteomic analysis. *Eur J Neurosci* 2006;24:1265–1276.
116. Berchtold NC, Kesslak JP, Cotman CW. Hippocampal brain-derived neurotrophic factor gene regulation by exercise and the medial septum. *J Neurosci Res* 2002;68:511–521.
117. Tong L, Shen H, Perreau VM, Balazs R, Cotman CW. Effects of exercise on gene-expression profile in the rat hippocampus. *Neurobiol Dis* 2001;8:1046–1056.
118. Rampon C, Jiang CH, Dong H, et al. Effects of environmental enrichment on gene expression in the brain. *Proc Natl Acad Sci U S A* 2000;97:12880–12884.
119. Sutoo D, Akiyama K. Regulation of brain function by exercise. *Neurobiol Dis* 2003;13:1–14.
120. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* 2002;287:742–748.
121. Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. *JAMA* 1987;257:1492–1495.
122. White H, Pieper C, Schmader K, Fillenbaum G. A longitudinal analysis of weight change in Alzheimer's disease. *J Am Geriatr Soc* 1997;45:531–532.
123. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA* 2002;288:1475–1483.
124. Taylor AH, Cable NT, Faulkner G, Hillsdon M, Narici M, Van Der Bij AK. Physical activity and older adults: a review of health benefits and the effectiveness of interventions. *J Sports Sci* 2004;22:703–725.
125. King DA, Caine ED. Cognitive impairment in major depression: Beyond the pseudodementia syndrome. In: Grant I, Adams KM, eds. *Neuropsychological Assessment of Neuropsychiatric Disorders*. Vol. I. New York, NY: Oxford University Press, 1996, p. 200–217.
126. Teri L, Gibbons LE, McCurry SM, et al. Exercise plus behavioral management in patients with Alzheimer disease: A randomized controlled trial. *JAMA* 2003;290:2015–2022.
127. Tappen RM, Roach KE, Applegate EB, Stowell P. Effect of a combined walking and conversation intervention on functional mobility of nursing home residents with Alzheimer disease. *Alzheimer Dis Assoc Disord* 2000;14:196–201.
128. Rolland Y, Pillard F, Klapouszczak A, et al. Exercise program for nursing home residents with Alzheimer's disease: A 1-year randomized, controlled trial. *J Am Geriatr Soc* 2007;55:158–165.
129. Logsdon RG, McCurry SM, Teri L. A home health care approach to exercise for persons with Alzheimer's disease. *Care Manag J* 2005;6:90–97.
130. Friedman R, Tappen RM. The effect of planned walking on communication in Alzheimer's disease. *J Am Geriatr Soc* 1991;39:650–654.
131. Mulrow CD, Gerety MB, Kanten D, et al. A randomized trial of physical rehabilitation for very frail nursing home residents. *JAMA* 1994;271:519–524.
132. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med* 1994;330:1769–1775.
133. Tappen RM. The effect of skill training on functional abilities of nursing home residents with dementia. *Res Nurs Health* 1994;17:159–165.
134. Alessi CA, Schnelle JF, MacRae PG, et al. Does physical activity improve sleep in impaired nursing home residents? *J Am Geriatr Soc* 1995;43:1098–1102.
135. McMurdo ME, Johnstone R. A randomized controlled trial of a home exercise programme for elderly people with poor mobility. *Age Ageing* 1995;24:425–428.
136. Schnelle JF, MacRae PG, Ouslander JG, Simmons SF, Nitta M. Functional incidental training, mobility performance, and incontinence care with nursing home residents. *J Am Geriatr Soc* 1995;43:1356–1362.
137. MacRae PG, Asplund LA, Schnelle JF, Ouslander JG, Abrahamse A, Morris C. A walking program for nursing home residents: Effects on walk endurance, physical activity, mobility, and quality of life. *J Am Geriatr Soc* 1996;44:175–180.
138. Pomeroy VM, Warren CM, Honeycombe C, et al. Mobility and dementia: Is physiotherapy treatment during respite care effective? *Int J Geriatr Psychiatry* 1999;14:389–397.
139. Lazowski DA, Ecclestone NA, Myers AM, et al. A randomized outcome evaluation of group exercise programs in long-term care institutions. *J Gerontol A Biol Sci Med Sci* 1999;54:M621–628.
140. Alessi CA, Yoon EJ, Schnelle JF, Al-Samarrai NR, Cruise PA. A randomized trial of a combined physical activity and environmental intervention in nursing home residents: Do sleep and agitation improve? *J Am Geriatr Soc* 1999;47:784–791.
141. Schnelle JF, Alessi CA, Simmons SF, Al-Samarrai NR, Beck JC, Ouslander JG. Translating clinical research into practice: A randomized controlled trial of exercise and incontinence care with nursing home residents. *J Am Geriatr Soc* 2002;50:1476–1483.

142. Van de Winckel A, Feys H, De Weerd W, Dom R. Cognitive and behavioural effects of music-based exercises in patients with dementia. *Clin Rehabil* 2004;18:253–260.
143. Stevens J, Killeen M. A randomised controlled trial testing the impact of exercise on cognitive symptoms and disability of residents with dementia. *Contemp Nurse* 2006;21:32–40.
144. Williams CL, Tappen RM. Effect of exercise on mood in nursing home residents with Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 2007;22:389–397.
145. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. *Arch Phys Med Rehabil* 2004;85:1694–1704.
146. Ballard C, Fossey J, Chithramohan R, et al. Quality of care in private sector and NHS facilities for people with dementia: cross sectional survey. *BMJ* 2001;323:426–427.
147. Cohen-Mansfield J, Mintzer JE. Time for change: The role of nonpharmacological interventions in treating behavior problems in nursing home residents with dementia. *Alzheimer Dis Assoc Disord* 2005;19:37–40.
148. Hakim AA, Curb JD, Petrovitch H, et al. Effects of walking on coronary heart disease in elderly men: The Honolulu Heart Program. *Circulation* 1999;100:9–13.
149. Fratiglioni L, Wang HX. Brain reserve hypothesis in dementia. *J Alzheimers Dis* 2007;12:11–22.
150. Verghese J, LeValley A, Derby C, et al. Leisure activities and the risk of amnesic mild cognitive impairment in the elderly. *Neurology* 2006;66:821–827.
151. Hagberg JM, Ferrell RE, Dengel DR, Wilund KR. Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. *Hypertension* 1999;34:18–23.
152. Hagberg JM, Ferrell RE, Katzel LI, Dengel DR, Sorkin JD, Goldberg AP. Apolipoprotein E genotype and exercise training-induced increases in plasma high-density lipoprotein (HDL)- and HDL2-cholesterol levels in overweight men. *Metabolism* 1999;48:943–945.
153. St-Amand J, Prud'homme D, Moorjani S, et al. Apolipoprotein E polymorphism and the relationships of physical fitness to plasma lipoprotein-lipid levels in men and women. *Med Sci Sports Exerc* 1999;31:692–697.
154. Kramer AF, Erickson KI. Capitalizing on cortical plasticity: Influence of physical activity on cognition and brain function. *Trends Cogn Sci* 2007;11:342–348.
155. Agüero-Torres H, Fratiglioni L, Guo Z, Viitanen M, von Strauss E, Winblad B. Dementia is the major cause of functional dependence in the elderly: 3-year follow-up data from a population-based study. *Am J Public Health* 1998;88:1452–1456.
156. Wang L, van Belle G, Kukull WB, Larson EB. Predictors of functional change: A longitudinal study of nondemented people aged 65 and older. *J Am Geriatr Soc* 2002;50:1525–1534.
157. Moritz DJ, Kasl SV, Berkman LF. Cognitive functioning and the incidence of limitations in activities of daily living in an elderly community sample. *Am J Epidemiol* 1995;141:41–49.
158. Briones TL. Environment, physical activity, and neurogenesis: Implications for prevention and treatment of Alzheimer's disease. *Curr Alzheimer Res* 2006;3:49–54.
159. Mathews RM, Clair AA, Kosloski K. Keeping the beat: Use of rhythmic music during exercise activities for the elderly with dementia. *Am J Alzheimers Dis Other Demen* 2001;16:377–380.
160. Jirovec MM. The impact of daily exercise on the mobility, balance and urine control of cognitively impaired nursing home residents. *Int J Nurs Stud* 1991;28:145–151.