

# Physical Activity and Risk of Cognitive Impairment and Dementia in Elderly Persons

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**Context:** Dementia is common, costly, and highly age related. Little attention has been paid to the identification of modifiable lifestyle habits for its prevention.

**Objective:** To explore the association between physical activity and the risk of cognitive impairment and dementia.

**Design, Setting, and Subjects:** Data come from a community sample of 9008 randomly selected men and women 65 years or older, who were evaluated in the 1991-1992 Canadian Study of Health and Aging, a prospective cohort study of dementia. Of the 6434 eligible subjects who were cognitively normal at baseline, 4615 completed a 5-year follow-up. Screening and clinical evaluations were done at both waves of the study. In 1996-1997, 3894 remained without cognitive impairment, 436 were diagnosed as having cognitive impairment–no dementia, and 285 were diagnosed as having dementia.

**Main Outcome Measure:** Incident cognitive impairment and dementia by levels of physical activity at baseline.

**Results:** Compared with no exercise, physical activity was associated with lower risks of cognitive impairment, Alzheimer disease, and dementia of any type. Significant trends for increased protection with greater physical activity were observed. High levels of physical activity were associated with reduced risks of cognitive impairment (age-, sex-, and education-adjusted odds ratio, 0.58; 95% confidence interval, 0.41-0.83), Alzheimer disease (odds ratio, 0.50; 95% confidence interval, 0.28-0.90), and dementia of any type (odds ratio, 0.63; 95% confidence interval, 0.40-0.98).

**Conclusion:** Regular physical activity could represent an important and potent protective factor for cognitive decline and dementia in elderly persons.

*Arch Neurol.* 2001;58:498-504

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**D**EMENTIA represents a major health problem in aging societies.<sup>1</sup> Apart from hormonal replacement therapy<sup>2,3</sup> and anti-hypertensive<sup>4,5</sup> and nonsteroidal anti-inflammatory drug<sup>6</sup> treatments, few preventive strategies for dementia and its leading cause, Alzheimer disease, have been explored.<sup>7-9</sup> Comparatively little attention has been paid to the identification of modifiable environmental factors such as diet and lifestyle habits, including physical fitness.

Physical activity has well-known benefits for several chronic disorders,<sup>1,10,11</sup> including coronary artery disease, stroke, diabetes mellitus, and osteoporosis. While its influence on premature mortality among both young and old segments of the elderly population is also well established,<sup>12-15</sup> the evidence that physical activity may delay cognitive loss and impairment is more equivocal.<sup>10,16,17</sup> In clinical

settings, beneficial effects of physical fitness interventions on memory and other aspects of cognition have been documented in elderly persons,<sup>18-30</sup> although inconsistently.<sup>31-34</sup>

Few epidemiological studies have examined the role of physical activity on the risk of cognitive impairment and dementia in elderly persons. Suggestions that exercise may be protective for dementia, and for Alzheimer disease in particular, have been made in some case-control studies using prevalent cases,<sup>35,36</sup> but again these findings have not consistently been replicated.<sup>37-39</sup> In these studies, retrospective assessment of physical activity limits the validity of the results. Discordant results have also been reported in a few prospective studies.<sup>40-42</sup>

This study evaluates the association between regular physical activity and subsequent occurrence of cognitive impairment and dementia, within the Canadian Study of Health and Aging (CSHA), a large-

## SUBJECTS AND METHODS

Data come from the community sample of the CSHA, a national, multicenter, prospective cohort study, designed to focus on the prevalence, incidence, and risk factors for dementia and Alzheimer disease in elderly Canadians. Methodological details of the study have been described elsewhere.<sup>43-45</sup> Briefly, during the first wave of the study conducted in 1991-1992 (CSHA-1), representative samples of men and women 65 years or older were drawn from population-based listings for 36 urban and surrounding rural areas in all 10 Canadian provinces. Of the 10263 people involved, 9008 were living in the community and constituted our initial pool of subjects. All subjects were interviewed to ascertain their perceived health status, general chronic conditions, and functional ability in basic and instrumental activities of daily living, based on a modified version of the Older Americans Research Survey scale.<sup>46</sup> Participants were screened for dementia using the Modified Mini-Mental State (3MS) Examination.<sup>47,48</sup> Subjects who screened positive (3MS Examination score  $\leq 77$ ), and a random sample of those who screened negative (3MS Examination score  $\geq 78$ ) were asked to attend an extensive standardized 3-stage clinical evaluation.<sup>49</sup> A nurse first screened for hearing and vision problems, and collected information about medication regimen and medical and family histories. Next, a physician carried out standardized physical and neurologic examinations. Third, a psychometrist administered a neuropsychological test battery<sup>50</sup> to all individuals deemed testable (3MS Examination score  $\geq 50$ ), the results of which were interpreted by a neuropsychologist. Preliminary diagnoses were made independently according to *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria<sup>51</sup> by the physician and the neuropsychologist who subsequently arrived at a diagnosis in a consensus conference. Consensus diagnoses constituted the following: no cognitive impairment, cognitive impairment–no dementia [CIND],<sup>52</sup> Alzheimer disease (probable or possible) according to NINCDS-ADRDA (National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association) criteria,<sup>53</sup> vascular dementia according to World Health Organization *International Classification of Diseases, 10th Revision* criteria,<sup>54</sup> other specific dementia and unclas-

sifiable dementia. All subjects without dementia were asked to complete and return by mail a self-administered risk factor questionnaire covering specific expositions for which prior hypotheses existed. This questionnaire included questions about demographic characteristics, occupational and environmental exposures, lifestyle, and medical and family histories.

Follow-up was carried out in 1996-1997 (CSHA-2). All subjects who could be contacted and who agreed to participate in the second wave were reinterviewed to measure changes in health status and functioning following a 5-year period on average. Subjects took part in the same diagnostic process as in CSHA-1, including screening and clinical evaluation. Diagnoses from consensus conferences in CSHA-2 were made without knowledge of CSHA-1 diagnoses. Two final diagnoses were made for dementia and vascular dementia, one according to the same criteria used in CSHA-1, and the other according to more recent *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*<sup>55</sup> and NINDS-AIREN (National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences) criteria.<sup>56</sup>

Exercise data were collected as part of CSHA-1 when subjects were not demented and represent a proxy for earlier activity up until the time of baseline. The level of physical activity was assessed by combining 2 questions from the risk factor questionnaire regarding frequency and intensity of exercise for subjects who reported regular physical activity. A composite score rating physical activity as either low, moderate, or high, was obtained by summing answers to the frequency question ( $\geq 3$  times per week, weekly, or less than weekly) and the intensity question (more vigorous, equal to, or less vigorous than walking). A high level of physical activity corresponded to an exercise engaged 3 or more times per week at an intensity greater than walking, while a moderate level of physical activity corresponded to exercise also engaged 3 or more times per week, but of an intensity equal to walking. All other combinations of frequency and intensity were considered as a low level of physical activity. Subjects who reported no regular exercise constituted the reference category. The measurement properties of this index were

Continued on next page

scale, prospective cohort study, based on a representative sample of the elderly Canadian population.

## RESULTS

Unimpaired subjects were younger and had completed more years of education (medians of 72 and 11 years, respectively) than those with CIND (medians of 78 and 9 years) or dementia (medians of 80 and 10 years) (**Table 1**). The sex distribution was similar across categories. Reported regular exercise was more frequent for controls than for subjects with CIND or dementia. Table 1 also lists the distribution of these characteristics for eligible subjects in CSHA-1 who died during follow-up or did not participate in CSHA-2. Decedents and nonrespondents were older, less educated, and less physically active at baseline than subjects in the control group, and were generally similar to the group of subjects with CIND or dementia.

After adjusting for age, sex, and education, low, moderate, and high levels of physical activity were related to lower risks for CIND compared with no physical activity (**Table 2**). Likewise, moderate and high levels of physical activity were associated with significantly lower risks for Alzheimer disease and for dementia of any type. A similar but nonsignificant effect was observed with vascular dementia. Significant trends for lower risk with a higher level of physical activity were observed in the groups with CIND ( $P < .001$ ), Alzheimer disease ( $P = .02$ ), and dementia of any type ( $P = .04$ ).

Associations between physical activity and risk of CIND and dementia were examined separately for men and women (**Table 3**). Among women, after adjusting for age and education, regular exercise was associated with significantly lower risks of CIND, Alzheimer disease, and dementia. The ORs were lowest for the highest level of physical activity, showing approximately 50% reduc-

assessed with an independent sample of 738 elderly individuals, to whom the risk factor questionnaire was administered by an interviewer. Construct validity was assessed by comparing the combined score with other reported markers of health hypothesized to be related to exercise and self-rated health. The average intraclass coefficient for the combined score was 0.76 (95% confidence interval [CI], 0.72-0.79;  $P=.002$ ), while the combined score demonstrated satisfactory construct validity, and seemed to be well associated with mortality over 5 years.<sup>57</sup>

Ethical approval for the study was obtained from ethics review boards in all participating centers. Subjects living in the province of Newfoundland had to be excluded from CSHA-2 final analyses, because of recent provincial legislation restricting the possibility of obtaining consent from proxies for participation of mentally incompetent subjects.

## DESIGN

The effect of physical activity on cognitive impairment and dementia was analyzed using a case-control approach within the CSHA-1 cohort, with incident cases and controls selected at the end of CSHA-2. To be included in the analysis, subjects initially had to be screened negative or without dementia or CIND according to the clinical evaluation. The following 4 outcomes were examined according to CSHA-2 final diagnoses: CIND, Alzheimer disease, vascular dementia, and any type of dementia. The diagnosis of dementia for these analyses was based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria.<sup>55</sup> Subjects who remained without cognitive impairment or dementia in CSHA-2, according to the screening test and/or the clinical evaluation, served as controls. A fifth end point was examined among controls only and consisted of whether they experienced a reduction of 5 points or more on the 3MS Examination score from CSHA-1 to CSHA-2.

## STUDY POPULATION

Of the 9008 subjects in the original sample at CSHA-1, 442 subjects from Newfoundland were excluded from the

analyses as were 826 subjects diagnosed as having CIND or dementia in CSHA-1. Of the remaining 7740 eligible subjects, 6434 (83.1%) subjects had a risk factor questionnaire available. Subjects who died during the follow-up period ( $n=1172$ ), who refused to participate in CSHA-2 ( $n=374$ ), or who were lost to follow-up ( $n=273$ ) also were excluded, leaving 4615 subjects. Of these, 3894 were still not cognitively impaired in CSHA-2 (controls) and 436 were diagnosed as having CIND, 194 Alzheimer disease, 61 vascular dementia, and 30 other specific or unclassifiable dementia.

## STATISTICAL ANALYSIS

Five separate analyses were performed to assess the associations between exercise and incident cognitive loss, CIND, Alzheimer disease, vascular dementia, and any type of dementia. Univariate and multivariate logistic regression models were used to analyze the crude and adjusted odds ratios (ORs) for the 5 end points. Age, sex, and education were included in all multivariate models as potential confounders; age and education were entered as continuous variables. Other variables examined as potential confounders included the following: family history of dementia; regular smoking; regular alcohol consumption; use of nonsteroidal anti-inflammatory drugs; a summation score for the 7 items of activities of daily (ie, eating, transferring [ie, the capacity to get in and out of bed], toileting, grooming, dressing, walking, and bathing); a summation score for the 7 items of instrumental activities of daily living (ie, self-medicating, telephone use, handling money, meal preparation, walking outside, shopping, and housework); self-rated health; and number of reported chronic diseases from a list of 10 conditions (ie, heart disease, hypertension, cancer, stroke and other neurologic diseases, arthritis, ulcer, diabetes mellitus, thyroid disease, kidney disease, and depression). Modification of risk by age, sex, education, and family history of dementia was investigated using interaction terms.  $\chi^2$  Tests for linear trend were performed using the 4-level physical activity variable as an ordinal variable in adjusted models.

tions in risk of CIND and dementia, and a 60% reduction for Alzheimer disease, as compared with no physical activity. Trends in decreasing risk with increasing levels of activity were significant for CIND ( $P<.001$ ), Alzheimer disease ( $P=.03$ ), and dementia ( $P=.02$ ). Among men, associations between levels of physical activity and decreased risk of CIND and dementia were observed, but none were of statistical significance. No interaction was found between regular physical activity and age, education, or family history of dementia (data not shown). The association between physical activity and risk of CIND, Alzheimer disease, and dementia, according to sex and adjusted for several potential confounders, is given in **Table 4**. Estimates of ORs for men and women were similar to those reported earlier, but some lost statistical significance. Among women, tests for trend remained significant for CIND ( $P<.003$ ) and Alzheimer disease ( $P=.05$ ), but did not reach statistical significance for dementia of any type ( $P=.18$ ).

**Table 5** gives the association between physical activity and risk of a 5-point loss on the 3MS Examination, according to sex among controls only. After adjusting for age and education, no association was found for men, whereas a significant protective effect was observed for the highest level of physical activity among women (OR, 0.58; 95% CI, 0.40-0.82). A significant trend for an increased protective effect with higher level of physical activity was noted in women ( $P<.01$ ), but not in men.

## COMMENT

This large-scale, prospective cohort study showed a significant protective effect of regular physical activity on the risk of cognitive impairment and dementia, particularly of the Alzheimer type, in a representative sample of the Canadian elderly population. These associations were observed mainly in women and revealed a significant dose-response relationship showing decreasing risk

**Table 1. Characteristics at Baseline of Study Population, Decedents, and Nonrespondents\***

Variable	Study Population (n = 4615)			Decedents (n = 1172)	Nonrespondents (n = 647)
	Controls (n = 3894)	Subjects With CIND (n = 436)	Subjects With Dementia (n = 285)		
Age, y					
65-74	2317 (59.5)	138 (31.7)	53 (18.6)	345 (29.4)	288 (44.5)
75-84	1425 (36.6)	210 (48.2)	153 (53.7)	549 (46.8)	282 (43.6)
≥85	152 (3.9)	88 (20.2)	79 (27.7)	278 (23.7)	77 (11.9)
Sex					
Male	1543 (39.6)	179 (41.1)	109 (38.2)	565 (48.2)	227 (35.1)
Female	2351 (60.4)	257 (58.9)	176 (61.8)	607 (51.8)	420 (64.9)
Educational level, y					
0-8	980 (25.2)	201 (46.2)	98 (34.9)	392 (33.5)	213 (33.0)
9-12	1759 (45.3)	163 (37.5)	117 (41.6)	523 (44.7)	276 (42.8)
≥13	1147 (29.5)	71 (16.3)	66 (23.5)	255 (21.8)	156 (24.2)
Regular physical activity†					
None	1103 (30.0)	169 (44.2)	110 (44.4)	556 (51.0)	219 (37.1)
Low	485 (13.2)	44 (11.5)	28 (11.3)	138 (12.7)	69 (11.7)
Moderate	1360 (37.0)	122 (31.9)	79 (31.9)	287 (26.3)	211 (35.8)
High	731 (19.9)	47 (12.3)	31 (12.5)	109 (10.0)	91 (15.4)

\*All values are expressed as numbers (percentages). CIND indicates cognitive impairment–no dementia.

†Physical activity was the composite score obtained by summing answers to the frequency question (≥3 times per week, weekly, or less than weekly) and the intensity question (more vigorous, equal to, or less vigorous than walking) on the Canadian Study of Health and Aging. See the “Subjects and Methods” section for further explanation.

**Table 2. Relationship Between Physical Activity and Risk of Cognitive Impairment–No Dementia (CIND) and Dementia**

	CIND		Dementia					
			Alzheimer Disease		Vascular Type		Any Type	
	No. of Cases/ No. of Controls	OR (95% CI)*	No. of Cases/ No. of Controls	OR (95% CI)	No. of Cases/ No. of Controls	OR (95% CI)	No. of Cases/ No. of Controls	OR (95% CI)
Physical activity†								
None	169/1103	1.00	80/1103	1.00	23/1103	1.00	110/1103	1.00
Low	44/485	0.66 (0.46-0.96)	21/485	0.67 (0.39-1.14)	5/485	0.54 (0.20-1.44)	28/485	0.64 (0.41-1.02)
Moderate	122/1360	0.67 (0.52-0.87)	52/1360	0.67 (0.46-0.98)	18/1360	0.70 (0.37-1.31)	79/1360	0.69 (0.50-0.95)
High	47/731	0.58 (0.41-0.83)	16/731	0.50 (0.28-0.90)	8/731	0.63 (0.27-1.44)	31/731	0.63 (0.40-0.98)
Test for trend	P<.001		P= .02		P= .46		P= .04	

\*OR indicates odds ratio; CI, confidence interval.

†Data are adjusted for age, sex, and educational level. See the “Subjects and Methods” section for an explanation of the physical activity categories.

with increasing level of physical activity. We also found a lower risk of cognitive loss associated with intensive regular physical activity among elderly women who remained cognitively normal during the study period.

Few other prospective studies have examined the association of regular exercise with the risk of dementia in elderly populations. In Japan, Yoshitake et al<sup>41</sup> followed up a cohort of 828 people for 7 years and reported a relative risk of 0.20 for Alzheimer disease in physically active compared with nonactive subjects, but did not find any association for vascular dementia. These analyses were based on small samples of incident cases, and measurement of physical activity was limited to a 4-category question on intensity of physical activities from leisure to work. Li et al<sup>40</sup> completed a 3-year follow-up study of 1090 people in China and found a relative risk of 8.7 for dementia in subjects limited to indoor activities, compared with those without such limitations. The study, however, was based on only 13 incident cases of

dementia and did not include specific measures of physical exercise. Finally, Broe et al<sup>42</sup> conducted a 3-year follow-up study of 327 people in Australia and reported no association between physical exercise (ranging from gardening to sports or walking) and risk of dementia or performance to a series of cognitive tests.

Our results are based on a large representative sample, using a rigorous prospective design, avoiding biases related to retrospective assessment of regular exercise and other exposures. In addition, participation rates remained high<sup>58</sup> throughout all phases of the study<sup>44</sup> and, subjects were assessed using an extensive standardized diagnostic protocol including clinical evaluations by a physician and a neuropsychologist.

Our study also has limitations. Of all eligible subjects at baseline for whom a risk factor questionnaire was available, 1172 (18.2%) died during the 5-year follow-up period and were excluded from the analyses. These subjects were, at baseline, generally older, less

**Table 3. Relationship Between Physical Activity and Risk of Cognitive Impairment–No Dementia (CIND) and Dementia, According to Sex**

	CIND		Dementia			
	No. of Cases/ No. of Controls	OR (95% CI)*	Alzheimer Disease		Any Type	
			No. of Cases/ No. of Controls	OR (95% CI)	No. of Cases/ No. of Controls	OR (95% CI)
<b>Men</b>						
Physical activity†						
None	55/393	1.00	19/393	1.00	30/393	1.00
Low	13/169	0.58 (0.30-1.11)	8/169	0.87 (0.34-2.19)	12/169	0.88 (0.42-1.86)
Moderate	66/525	0.92 (0.62-1.38)	17/525	0.68 (0.34-1.37)	33/525	0.82 (0.48-1.41)
High	29/386	0.68 (0.42-1.11)	9/386	0.67 (0.29-1.54)	19/386	0.83 (0.45-1.55)
Test for trend		<i>P</i> = .16		<i>P</i> = .43		<i>P</i> = .78
<b>Women</b>						
Physical activity						
None	114/710	1.00	61/710	1.00	80/710	1.00
Low	31/316	0.71 (0.46-1.09)	13/316	0.60 (0.31-1.14)	16/316	0.55 (0.31-0.97)
Moderate	56/835	0.52 (0.37-0.74)	35/835	0.67 (0.42-1.06)	46/835	0.64 (0.43-0.95)
High	18/345	0.53 (0.31-0.89)	7/345	0.38 (0.16-0.91)	12/345	0.48 (0.25-0.94)
Test for trend		<i>P</i> < .001		<i>P</i> = .03		<i>P</i> = .02

\*OR indicates odds ratio; CI, confidence interval.

†Data are adjusted for age and educational level. See the “Subjects and Methods” section for an explanation of the physical activity categories.

**Table 4. Relationship Between Physical Activity and Risk of Cognitive Impairment–No Dementia (CIND) and Dementia, According to Sex and Adjusted for Several Potential Confounders**

	Dementia			
	CIND, OR (95% CI)*	Alzheimer Disease, OR (95% CI)		Any Type, OR (95% CI)
<b>Men</b>				
Regular physical activity†				
None	1.00	1.00	1.00	
Low	0.65 (0.30-1.38)	0.87 (0.26-2.90)	0.96 (0.40-2.31)	
Moderate	0.84 (0.53-1.34)	0.61 (0.25-1.50)	0.72 (0.38-1.38)	
High	0.68 (0.39-1.20)	0.73 (0.27-1.98)	0.91 (0.45-1.83)	
Test for trend	<i>P</i> = .24	<i>P</i> = .62	<i>P</i> = .90	
<b>Women</b>				
Regular physical activity				
None	1.00	1.00	1.00	
Low	0.69 (0.41-1.16)	0.70 (0.33-1.49)	0.63 (0.32-1.25)	
Moderate	0.55 (0.36-0.82)	0.87 (0.51-1.48)	0.87 (0.55-1.39)	
High	0.47 (0.25-0.90)	0.27 (0.08-0.90)	0.55 (0.25-1.21)	
Test for trend	<i>P</i> = .003	<i>P</i> = .05	<i>P</i> = .18	

\*OR indicates odds ratio; CI, confidence interval.

†Odds ratios are adjusted for age, sex, educational level, smoking, alcohol, use of nonsteroidal anti-inflammatory drugs, functional ability in basic and instrumental activities of daily living, self-rated health, and the number of chronic health conditions. See the “Subjects and Methods” section for an explanation of the physical activity categories.

educated, less physically active, and suffered more frequently from chronic diseases than subjects who completed follow-up. Excluding decedents may have produced distortions in the results, if they were both less physically active at baseline and at high risk of developing cognitive impairment or dementia. In a recent article by CSHA investigators presenting incidence figures for dementia in Canada,<sup>44</sup> an effort was made to estimate the probability of dementia for subjects who died during follow-up, from the following 3 sources: (1) the mention of dementia on death certificates; (2) information from proxies about a diagnosis of memory

problem, Alzheimer disease, or senile dementia prior to death; and (3) a logistic regression model estimating the probability that the deceased person was demented prior to death, based on an analysis of 71 people who died within 2 to 5 months of undergoing a complete diagnostic evaluation. These estimates could be obtained for most decedents, but were unavailable for nonrespondents. Using one or more of these criteria, 21.2% of decedents could be classified as having developed dementia during follow-up. When analyses were redone including 249 decedents as demented cases and 773 as nondemented controls, the observed associations

**Table 5. Relationship Between Physical Activity and Risk of Cognitive Loss, According to Sex, Among Cognitively Normal Subjects**

	Cognitive Loss			
	Men		Women	
	No. of Cases/No. of Controls	OR (95% CI)*	No. of Cases/No. of Controls	OR (95% CI)
Physical activity†				
None	113/280	1.00	176/53	1.00
Low	46/123	0.96 (0.63-1.44)	79/237	1.06 (0.78-1.45)
Moderate	134/391	0.85 (0.63-1.15)	182/653	0.92 (0.72-1.17)
High	103/283	0.98 (0.71-1.35)	49/296	0.58 (0.40-0.82)
Test for trend	P = .57		P = .01	

\*OR indicates odds ratio; CI, confidence interval.

†Data are adjusted for age and educational level. See the "Subjects and Methods" section for an explanation of the physical activity categories.

between physical activity and risk of dementia persisted and were even more statistically significant. This suggests that exclusion of deceased subjects from our study had little effect on our results, if anything making estimates somewhat conservative.

It might be argued that engaging in regular physical activity does not per se play a protective role on cognition and cognitive disorders, as suggested by our study, but rather can be viewed merely as a marker of good health, being itself related to lower risk of cognitive impairment and dementia. We tried to examine this hypothesis by adding in our logistic models variables related to health status, and observed that risk estimates remained very similar to those reported for men and women when controlling for age and education only.

Despite the prospective nature of the study, our results might possibly be explained by some preclinical cognitive decline (not yet detectable by screening and clinical evaluations at CSHA-1) among subjects who later developed CIND or dementia by CSHA-2. If so, lower physical activity could then be a consequence of CIND or dementia at its preclinical state rather than a risk factor. In this context, we reanalyzed our data excluding subjects who reported early cognitive symptoms in the first 2 years of follow-up and obtained practically unchanged results. Moreover, the fact that the protective effect of exercise on cognitive loss persisted among subjects who remained without CIND or dementia during the whole 5-year follow-up period does not favor this hypothesis of a preclinical state for explaining our results, although it cannot be ruled out.

Several mechanisms may underlie the potentially protective effects of physical activity on cognitive function. It has been shown that physical activity sustains cerebral blood flow<sup>19</sup> by decreasing blood pressure, lowering lipid levels, inhibiting platelet aggregability, or enhancing cerebral metabolic demands. There is also evidence that exercise may improve aerobic capacity and cerebral nutrient supply.<sup>24,59</sup> More recently, experimental studies in rodents indicated that growth factors could be involved.<sup>60</sup> To our knowledge, our results suggest, for the first time, that exercise may be protective especially for women. Apparent lack of association between exercise and CIND and dementia in men could be attributed to insufficient numbers of cases. Stronger associations found in women could also be related to some interaction between exercise and hormone metabolism. Endurance exercise training has been

shown to have an independent but complementary effect to hormone replacement therapy on serum lipid profiles in healthy postmenopausal women.<sup>61</sup>

Our study suggests that engaging in regular physical activity, among other health benefits, may delay or prevent the onset of cognitive impairment and dementia in the elderly, especially in women. Although these findings will need confirmation in further epidemiological and intervention studies, this study suggests that regular practice of physical activity could represent an important and potent protective factor for cognitive impairment, Alzheimer disease, and other dementia in the elderly population.

Accepted for publication November 29, 2000.

Data reported in this article were collected as part of the CSHA. The core study was funded by the Seniors' Independence Research Program, through the National Health Research and Development Program (NHRDP) of Health Canada (Project No. 6606-3954-MC [S]). Additional funding was provided by Pfizer Canada Inc through the Medical Research Council/Pharmaceutical Manufacturers Association of Canada Health Activity Program, NHRDP (Project No. 6603-1417-302 [R]), Bayer Inc, and the British Columbia Health Research Foundation (Project Nos. 38 [93-2] and 34 [96-1]). Ms Laurin was supported in part by a National Health PhD Fellowship provided by the NHRDP (Project No. 6605-5228-47) and by the Laval University Chair for Geriatric Research. Dr Verreault is supported by the Laval University Chair for Geriatric Research.

This study was coordinated through the University of Ottawa and the Division of Aging and Seniors, Health Canada.

We are grateful to Susan Kirkland, PhD, for her comments on an earlier draft of the manuscript.

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