

Risk Factors for Alzheimer's Disease: A Prospective Analysis from the Canadian Study of Health and Aging

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Received for publication December 14, 2001; accepted for publication May 9, 2002.

A prospective analysis of risk factors for Alzheimer's disease was a major objective of the Canadian Study of Health and Aging, a nationwide, population-based study. Of 6,434 eligible subjects aged 65 years or older in 1991, 4,615 were alive in 1996 and participated in the follow-up study. All participants were cognitively normal in 1991 when they completed a risk factor questionnaire. Their cognitive status was reassessed 5 years later by using a similar two-phase procedure, including a screening interview, followed by a clinical examination when indicated. The analysis included 194 Alzheimer's disease cases and 3,894 cognitively normal controls. Increasing age, fewer years of education, and the apolipoprotein E ϵ 4 allele were significantly associated with increased risk of Alzheimer's disease. Use of nonsteroidal anti-inflammatory drugs, wine consumption, coffee consumption, and regular physical activity were associated with a reduced risk of Alzheimer's disease. No statistically significant association was found for family history of dementia, sex, history of depression, estrogen replacement therapy, head trauma, antiperspirant or antacid use, smoking, high blood pressure, heart disease, or stroke. The protective associations warrant further study. In particular, regular physical activity could be an important component of a preventive strategy against Alzheimer's disease and many other conditions. *Am J Epidemiol* 2002;156:445–53.

Alzheimer disease; anti-inflammatory agents, non-steroidal; apolipoproteins; cohort studies; education; exercise; risk factors; wine

Abbreviations: APOE, apolipoprotein E; *APOE4*, apolipoprotein E ϵ 4 allele; CI, confidence interval; CSHA, Canadian Study of Health and Aging; EURODEM, European Community Concerted Action on Epidemiology and Prevention of Dementia; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; 3MS, Modified Mini-Mental State.

Dementia is a growing problem in aging populations. Its impact on health services and society is of increasing concern to health policy makers and service providers as life expectancy increases and, more particularly, as the baby-boom generation ages. Among Canadians aged 65 years or older, Alzheimer's disease accounts for almost two thirds of prevalent cases of dementia (1). The majority of epidemiologic studies of risk factors for Alzheimer's disease to date have been retrospective case-control studies that compared

prevalent Alzheimer's disease cases with nondemented controls (2). Retrospective studies are subject to methodological problems including survival bias and recall bias. In addition, collecting very detailed exposure information is difficult because the information must be obtained from proxies (3). Some risk or protective factors for Alzheimer's disease suggested in prevalence studies, such as family history of dementia, have not been upheld in prospective studies.

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Even though investigations using prospective designs should reveal a more defined picture of the pathogenesis of Alzheimer's disease, results obtained so far are not consistent. The European Community Concerted Action on Epidemiology and Prevention of Dementia (EURODEM) group associated smoking with a higher risk of Alzheimer's disease (3), whereas other studies did not observe any significant relation between smoking and the onset of Alzheimer's disease (4–6). The EURODEM group also found that female sex and low educational level were associated with increased risks of Alzheimer's disease. Conversely, sex and education were not reported as risk factors for incident Alzheimer's disease in other studies (7, 8). Methodological differences, such as duration of follow-up, and selection and number of study participants may account for these discrepancies.

The Canadian Study of Health and Aging (CSHA) is a large, national, multicenter, longitudinal study of dementia in elderly people focusing on its prevalence (1), incidence (9), and risk factors (10–12). As part of the first phase (CSHA-1), a case-control study was conducted. Age, family history of dementia, educational level, arthritis, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) were significantly related to Alzheimer's disease (10). We report here the results of a prospective analysis of risk factors for incident cases of late-onset Alzheimer's disease, which were based on risk factor data collected at CSHA-1 from those who were cognitively normal and on diagnosis of incident Alzheimer's disease 5 years later at CSHA-2.

MATERIALS AND METHODS

The study methods have been described in detail elsewhere (1, 9) and are summarized here. Eighteen field centers across Canada participated in this national study, which was coordinated jointly by the University of Ottawa and Health Canada.

Initial assessment (CSHA-1)

In 1991–1992, representative samples of men and women aged 65 years or older were drawn from 36 urban and surrounding rural areas; all 10 Canadian provinces were covered. Of the 10,263 participants, 9,008 lived in the community while 1,255 resided in institutions and were excluded from this analysis. Those in the community were interviewed about their health, presence of specific disorders, and limitations in performing basic and instrumental activities of daily living based on the Older Americans Resources and Services Activities of Daily Living scale (13). All participants were screened for dementia by using the Modified Mini-Mental State (3MS) Examination (14, 15). Those who screened positive (a 3MS Examination score of below 78/100) and a random sample of those who screened negative (a score of 78 or above) were invited to participate in an extensive clinical evaluation, which followed a three-stage protocol. A nurse first readministered the 3MS Examination and collected information on the participant's medical and family history. Next, a physician conducted a standardized physical and neurologic examination. Finally, for those participants deemed testable (a 3MS Examination score of

50 or above), a psychometrist administered a series of neuropsychological tests (16), which were interpreted later by a neuropsychologist.

Independent preliminary diagnoses were made by the physician and neuropsychologist, which was followed by a case conference in which a consensus diagnosis was reached according to *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised, criteria for dementia (17); the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer's disease (18); and other specific criteria for cognitive impairment (19) and vascular dementia (20). Diagnoses comprised the following categories: no cognitive impairment; cognitive impairment, no dementia; probable and possible Alzheimer's disease; vascular dementia; other specific dementia; and unclassifiable dementia.

Detailed information about risk factors was gathered from a self-administered questionnaire completed at CSHA-1 by those participants found to be cognitively normal on the basis of either the screening test or clinical examination. The risk factor questionnaire covered sociodemographic characteristics, occupational and environmental exposures, lifestyle (smoking, alcohol consumption, intake of selected food items, and regular exercise), and family and medical history (prior head injury with and without loss of consciousness, chronic diseases, and medication use). Participants were asked whether they engaged in regular exercise (yes/no), but "regular" was not explicitly defined. Regular consumption of beer, wine, and spirits was defined as at least once a week. Regular consumption of tea and coffee was defined as nearly every day.

Follow-up study (CSHA-2)

In 1996–1997, all subjects who could be contacted and who agreed to participate in the second wave of the study were interviewed to measure changes in their health status and functioning an average of 5 years after CSHA-1. Participants took part in the same diagnostic process as the one used at CSHA-1, including the screening test, the nurse evaluation, and the clinical evaluation. Two diagnoses of dementia were made at a consensus conference, one according to the same criteria used at CSHA-1 and the other according to the more recent *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria (21) for Alzheimer's disease and the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia (22). The more recent criteria were used to define cases for the current analysis. Blood samples were collected, and apolipoprotein E (APOE) allele status was determined in a subsample of subjects examined clinically (23).

For participants who died before the follow-up study was conducted, the date and cause of death were obtained from the relevant provincial Registrar of Vital Statistics, and a relative or other informant was interviewed to assess the subject's physical and cognitive status 3 months prior to death. For subjects who died during follow-up, the proba-

bility of dementia was estimated from three different sources (9): 1) mention of dementia on death certificates; 2) information from proxies about a diagnosis of memory problems, Alzheimer's disease, or senile dementia prior to death; and 3) a logistic regression model, based on an analysis of 71 people who died within 2–5 months of a complete diagnostic evaluation, estimating the probability that the deceased person was demented prior to death. These estimates were available for 1,022 decedents (87.2 percent). Because this procedure did not permit diagnosis of the type of dementia, decedents were omitted from the main analysis. A secondary analysis was then conducted to assess the potential impact of omitting decedents; all deaths classified as due to dementia were included as Alzheimer's disease cases, and deaths not due to dementia were considered controls.

Both phases of the CSHA were approved by the ethics review committees in all 18 participating study centers as well as at the coordinating center. Participants or their proxies provided informed consent for each component of the study. However, residents of the province of Newfoundland had to be omitted from the prospective analysis because a 1996 legal interpretation of the province's advance directives legislation prohibited the use of proxy consent for persons unable to give full, informed consent to participate in research studies. This interpretation meant that people with dementia could not provide consent for the clinical examination (i.e., the outcome measure could not be obtained). Therefore, all Newfoundland participants were excluded.

Analysis

This analysis included only those participants living in the community as of CSHA-1. A case-control analysis was conducted, with incident cases and controls selected at CSHA-2. To be included, participants' initial screening results had to be negative or, at CSHA-1, participants had to be clinically diagnosed without 1) cognitive impairment, no dementia or 2) dementia. Cases were diagnosed with probable or possible Alzheimer's disease at CSHA-2. Comparisons were made with controls who, at CSHA-2, remained without cognitive impairment, no dementia or dementia according to the clinical evaluation or screening test at follow-up.

Differences between cases and controls regarding means and proportions were compared by using the *t* test and the chi-square test, respectively. Univariate and multivariate logistic regression models were used to calculate crude and adjusted odds ratios for the various risk factors. Under the rare disease assumption, the odds ratio can be considered a valid estimate of the relative risk. Age, sex, and education (age and education both as continuous variables with 1-year increments) were introduced into all multivariate models as potential confounders. Modification of risk by age, sex, and APOE $\epsilon 4$ allele (*APOE4*) status was examined by using interaction terms.

RESULTS

For community participants, the overall response rates for the screening interview and the clinical examination were 88.3 percent and 87 percent, respectively (9). Figure 1 shows the categories of ineligible study subjects excluded from this analysis, leaving 194 cases and 3,894 controls. APOE allele status was available for 613 subjects (98 cases and 515 controls). Table 1 presents selected characteristics at CSHA-1 of cases, controls, decedents (considered demented or not demented), and subjects who refused to participate or for whom data were missing. Cases, including decedents, were older than subjects in other categories; the percentage of female controls, including decedents, was smaller; living cases had lower 3MS Examination scores; and living cases and controls had somewhat fewer chronic conditions.

Using the more recent criteria for diagnosing Alzheimer's disease resulted in a change in status for fewer than 10 percent of the cases included in this analysis. That is, the new criteria identified 116 incident cases of probable Alzheimer's disease compared with 107 cases when the old criteria were used and 78 cases of possible Alzheimer's disease compared with 74. Results of analyses conducted by including only cases of probable Alzheimer's disease were consistent with the results presented here.

Demographic characteristics of the subjects are summarized in table 2. The distributions of age, sex, and education across cases and controls were significantly different. The cases were older than the controls (median age and range at CSHA-2 screening: 87 years; range, 69–105 vs. 78 years; range, 70–100). The cases had also completed fewer years of education (median, 10 vs. 11 years). Table 2 also presents the adjusted odds ratios for age, sex, and education. As expected, advanced age was strongly associated with higher risk of Alzheimer's disease after we controlled for sex and education. When age was treated as a continuous variable, the risk of Alzheimer's disease increased by 23 percent (95 percent confidence interval (CI): 1.19, 1.26) per additional year of age. The age- and sex-adjusted risk of Alzheimer's disease for those with the lowest level of education was almost twice that for more educated participants. No association was observed between sex and risk of Alzheimer's disease.

Table 3 shows the odds ratios for selected putative risk factors after adjustment for age, sex, and education. Family history of Alzheimer's disease or senile dementia was not associated with late-onset Alzheimer's disease. Those participants who had at least one *APOE4* allele had 3.28 times the risk of Alzheimer's disease compared with those who had two $\epsilon 3$ alleles. Of the antecedent or coexisting chronic conditions included in the risk factor questionnaire, only arthritis was significantly related to a reduced risk of Alzheimer's disease. No statistically significant relation was observed between Alzheimer's disease risk and high blood pressure, stroke, heart disease, depression, head trauma, diabetes, thyroid condition, cancer (any type), or stomach ulcer. Use of NSAIDs reduced the risk of Alzheimer's disease by 35 percent. This effect was due mostly to nonsteroidal anti-inflammatory drugs. Inclusion of both NSAID use and arthritis along with age, sex, and education in the same model yielded

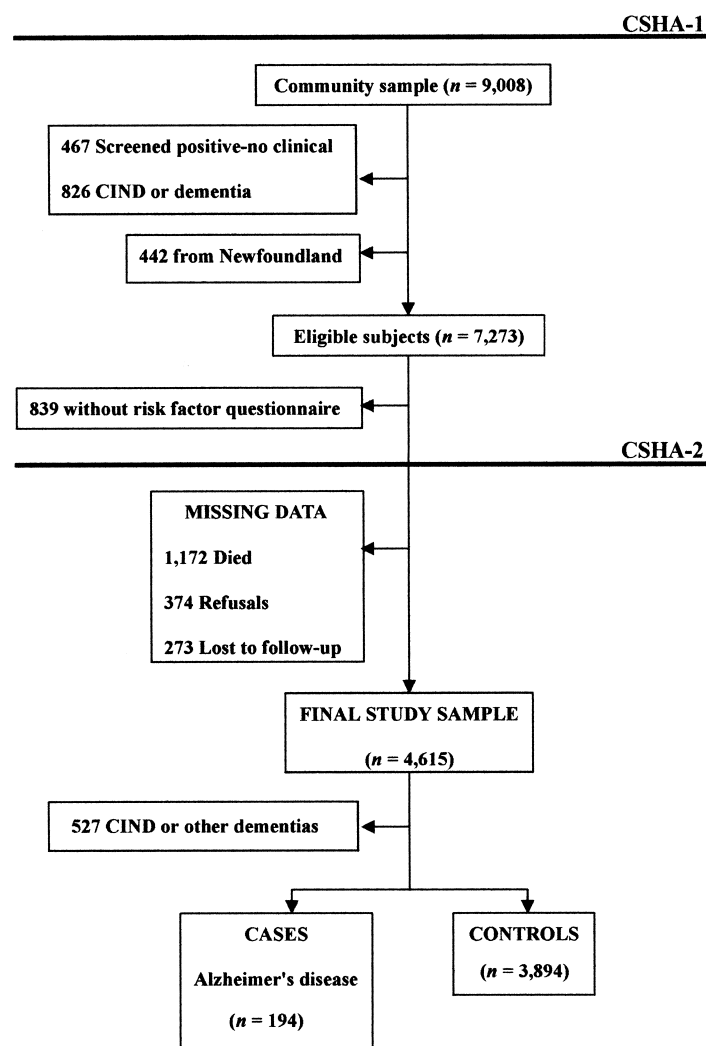


FIGURE 1. Study sample for the analysis of risk factors for incident Alzheimer's disease, Canadian Study of Health and Aging (CSHA), 1991–1992 (CSHA-1) and 1996–1997 (CSHA-2). no clinical: no clinical examination; CIND: cognitive impairment, no dementia.

similar odds ratio estimates; both factors remained protective for Alzheimer's disease, while testing of the interaction between NSAIDs and arthritis was not significant ($p = 0.10$). No association of Alzheimer's disease with antihypertensive agents, antacids, corticosteroids, or estrogen therapy was found.

Table 4 shows the age-, sex-, and education-adjusted risk estimates for Alzheimer's disease for some lifestyle-related variables. Over the 5-year follow-up, smoking was not significantly associated with Alzheimer's disease risk. Regular alcohol consumption was associated with a reduced risk of Alzheimer's disease; more particularly, wine consumption reduced the risk by 50 percent. Other variables observed to be significantly associated with a lower risk of Alzheimer's disease were daily coffee consumption and regular physical activity (31 percent reductions for both). No association with tea drinking, antiperspirant use, or depression was noted. For all reported risk factors, no evidence was

found of modification of risk by age, sex, or *APOE4* status. Furthermore, no relation with the risk of Alzheimer's disease was observed for marital status; parental age at subject's birth; birth order; occupational history; exposure to inks, paints, solvents, rubbers, glues, pesticides, fumigants, radiation, or anesthetics; or family history of Down's syndrome, mental retardation, Parkinson's disease, or thyroid disease (data not shown).

Table 5 presents estimates of the odds ratios for selected risk factors. Decedents were excluded; in addition, all deaths classified as due to dementia were included as Alzheimer's disease cases, and deaths not due to dementia were included as controls. The beneficial effect of regular physical activity remained strong and highly significant, whereas the associations with arthritis, NSAID use, wine consumption, and coffee consumption remained below 1.0 but were no longer statistically significant.

TABLE 1. Characteristics of participants, decedents, and subjects who refused or for whom data were missing, risk factor analysis of Alzheimer's disease, Canadian Study of Health and Aging, 1996–1997

Characteristics at CSHA-1*	Cases (n = 194)	Controls (n = 3,894)	Decedents		Subjects who refused or for whom data were missing (n = 647)
			Considered demented (n = 249)	Considered not demented (n = 773)	
Mean age (years)	81.0	72.9	80.0	77.9	75.3
Sex (% women)	67.5	57.5	60.2	49.7	64.8
Mean educational level (no. of years)†	9.9	11.1	10.3	10.0	10.3
Mean 3MS* Examination score‡	84.0	91.1	86.0	87.6	87.4
Mean no. of chronic health problems§	1.6	1.8	2.1	2.0	1.7
Mean ADL* score¶	13.7	13.9	13.3	13.6	13.8

* CSHA-1, first phase of the Canadian Study of Health and Aging (1991–1992); 3MS, Modified Mini-Mental State; ADL, activities of daily living.

† Information was missing for four cases, 58 controls, two decedents considered not demented, and six subjects who refused to participate or for whom data were missing in 1996–1997.

‡ Information was missing for one case.

§ Presence of chronic health conditions (range, 0–10).

¶ Range, 0–14; information was missing for two cases, seven controls, six decedents considered not demented, and six who refused to participate or who were lost to follow-up in 1996–1997.

DISCUSSION

The CSHA is a large-scale cohort study based on a representative, nationwide sample of the Canadian population aged 65 years or older. The prospective nature of this analysis, high response rates, careful standardization of screening and clinical assessments, and thorough checking of questionnaires as well as coding and editing of the data constitute further strengths of the study.

We found that increasing age, low educational level, and the *APOE4* allele were associated with increased risks of incident Alzheimer's disease, while arthritis, regular use of NSAIDs, wine consumption, coffee consumption, and regular physical activity were associated with reduced risks. Of note, family history of dementia and smoking were not related to the risk of Alzheimer's disease. In addition, estrogen was not shown to be protective.

TABLE 2. Distributions of and Alzheimer's disease risk estimates for age, sex, and education, Canadian Study of Health and Aging, 1996–1997

Variable	Cases (n = 194)		Controls (n = 3,894)		Odds ratio	95% confidence interval
	No.	%	No.	%		
Age (years) at screening, CSHA-2*,†						
70–79	23	11.9	2,216	56.9	1.00	
80–89	104	53.6	1,506	38.7	7.10	4.53, 11.12
≥90	67	34.5	172	4.4	37.82	22.75, 62.89
Sex‡						
Male	63	32.5	1,543	39.6	1.00	
Female	131	67.5	2,351	60.4	0.93	0.67, 1.31
No. of years of education§						
≥13	41	21.1	1,147	29.5	1.00	
9–12	79	40.7	1,759	45.2	1.37	0.91, 2.06
0–8	70	36.1	980	25.2	1.90	1.25, 2.90

* CSHA-2, second phase of the Canadian Study of Health and Aging (1996–1997).

† Odds ratios were adjusted for sex and education.

‡ Odds ratios were adjusted for age and education.

§ Odds ratios were adjusted for age and sex.

TABLE 3. Association of selected risk factors with Alzheimer's disease, Canadian Study of Health and Aging, 1996–1997

Variable	Cases exposed/total (no.)	Controls exposed/total (no.)	Odds ratio*	95% confidence interval
Family history of dementia	17/156	370/3,299	1.02	0.59, 1.77
<i>APOE</i> 4†,‡	39/98	97/515	3.28	1.98, 5.44
Coexisting conditions				
High blood pressure	59/157	1,303/3,409	0.88	0.62, 1.27
Stroke	18/148	236/3,189	1.54	0.88, 2.67
Heart disease	42/151	937/3,299	0.83	0.56, 1.22
Depression	19/145	324/3,171	1.44	0.84, 2.48
Prior head injury§	28/179	603/3,566	0.87	0.56, 1.36
Arthritis	90/167	2,013/3,452	0.61	0.43, 0.87
Diabetes	15/149	330/3,225	1.03	0.58, 1.84
Thyroid condition	32/154	505/3,261	1.48	0.95, 2.31
Cancer	17/140	495/3,128	0.64	0.37, 1.10
Stomach ulcer	35/152	561/3,256	1.36	0.89, 2.08
Medication				
Antihypertensive agents	66/152	1,269/3,086	0.91	0.64, 1.30
NSAIDs†				
Salicylates	30/152	793/3,086	0.85	0.55, 1.31
Nonsalicylates	20/152	515/3,086	0.62	0.37, 1.04
Any NSAIDs	45/152	1,224/3,086	0.65	0.44, 0.95
Antacids	73/185	1,427/3,763	0.91	0.65, 1.26
Corticosteroids	10/152	177/3,086	1.03	0.49, 2.15
Estrogen replacement therapy¶	4/110	125/1,969	1.37	0.48, 3.95

* Adjusted for age, sex, and education.

† *APOE*4, apolipoprotein E ε4 allele; NSAIDs, nonsteroidal anti-inflammatory drugs.

‡ Referent group, ε3/ε3.

§ With and without loss of consciousness.

¶ Calculated for women only.

However, our results are subject to potential limitations. First, of all eligible community subjects at baseline for whom a risk factor questionnaire was available, 1,172 (18.2 percent) died during the 5-year follow-up period and were not included in the main analyses. This group of decedents included proportionately more men, was generally older, was less educated, and suffered more frequently from chronic diseases than did subjects who completed follow-up. Exclusion of these participants may have distorted the results if, for example, these subjects were both more frequently exposed to a particular risk factor and at higher risk of developing Alzheimer's disease. Results from the simulation that included those subjects who died suggest that, although arthritis, NSAID use, wine consumption, and coffee consumption might be potentially valid protective factors for Alzheimer's disease, some bias due to exclusion of decedents during follow-up might also partially explain these associations.

Another limitation of our analysis is the possibility of bias in assessing risk factor exposures. In spite of the prospective

nature of the study, our results could be explained, at least in part, by some preclinical cognitive decline (not yet detectable by screening and clinical evaluations at CSHA-1) among subjects who had developed Alzheimer's disease by CSHA-2. Although it cannot be ruled out, this explanation seems improbable in view of the extensive screening and clinical evaluation process that was used at CSHA-1 to diagnose cognitive impairment, no dementia as well as dementia, along with the relatively long follow-up period. Nevertheless, to test this possibility, results were reanalyzed by excluding cases whose symptoms of Alzheimer's disease were reported by their proxies to have started within 2 years after CSHA-1 (up to the end of 1993). The persistence of a protective effect on Alzheimer's disease of NSAIDs (odds ratio (OR) = 0.61, 95 percent CI: 0.40, 0.97), wine (OR = 0.55, 95 percent CI: 0.30, 1.03), coffee (OR = 0.69, 95 percent CI: 0.48, 0.99), and physical activity (OR = 0.66, 95 percent CI: 0.47, 0.94) does not support the hypothesis that a preclinical decline explains our results.

TABLE 4. Association of specific lifestyle variables with risk of Alzheimer's disease, Canadian Study of Health and Aging, 1996–1997

Variable	Cases exposed/total (no.)	Controls exposed/total (no.)	Odds ratio*	95% confidence interval
Smoking	68/182	1,983/3,791	0.82	0.57, 1.17
At least weekly consumption of				
Beer	25/187	738/3,809	0.84	0.51, 1.41
Wine	15/186	668/3,789	0.49	0.28, 0.88
Spirits	35/186	1,059/3,797	0.78	0.52, 1.19
Alcohol (any type)	51/186	1,588/3,799	0.68	0.47, 1.00
Daily consumption of				
Coffee	107/188	2,878/3,831	0.69	0.50, 0.96
Tea	141/186	2,673/3,815	1.12	0.78, 1.61
Regular physical activity (yes/no)	108/188	2,728/3,831	0.69	0.50, 0.96
Regular use of antiperspirants	100/179	2,689/3,786	0.77	0.55, 1.08

* Adjusted for age, sex, and education.

Since multiple comparisons were performed, it is possible that some statistically significant associations may have occurred because of chance. For new associations that were found, for example, the protective effect of coffee drinking, replication in other studies will be needed to determine the validity of the association. Our results are generalizable to populations of largely European descent. Inclusion of different ethnic groups living in Canada was determined by their ability to speak either English or French.

Family history of dementia, similar to advancing age and the *APOE4* allele, frequently has been associated with an increased risk of Alzheimer's disease and is generally

considered a definite risk factor (24). The CSHA-1 case-control study found an increased risk of Alzheimer's disease that increased significantly by two- to threefold for family history of dementia (10). However, as in the EURODEM pooled data set (3), the prospective analysis of CSHA data did not find this association. These contradictory findings might reflect misclassification of the information because of recall bias and/or the uncertainty of information collected with the help of informants in retrospective investigations compared with longitudinal studies. In a case-control study, Mayeux et al. (25) observed that relatives of patients whose onset of Alzheimer's disease began at age 70 years or older

TABLE 5. Risk of Alzheimer's disease, between 1991–1992 and 1996–1997, associated with selected variables, according to original analysis and an assumption concerning decedents, Canada

Variable	Original results*		With decedents†	
	Odds ratio‡	95% confidence interval	Odds ratio‡	95% confidence interval
Age (by year)	1.23	1.19, 1.26	1.16	1.14, 1.17
Sex (female)	0.93	0.67, 1.31	0.98	0.79, 1.21
Educational level (by year)	0.92	0.88, 0.97	0.97	0.94, 0.99
<i>APOE4</i> §,¶	3.28	1.98, 5.44	3.23	1.96, 5.31
Family history of dementia	1.02	0.59, 1.77	1.15	0.81, 1.63
Arthritis	0.61	0.43, 0.87	0.94	0.75, 1.18
NSAIDs§	0.65	0.44, 0.95	0.97	0.77, 1.22
Wine consumption	0.49	0.28, 0.88	0.79	0.57, 1.10
Coffee consumption	0.69	0.50, 0.96	0.91	0.73, 1.14
Regular physical activity (yes/no)	0.69	0.50, 0.96	0.59	0.48, 0.73

* Decedents were excluded from the analysis.

† A total of 249 decedents with dementia were considered to have Alzheimer's disease and were included with cases; 773 decedents were presumed not to be demented and were included with controls.

‡ Adjusted for age, sex, and education.

§ *APOE4*, apolipoprotein E ε4 allele; NSAIDs, nonsteroidal anti-inflammatory drugs.

¶ Referent group, ε3/ε3.

did not have an increased risk of Alzheimer's disease, whereas there was an increased risk for first-degree relatives of patients whose onset occurred prior to age 70 years. Thus, it would seem reasonable that we did not observe this association in our older cohort. It may be surprising that family history of dementia was not associated with Alzheimer's disease while an increased risk of Alzheimer's disease was observed for subjects who had the *APOE4* allele, since family history of dementia is believed to be a potential indicator of this genetic factor. However, it has been suggested that the *APOE4* allele does not explain a large part of family history of dementia (26). In this study, 13 percent of those who had at least one *APOE4* allele reported a parent with dementia compared with 10 percent of those who had no $\epsilon 4$ allele.

The association between low educational level and the risk of Alzheimer's disease is consistent with findings from several retrospective and prospective studies (3, 10, 27–29). As in other large-scale population-based studies, CSHA cases were ascertained by means of a two-phase diagnostic procedure (screening and clinical examination). The cutpoint for screening with the 3MS Examination was chosen to achieve high sensitivity, even though this cutpoint could have missed mild cases of Alzheimer's disease in people with higher levels of education who could still perform well on cognitive screening tests. Whether the risk of Alzheimer's disease associated with less education corresponds to an artifact or represents a true risk factor is still unclear. Explanations for the education effect include increased brain reserve (30), selection bias resulting from selective attrition or use of a two-phase diagnostic procedure (27, 31), and confounding by indicators of socioeconomic status linked to education, such as diet, lifestyle, and occupational history (32, 33).

The present analysis supports the hypothesis of a negative association between NSAIDs and the risk of Alzheimer's disease. This protective relation was also found in several population-based case-control studies, including the CSHA-1 analysis (34). At least one longitudinal study supports the protective effect of anti-inflammatory drugs against Alzheimer's disease and dementia (35), while some studies remain inconclusive (36, 37).

Regular wine consumption was also associated with a reduced risk of Alzheimer's disease. Results from the PAQUID Study, a longitudinal study of community residents, showed a similar negative relation between wine consumption and Alzheimer's disease (38). This protective effect remained significant after more in-depth statistical analyses were conducted (39). It has been suggested that specific substances in wine, but not in other alcoholic beverages, could be responsible for this positive effect on nerve cells in dementia (40).

In our analysis, regular consumption of coffee seemed to be protective for Alzheimer's disease. Low coffee intake was reported to be related to mental disability after a 25-year follow-up of 716 Finnish men (41). Without confirmation from other prospective studies of Alzheimer's disease, this finding may have been due to chance.

The potential protective effect of regular physical activity on the risk of Alzheimer's disease is important because it

represents a modifiable lifestyle habit. Few epidemiologic studies have evaluated the possible protective role of regular physical activity on the risk of cognitive impairment and dementia in the elderly, and results have been inconsistent (7, 42). However, in clinical trials, exercise has been shown to benefit cognitive function (43, 44). More recently, regular physical activity has been found to be protective against cognitive impairment as well as all types of dementia, including Alzheimer's disease, and an interaction with sex has been reported, suggesting greater protection in women than in men (45).

In conclusion, this large-scale prospective study of older-age onset of Alzheimer's disease confirmed some of the most frequently suggested etiologic hypotheses about the disease, but not all. Intriguing protective associations observed in our study warrant further research. Few preventive strategies for Alzheimer's disease have been explored. Regular physical activity could represent a novel and safe preventive strategy against Alzheimer's disease and many other conditions, and it should be examined further.

ACKNOWLEDGMENTS

The data reported in this paper were collected as part of the CSHA study. 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 Incorporated through the Medical Research Council/Pharmaceutical Manufacturers Association of Canada Health Activity Program, NHRDP (project no. 6603-1417-302 (R)), Bayer Incorporated, and the British Columbia Health Research Foundation (project no. 38 (93-2) and no. 34 (96-1)). The study was coordinated through the University of Ottawa and the Division of Aging and Seniors, Health Canada. Dr. René Verreault was supported by the Laval University Chair for Geriatric Research. Dr. Danielle Laurin was supported in part by a National Health Ph.D. Fellowship provided by the NHRDP (project no. 6605-5228-47) and by the Laval University Chair for Geriatric Research.

The authors are grateful to Richard Aylesworth and Louis Rochette for statistical assistance.

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