# The Canadian Study of Health and Aging* : Risk factors for Alzheimer's disease in Canada

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**Article abstract**—*Objective*: To study risk factors for Alzheimer's disease (AD) based on data from the Canadian Study of Health and Aging. *Design*: Population-based case-control study. *Setting*: Communities and institutions in 10 Canadian provinces. *Participants*: Two hundred fifty-eight cases clinically diagnosed with probable AD, with onset of symptoms within 3 years of diagnosis, and 535 controls, frequency matched on age group, study center, and residence in community or institution, clinically confirmed to be cognitively normal. *Main outcome measure*: Odds ratios (ORs) were calculated using unconditional logistic regression for previously hypothesized and potential risk factors for AD. *Results*: The OR for family history of dementia was significantly elevated (2.62; 95% confidence interval [CI], 1.53 to 4.51) and increased with the number of relatives with dementia. Those with less education were at higher risk of AD, with an OR of 4.00 (95% CI, 2.49 to 6.43) for those with 0 to 6 years, in comparison with those with 10 or more years. Head injury achieved borderline significance. A history of arthritis resulted in a low risk of AD (OR = 0.54; 95% CI, 0.36 to 0.81), as did a history of use of nonsteroidal anti-inflammatory drugs. Initial analyses showed an increased risk of AD for occupational exposure to glues as well as to pesticides and fertilizers; the increased risk was greater in those with less education. *Conclusion*: This study confirmed a number of previously reported risk factors for AD, but provided little support for others. A new finding was an increased risk for those with occupational exposure to glues as well as pesticides and fertilizers, but this needs further study.

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The problem of Alzheimer's disease (AD) is becoming increasingly important as more people reach ages at which the risk of AD increases markedly.[1] In Canada, the population aged 65 and over numbered 3.2 million in 1991. This represents the fastest growing segment of the population, and it is expected to more than double to 7.8 million by the year 2031.[2]

Little is known with any certainty about the risk factors for AD. Except for age and a positive family history of AD, no definite risk factors have been established, although there is some indication of an association with a positive family history of Parkinson's disease and Down's syndrome, a history of depression, severe head trauma, and smoking.[3]

The data from 11 major case-control studies on AD[4-14] were re-analyzed by the EURODEM group.[15-23] A family history of dementia was one of the strongest and most consistently observed associations; a positive history of Down's syndrome was also associated with AD. There was a somewhat weaker association between a family history of Parkinson's disease and AD, based on two of the studies.[7,11,16]

There was some evidence of an increased risk in subjects with mothers aged 15 to 19, but stronger evidence of an association between late maternal ages and the risk of AD, particularly for those without a positive family history of AD.[17]

Pooling data from seven studies on history of head trauma with loss of consciousness resulted in an elevated odds ratio (OR) among AD patients that was statistically significant.[7,8,10-12,18,24,25]

The EURODEM group examined the history of several medical conditions.[19] The risk of AD in those with hypothyroidism was significantly increased, whereas there was no association with hyperthyroidism or goiter. A history of depression was positively associated with AD in late-onset cases, based on the re-analysis of four studies.[6,9,10,12,20] The risk of AD was statistically significantly inversely related to the presence of osteoarthritis. Headaches including migraine were negatively associated with AD. The analysis included

*See page 2079 for the CSHA study centers and investigators.

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two medical treatments: blood transfusions were negatively associated with AD, and exposure to anesthesia was not associated with AD.

The EURODEM analysis did not show alcohol consumption to be related to risk of AD[21]; smoking was inversely related to risk of AD,[21] with the exception of one study.[9] In a Dutch study,[26] an inverse association with smoking was evident only for familial cases.

Occupational exposure to solvents was not associated with AD.[22]

Evidence that aluminum may be a risk factor for AD is inconsistent and inconclusive,[27] but the matter deserves further investigation. Evidence from ecological studies of aluminum in drinking water and AD and dementia is inconsistent.[28-35] Occupational exposure to aluminum dust was associated with increased risk of cognitive impairment, but not of AD.[36] Graves et al[37] found an association between aluminum-containing antiperspirants and AD, but not for aluminum-containing antacids; other studies that examined antacids were also negative.[5,7,12]

Katzman[38] presented the theory that education (or some factor highly correlated with more education) results in decreased risk of AD. This involves increased brain reserve due to increased synaptic density in neocortical association cortex and the delay of onset of symptoms by 4 to 5 years. Epidemiologic studies in Rochester, MN,[39] Stockholm,[40] and Framingham[41] do not support this theory; however, studies in Shanghai,[42] Bordeaux,[43] The Netherlands,[44] Israel,[44] Italy,[45] and Lundby, Sweden,[46] provide support. In addition, Stern et al[47] found an inverse relationship between education and parietotemporal perfusion deficit in AD.

The opportunity to add to our understanding of risk factors for AD was provided by the Canadian Study of Health and Aging (CSHA), which had four objectives: (1) to estimate the prevalence of dementia among elderly Canadians using a common research protocol; (2) to identify risk factors for AD; (3) to describe patterns of caring for demented patients in Canada, and to assess the burden that the process of caring places on the caregivers and the need for support that this produces; and (4) to establish a uniform database for subsequent studies of the natural history of dementia, as well as for planning and evaluation of interventions.

The study was conducted in 18 CSHA study centers distributed across all Canadian provinces, and was coordinated by the University of Ottawa in collaboration with the Laboratory Centre for Disease Control. This paper describes the risk factor component of the CSHA, which consisted of a population-based case-control study. We used the case-control design since it was the only feasible way of assessing risk factors for AD in the limited time available to carry out the study; however, we collected data on exposure to potential risk factors from cognitively normal participants so that it will be possible to conduct a cohort study in the future.

We collected data to test most of the risk factor hypotheses proposed in the literature, whether previous findings were significant or not. The study tested hypotheses concerning family history of dementia; little education; exposure to aluminum; history of head injury; family history of Parkinson's disease, Down's syndrome, depression, or mental retardation; age of mother and father at subject's birth; antecedent thyroid condition, depression, or migraine; exposure to anesthetic agents; solvents; and alcohol consumption. We hypothesized that smoking and history of arthritis were protective factors.

**Methods.** The overall design of the CSHA has been described in detail.[1]

*Sample.* Study subjects were recruited from both the community and institutions. Samples, stratified by age group (65 to 74, 75 to 84, 85+), of potential study participants were drawn from lists of community residents in 36 cities and surrounding areas based on health insurance plans in all provinces except Ontario. The Canadian health insurance system provides free coverage to all residents and has virtually universal coverage. In Ontario, we used the Enumeration Composite Record, an aggregated list based on election and other municipal records. In three study centers, the institutional samples were drawn by sampling in the same way from health insurance lists. In other centers, an institutional sampling frame was created by merging available lists of institutions. Institutions were stratified according to size, with a random sample of institutions being drawn from each stratum; a probability sample of people in these institutions was then selected.

Subjects were aged 65 or older as of October 1, 1990, and fluent in English or French. Data collection took place between February 1991 and May 1992. In all, 9,008 community residents and 1,255 residents of institutions were surveyed for the prevalence study of dementia.

*Diagnostic assessment.* Participants living in the community were first screened for cognitive impairment using the Modified Mini-Mental State Examination (3MS),[48] and were asked to undergo a clinical examination if the screening test indicated cognitive impairment (defined for this study as a score of less than 78/100) or if they were unable to complete the screening test because of deafness or other impairments.

A number of subjects who screened cognitively normal, equal to the number expected to be diagnosed as suffering from dementia (including AD), were also examined clinically. All institutionalized participants were examined clinically without first being screened. Diagnostic criteria for dementia followed the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III–R) to define dementia, as well as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for possible and probable AD.[49,50]

*Risk factor study.* Cases were selected for the risk factor study if they were diagnosed with "probable" AD. In order to reduce the potential for prevalence-incidence bias, only cases of recent onset (ie, when symptoms first appeared not more than 3 years prior to the study diagnosis) were included. The time interval since diagnosis for cases was liberally defined for two reasons: it is very difficult to pinpoint accurately the onset of symptoms of

AD, and the disease does not usually progress quickly. Those who were diagnosed as cognitively normal in institutions and those who were screened and were diagnosed as normal in the community formed the control group for the risk factor study. An exception was made to the composition of the case and control groups when we looked at education as a risk factor. Education is associated with performance on the screening test, which would bias these results. We corrected for this in the analysis by applying sliding cut points such that there was an equal probability of being included as a case or control at different levels of education (see Discussion for more detail). The study design involved frequency matching of controls to cases by study center, residence in community or institution, and age group (65 to 74, 75 to 84, 85+). Subsequent experience showed this to be infeasible, so we controlled for age and residence in all analyses.

Risk factor questionnaires were, of necessity, completed by proxy respondents (usually a close relative) for the cases; to minimize potential bias, the questionnaires for the controls were also completed by proxies. The questionnaire covered demographic characteristics, occupational and environmental exposures, lifestyle (including smoking, alcohol, and a limited dietary history), as well as family and medical history (including head trauma, antecedent diseases, and medication use). The questionnaire was designed to be completed by the proxies themselves, although in seven centers an interviewer administered it.

*Analysis.* All analyses were conducted controlling for age, sex, education (as a continuous variable) except where otherwise specified, and residence in community or institution. Since there were demographic differences between residents in the community and in institutions, we analyzed them separately; where combining them masked a finding, the results for the subgroup are shown. We controlled for age (as a continuous variable) because frequency matching for age did not produce an exact balance. ORs were calculated, as estimates of the relative risk,[51] using unconditional logistic regression.

One of the objectives of the study was the establishment of a database for future study. Those who were screened as cognitively normal were requested to complete a risk factor questionnaire for a future study of incidence of AD and a cohort analysis of risk factors. This means that for most of the controls, we have both proxy and self-administered risk factor questionnaires. To assess the quality of data provided by proxy respondents for the controls, a preliminary analysis of the agreement between the two questionnaires was conducted using kappa statistics.

**Results.** The overall response rate for participation in screening by community residents was 72.1%.[1] Of those from the community who were requested to undergo clinical examination, 73.1% who screened as cognitively impaired and 75.0% who screened cognitively normal accepted. The acceptance rate for the clinical examination for those in institutions was 81.7%. Response rates for the risk factor questionnaire for the cases, ie, those diagnosed as having probable AD with duration of symptoms not more than 3 years, were 83.9% for those in institutions and 89.8% for those in the community who screened cognitively impaired. The response rate for the controls was 89%.

*Description of the study population.* Frequency matching on age group in the study design did not eliminate age differences between cases and controls (mean age for cases, 84.7 years; for controls, 79.0 years; $p < 0.01$). This reflected the difficulty of finding cognitively normal subjects in the older age groups.

There were more women than men, as both cases and controls. Controls had completed more years of education than cases (the average number of years for cases was 8.2; for controls, 10.6, $p < 0.01$). A higher proportion of cases than controls were residents in institutions (52.3% versus 25.6%). Proxies for controls were more likely to be spouses (25.1% versus 13.4%) and to be adult children for cases (54.9% versus 41.3%), reflecting the difference in age and social circumstances between the cases and controls. (Detailed information is available on request from the corresponding author.)

Results are presented for those variables for which there existed a prior hypothesis. In addition, results are presented for two variables that, in preliminary analyses, were statistically significantly elevated.

*Prior hypotheses.* A positive family history of AD or other dementia in first-degree relatives was elevated, with an OR of 2.62 and a 95% confidence interval (CI) of 1.53 to 4.51 (table 1). An examination of the risk of AD or other dementia according to the number of affected first-degree relatives shows increasing risk with increasing number of first-degree relatives. It should be noted, however, that cases had more brothers and sisters (7.64) than controls (6.32), a difference that is statistically significant ($p \leq 0.01$). It is not known how many brothers and sisters were alive and at risk of AD at the time of the study. Age at onset was not significantly different for those with a family history of AD (81.19) and those without (82.42).

Those with less education seemed to be at higher risk of AD. Using those with 10 or more years of education as the reference group, the OR was 1.72 for those with 7 to 9 years and 4.00 for those with 0 to 6 years.

A positive family history of mental retardation was more frequent among the cases, but not significantly. For institutional residents, the OR was significantly elevated, but this finding should be interpreted cautiously due to small numbers. Information was collected on family history of Down's syndrome, but the numbers were too small to analyze. ORs for family history of Parkinson's disease and depression were less than 1 among the cases, but not statistically significant.

The OR for antecedent thyroid condition was less than 1.00, but not significant; however, for community residents, the OR was significantly below 1. The OR for peptic ulcer (an indication for the use of antacids, some of which contain aluminum) was slightly over 1.00. Those with arthritis had a significantly reduced risk of AD. The fre-

**Table 1. Associations for which prior hypotheses existed**

| Putative risk factor | Cases | Controls | Odds ratio* | 95% Confidence interval |
|---|---|---|---|---|
| Number of first-degree relatives with dementia | | | | |
| None | 119 | 350 | 1.00 | Reference |
| 1 relative | 31 | 50 | 2.39 | 1.38-4.28 |
| 2 or more relatives | 11 | 5 | 4.24 | 1.23-14.60 |
| Combined | 42 | 55 | 2.62 | 1.53-4.51 |
| Years of education† | | | | |
| 0-6 years | 63 | 72 | 4.00 | 2.49-6.43 |
| 7-9 years | 71 | 168 | 1.72 | 1.12-2.61 |
| 10 or more years | 76 | 329 | 1.00 | Reference |
| Family history of | | | | |
| Mental retardation | 10/161 | 7/405 | 3.23 | 0.98-10.6 |
| Institutional residents | 7/74 | 1/93 | 9.45 | 1.02-88.0 |
| Parkinson's disease | 6/161 | 18/405 | 0.86 | 0.28-2.61 |
| Depression | 20/161 | 56/405 | 0.87 | 0.46-1.67 |
| Coexisting or antecedent conditions | | | | |
| Thyroid condition | 17/196 | 61/448 | 0.59 | 0.31-1.14 |
| Community residents | 6/104 | 52/351 | 0.35 | 0.14-0.91 |
| Peptic ulcer | 38/200 | 79/454 | 1.19 | 0.72-1.96 |
| Arthritis | 104/201 | 280/468 | 0.54 | 0.36-0.81 |
| Depression | 37/188 | 75/455 | 1.05 | 0.63-1.77 |
| Migraine | 17/195 | 46/440 | 0.98 | 0.49-1.95 |
| Head injury | 35/184 | 60/453 | 1.66 | 0.97-2.84 |
| Contact sports (eg, boxing) | 5/166 | 10/392 | 1.53 | 0.39-6.03 |
| Aluminum-containing antacids | 36/153 | 104/373 | 0.75 | 0.45-1.23 |
| All antiperspirants | 102/169 | 260/406 | 1.33 | 0.85-2.07 |
| Institutional residents | 47/71 | 51/87 | 3.03 | 1.30-7.05 |
| Antiperspirants containing aluminum | 47/116 | 123/270 | 1.33 | 0.78-2.26 |
| Institutional residents | 25/49 | 24/60 | 4.81 | 1.67-13.9 |
| Tea | 185/218 | 383/498 | 1.40 | 0.86-2.28 |
| Nonsteroidal anti-inflammatory drugs‡ | 61/224 | 205/529 | 0.55 | 0.37-0.82 |
| Corticosteroids‡ | 20/224 | 41/529 | 0.75 | 0.39-1.46 |
| Smoking (all cases) | 81/217 | 233/513 | 1.17 | 0.77-1.80 |
| Smoking (familial AD only) | 14/41 | 233/513 | 0.86 | 0.40-1.85 |
| Alcohol consumption | | | | |
| Beer | 31/215 | 66/508 | 1.55 | 0.85-2.81 |
| Wine | 19/219 | 64/505 | 0.94 | 0.50-1.75 |
| Spirits | 39/218 | 101/503 | 1.18 | 0.71-1.96 |
| Exposure to anesthetic | 176/204 | 420/480 | 1.07 | 0.60-1.90 |
| Difficulty recovering from anesthetic | 16/183 | 42/416 | 1.13 | 0.56-2.25 |
| Solvents | 18/148 | 60/373 | 0.76 | 0.38-1.54 |

* Adjusted for age, sex, residence in community or institution, and education.
† Controls adjusted for education bias of screening test.
‡ Information obtained from clinical examination data as well as proxy-completed risk factor questionnaires.

quency of occurrence of depression in cases was essentially no different than in controls. The OR for head injury was elevated and achieved borderline significance; previous participation in contact sports did not appear to be a risk. Looking at previous head injury with loss of consciousness, no elevated risk was seen by age group or sex (data not shown).

We did not see an association between use of aluminum-containing antacids and AD. For all antiperspirants/deodorants and for antiperspirants containing aluminum, the OR was 1.33 (not significant). However, the ORs for these variables among those living in institutions were significantly elevated. The OR for tea consumption at 1.40 was not significantly elevated.

**Table 2. Risk of AD according to pack-years smoked**

| Pack-years | Cases | Controls | Odds ratio* | 95% Confidence interval |
|---|---|---|---|---|
| 0 | 136 | 280 | 1.00 | Reference |
| 0.5-20 | 20 | 77 | 0.98 | 0.52-1.87 |
| 21-36 | 22 | 69 | 0.91 | 0.47-1.75 |
| 37+ | 19 | 30 | 2.79 | 1.27-6.14 |

* Controlling for age, sex, residence in community or institution, and education.

For use of nonsteroidal anti-inflammatory drugs (NSAIDs), the OR was significantly below 1.00. For corticosteroids, the OR was not significantly below 1.00. The OR for smoking was 1.17 (not significant). The mean age of onset of AD was lower in smokers (80.07) than in nonsmokers (83.85). This difference was statistically significant. When we restricted our definition of cases to only those with "familial AD" (at least one first-degree relative reported as having had dementia), this difference was maintained, with the average age at onset for smokers, 77.9 years, and for nonsmokers, 80.9 years. However, the OR for smoking as a risk for familial AD dropped to 0.86 (not significant). Looking at pack-years smoked (table 2), the OR stayed close to 1 for all except the highest group, for whom it was significantly elevated at 2.79. Alcohol did not seem to be a risk factor for AD, although the OR for beer was slightly elevated (table 1). Neither exposure to anesthesia nor difficulty in recovering from anesthetic was a risk factor for AD. This study did not support the hypothesis that occupational exposure to solvents is a risk factor for AD.

There was a slight suggestion of increased risk of AD for those whose mothers were under age 20 years at the time of their birth; however, the OR was not statistically significant (1.86; 95% CI, 0.52 to 6.61, with mothers aged 20 to 29 as the reference group). There was also some indication of increased risk of AD with fathers who were 40 or over at the time of the subjects' birth, but again, the OR was not statistically significant (1.49; 95% CI, 0.71 to 3.16, with fathers aged 20 to 29 as the reference group). (Detailed information is available on request from the corresponding author.)

*Other associations.* Occupational exposure to glues as well as to pesticides and fertilizers appeared to be risk factors for AD when controlling only for age, sex, and residence in the community or institution. However, when education was also controlled for, the strength of the association was reduced (table 3). When stratifying by level of education (0 to 6 years, 7 to 9 years, and 10 years and over), for glues, the ORs were elevated for the lower two levels, but not for the highest level. The same was true to a lesser degree for pesticides and fertilizers.

**Table 3. Other associations**

| | Cases | Controls | Odds ratio | 95% Confidence interval |
|---|---|---|---|---|
| Occupational exposure to | | | | |
| Glues* | 36/177 | 50/375 | 2.16 | 1.25-3.70 |
| † | 30/155 | 50/371 | 1.80 | 0.99-3.27 |
| Pesticides, fertilizers* | 33/179 | 30/368 | 2.17 | 1.18-3.99 |
| † | 29/157 | 29/364 | 1.58 | 0.81-3.10 |
| Stratified by level of education* | | | | |
| Glues | | | | |
| 0-6 years | 14/46 | 4/44 | 3.65 | 0.96-15.39 |
| 7-9 years | 9/50 | 14/104 | 3.56 | 1.08-11.73 |
| 10+ years | 7/59 | 32/223 | 1.06 | 0.40-2.79 |
| Pesticides, fertilizers | | | | |
| 0-6 years | 18/50 | 6/44 | 1.97 | 0.58-6.65 |
| 7-9 years | 7/47 | 11/104 | 1.57 | 0.49-5.02 |
| 10+ years | 4/60 | 12/216 | 1.06 | 0.28-4.03 |

* Adjusted for age, sex, and residence in community or institution.
† Adjusted for age, sex, residence in community or institution, and education.

**Table 4. Kappa statistics showing the level of agreement between risk factor questionnaires completed by proxies and controls**

| Risk factor | Kappa |
|---|---|
| Smoking | 0.85 |
| Coexisting or antecedent thyroid condition | 0.74 |
| Coexisting or antecedent stomach ulcer | 0.71 |
| Beer | 0.70 |
| Tea | 0.64 |
| Solvents–occupational exposure | 0.64 |
| Antecedent head injury | 0.62 |
| Spirits | 0.61 |
| Family history of Parkinson's disease | 0.60 |
| Family history of mental retardation | 0.59 |
| Coexisting or antecedent migraine | 0.59 |
| Coexisting or antecedent arthritis | 0.58 |
| All antiperspirants and deodorants | 0.53 |
| Cold sores | 0.53 |
| Family history of dementia | 0.49 |
| Exposure to anesthetic | 0.48 |
| Wine | 0.47 |
| Coexisting or antecedent depression | 0.46 |
| Aluminum-containing antacids | 0.45 |
| Antiperspirants containing aluminum | 0.45 |
| Pesticides, fertilizers–occupational exposure | 0.42 |
| Family history of depression | 0.40 |
| Difficulty recovering from anesthetic | 0.40 |
| Glues–occupational exposure | 0.38 |
| Raw meat | 0.35 |
| Organ meats (brain, kidney, sausage, etc) | 0.35 |
| Contact sports (eg, boxing) | 0.30 |

When we compared the proxy risk factor data with the corresponding data from the risk factor questionnaire completed by cognitively normal subjects, the kappa statistics ranged from a high of 0.85 for smoking history to a low of 0.30 for participation in contact sports (table 4).

**Discussion.** Response rates to the CSHA compared favorably with other studies of seniors, especially considering the size and complexity of the study.[52]

One of the major strengths of the study is that it is population based, with the controls drawn from the same population as the cases. This allows generalization of results to the population at large. Because of the sampling design, the participants in this study were older than those in most, if not all, other studies of AD. The advanced age of the study participants is neither a strength nor weakness in itself; however, it is no doubt directly related to the difficulty experienced in finding age-matched controls at the older age groups.

The difficulties of validity in using retrospective data are well known, and the use of information supplied by proxy respondents probably increases the degree of misclassification bias. To maximize accuracy, we limited the amount of detail requested of respondents to levels similar to other studies in which proxy respondents completed questionnaires. We also pilot-tested the questionnaire to determine that all questions could be answered by most proxies. We collected the same information directly from cognitively normal controls as part of a database for future studies. A future paper will analyze the comparability of the data from the two sources in more detail. The level of agreement between the information provided by the proxy and the subject for the variables presented varied considerably. According to a kappa-based scale used by Landis and Koch,[53] there was "almost perfect" agreement (kappa = over 0.8) between the two sources for smoking, a substantial level of agreement (kappa = 0.61 to 0.80) for seven variables, moderate agreement (0.41 to 0.60) for 13 variables, and poor agreement for six (<0.41). All but one of the variables reported as statistically significant in this paper obtained at least moderate agreement; doubt is cast on the association between AD and exposure to glues due to the low kappa.

The observation in the CSHA of an increased risk of AD in those with AD or other dementia in first-degree relatives is consistent with other studies. The level of the risk we observed is less striking than in the EURODEM analysis.[16] In familial cases of AD, the onset tends to occur at an earlier age, so the advanced age of our participants could account for the relative weakness of this association in this study.

Performance on the screening examination was affected by level of education, and this may have introduced a bias when considering education as a risk factor for AD. First, a higher proportion of early cases may have been detected among the less educated who screened positive than among the

more educated who would screen negative. Second, the requirement that controls screen negative (as well as be clinically diagnosed as cognitively normal) may have created a more highly educated control group. These factors could have accounted for all or part of the elevation in the OR.

To correct this bias, we introduced a sliding cutoff point on the 3MS according to number of years of education, which gave people with different levels of education an equal probability of being included as a case. We excluded cases whose 3MS score was above the new cutoff point according to their level of education. We also added new controls if their score was above the new cutoff point (ie, they now met the criteria of both screening negative and being diagnosed as cognitively normal). The resulting ORs (table 1) should give an unbiased estimate of the effect of education as a risk factor for AD. The bias was strongest in the group with 0 to 6 years of education (corrected OR = 4.00, uncorrected OR = 5.44). The difference in the ORs in the group with 7 to 9 years was minimal (corrected OR = 1.72, uncorrected OR = 1.73).

In this study, those with higher levels of education were at reduced risk of AD; this supports Katzman's argument that more education may be protective against AD,[38] or at least may delay the onset of obvious symptoms. Other studies have not been entirely consistent in showing this association, indicating the need for further study. As an indication of socioeconomic status, education might be a surrogate for other factors that affect the risk of AD, such as diet.

The inverse relationship between AD and arthritis was consistent with the findings of other studies.[19,54] This finding was strengthened by the significantly low OR for use of NSAIDs, which are commonly taken for arthritis. Although Breitner et al[55] found the inverse relationship between corticosteroids and AD to be stronger than for NSAIDs and AD, the reverse was true in our study. The role of NSAIDs and corticosteroids in the prevention of AD should be further studied.

This study provided little support for the hypothesis that exposure to aluminum is associated with AD. There was no evidence of an association with antacids containing aluminum. The situation was less clear with regard to antiperspirants, and was impossible to analyze meaningfully for the following reasons. We asked about use of specific brands of deodorants and antiperspirants, but not about subtypes of each brand. Such detailed information would be impossible to obtain from proxy respondents. The most commonly used brands generally have several subtypes (eg, solid, roll-on, aerosol; men's and women's versions), and two or more aluminum compounds are used in the various subtypes within each brand. Therefore, we were not able to analyze the data according to aluminum compound or type. Furthermore, most people reported using more than one brand of antiperspirant. The association that was observed only for institutionalized subjects is interesting. A more detailed prospective study focusing on risk in relation to subtypes of antiperspirant might help to clarify the situation.

Unlike the combined analysis of other studies that saw an inverse relationship between smoking and AD, we observed a slightly elevated OR for all cases. In one study, the inverse association was evident only for familial cases of AD, for whom the average age at onset of smokers in six families was 59 years, and in nonsmokers was 54 years.[26] Overall, in our study, the average age of onset for smokers was lower than for nonsmokers (80.1 versus 83.9). The increase in OR for the group with the greatest number of pack-years is consistent in suggesting a slightly increased risk of AD for smokers. When we restricted our definition of cases to those whose family members had had dementia, the OR dropped below 1, but was not significant. When looking at familial cases, the average age at onset was still higher in nonsmokers than in smokers (80.9 versus 77.9). This analysis is not exactly comparable with the familial analysis in the Dutch study,[26] in which cases were restricted to those with age at onset of 70 or less, and in which detailed information was collected on familial cases. On the other hand, a study by the UK Medical Research Council (MRC)[56] found an increased risk of dementia and, specifically AD, in smokers, including a dose-response effect. Our findings do not agree with the inverse association seen in the Dutch study or in the EURODEM analysis, but they are in keeping with the findings of the UK MRC study.

The preliminary associations between occupational exposure to glues as well as pesticides and fertilizers and AD are of interest. Those with less education would be more likely to work in jobs involving exposure to these substances. This was borne out by the frequencies obtained when stratifying by education: there were more exposed cases with less education, and they had higher ORs than the most educated group. The association with pesticides and fertilizers is particularly interesting since exposure to pesticides has been associated with Parkinson's disease,[57,58] another neurologic disease. A prospective study that collected more precise exposure data would be necessary to further study this association.

In conclusion, this study has confirmed a number of the hypothesized risk factors (and protective factors) for AD (family history of dementia; head injury, even though it was not quite significant; education; coexisting arthritis; and NSAID use). Age is also a risk factor for AD. It could not be examined as a risk factor in this case-control analysis since we controlled for age; however, the prevalence estimates of AD that were part of this study clearly demonstrate age as a risk factor.[1] Minimal support was provided for the aluminum hypothesis. Other hypothesized risk or protective factors were not supported. Although education was a con-

founder for the associations of glues, and pesticides and fertilizers with AD, these are still interesting and merit further investigation. We plan to conduct a cohort analysis based on the self-administered risk factor questionnaires and newly diagnosed cases of AD, which should further help to confirm hypothesized risk factors for AD.

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