Smoking and the Occurrence of Alzheimer's Disease: Cross-Sectional and Longitudinal Data in a Population-based Study

Hui-Xin Wang, Laura Fratiglioni, Giovanni B. Frisoni, Matti Viitanen, and Bengt Winblad

The authors tested the hypothesis that smoking exerts a protective effect on Alzheimer's disease or dementia in a population-based cohort of 668 people aged 75-101 years (Sweden). Smoking was negatively associated with prevalent Alzheimer's disease (adjusted odds ratio = 0.6, 95% confidence interval 0.4-1.1) and dementia (adjusted odds ratio = 0.6, 95% confidence interval 0.4-1.0). Over 3-year follow-up (1989-1992), the hazard ratios of incident Alzheimer's disease and dementia due to smoking were 1.1 (95% confidence interval 0.5-2.4) and 1.4 (95% confidence interval 0.8-2.7). Mortality over 5-year follow-up was greater among smokers in demented (hazard ratio = 3.4) than nondemented (hazard ratio = 0.8) subjects. Smoking does not seem protective against Alzheimer's disease or dementia, and the cross-sectional association might be due to differential mortality. Am J Epidemiol 1999; 149:640-4.

In spite of numerous studies published in the past few years on the topic, the effect of smoking on Alzheimer's disease and dementia remains uncertain. Most studies have reported inconclusive results (1-14) or an increased risk of Alzheimer's disease among smokers (15-17). Recently, results from some case-control studies have suggested an inverse association (18-22), confirmed by two meta-analyses (23, 24). This inverse association was supported by the finding of a significant dose-dependent relation (20, 23). A possible protective effect of smoking on Alzheimer's disease has been related to similar findings for Parkinson's disease (25-29), supporting the hypothesis that nicotine or nicotine receptors may hinder neurodegenerative mechanisms.

For several reasons, it is difficult to generalize concerning the studies carried out to date. Case-control studies have often included cases from hospital series and may not represent dementia cases in the general population (24). On the other hand, population-based studies on prevalent cases may introduce biases due to poorer survival of smokers. A few prospective studies have been carried out, but results have been discordant: one found a negative association (30), two found a positive one (31, 32), and another did not find any association (33).

We studied the occurrence of Alzheimer's disease and dementia in relation to smoking within the Kungsholmen Project, a population-based follow-up study; we were able to assess the association of smoking with both prevalent and incident Alzheimer's disease and dementia.

MATERIALS AND METHODS

Study population

Subjects were gathered from the Kungsholmen Project, which included all persons registered in a district of Stockholm, aged ≥75 years on October 1, 1987 (34-36). At baseline, after a screening phase in which the Mini-Mental State Examination (MMSE) (37) was used to detect cognitive impairment, all subjects with an MMSE score of ≤23 (n = 314) and a random sample of subjects with an MMSE score of ≥24 (n = 354) were extensively examined. Of these 668 subjects, information on smoking was available for 636. Among these, 198 prevalent dementia cases were detected. Of the remaining 438 dementia-free individuals, 95 showed cognitive impairment (MMSE score ≤ 23). In order to avoid recall bias in reporting smoking habits, we excluded these 95 persons from follow-up analyses that were performed with the 343 dementia-free subjects with no cognitive impairment.
Information on smoking was obtained at baseline by asking the subjects or informants (in the case of a cognitively impaired or demented person). Smoking history was assessed by asking whether the subjects had ever smoked, for how long, the number of cigarettes smoked per day, and at what age smoking was stopped in the case of exsmokers. In the present study, subjects with very low exposure were treated as nonsmokers. We defined smokers as 1) current smokers; 2) former smokers who had smoked for ≥5 years or had stopped smoking after age 40, irrespective of smoking dose; 3) smokers who had been smoking ≥5 cigarettes per day, if they had quit smoking before age 40 or had been smoking <5 years.

The diagnoses of Alzheimer’s disease and other types of dementia were made according to published criteria (38), with minor modifications (35). At both baseline and follow-up, diagnoses were made by two independent experts, plus a third in case of disagreement (39). The same diagnostic method was used for subjects who died before the follow-up examination, based on the clinical records, discharge diagnoses, and death certificates.

Statistical analysis

A chi-square or Student’s t test was used to assess differences between smokers and nonsmokers regarding demographic characteristics, diagnoses, and family history of dementia. Two separate analyses were performed to test the association of smoking with prevalent and incident Alzheimer’s disease and dementia. Univariate and multivariate logistic (prevalent Alzheimer’s disease and dementia) and Cox (incident cases) regression models were used to analyze the crude and adjusted odds ratio and hazard ratio due to smoking. Age, sex, and education were introduced into all multivariate models as potential confounders. Smoking was introduced into the model as a dichotomous variable (smokers vs. nonsmokers). Age was entered as a continuous variable (1-year increments), and sex and education were entered as dichotomous variables (female vs. male; ≥8 vs. <8 years). In all analyses, nonsmokers were used as the reference group.

RESULTS

Table 1 shows that, at baseline, smoking was less prevalent in the Alzheimer’s disease and demented group than in the nondemented group. The proportion of smokers declined with increasing age: 38 percent of all subjects were smokers at age 75–79 years, 31 percent at 80–84 years, 28 percent at 85–89 years, 23 percent at 90–94 years, and 17 percent at age 95 and over (p = 0.05). In the prospectively analyzed cohort, smokers were more often males and less educated (table 2).

Table 3 shows that prevalent Alzheimer’s disease and dementia were inversely associated with smoking. For the incident cases, the hazard ratio point estimates were mostly around 1, irrespective of dementia diagnosis and family history of dementia. The analyses of dose-response relations of smoking with Alzheimer’s disease and dementia from logistic (cross-sectional phase) and Cox (follow-up) regression models, in which smoking dosage was treated as an indicator variable, failed to show any significant effect (data not shown). The general picture of the associations (both cross-sectional and follow-up) shown in the table was not modified when blood pressure, stroke, and heart disease were controlled for in multivariate analysis or when stratification was made for family history.

All analyses were rerun, categorizing smoking into the three levels of never smokers, exsmokers, and current smokers, but again the general picture was confirmed.

All subjects alive at the end of the 3-year follow-up (95 nondemented and 16 demented smokers, 202 nondemented and 30 demented nonsmokers) were followed for another 2 years to assess mortality according to smoking and dementia status. While smoking in the nondemented group was not associated with greater

### TABLE 1. Characteristics of the 636 demented and nondemented individuals at baseline, the Kungsholmen Project, Stockholm, Sweden, 1989–1992

<table>
<thead>
<tr>
<th></th>
<th>Mean age (years)</th>
<th>Female sex</th>
<th>Education (&gt;7 years of schooling)†</th>
<th>Family history of dementia</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>No dementia (n = 438)</td>
<td>84.0 (5.3)‡</td>
<td>358</td>
<td>81.7</td>
<td>186</td>
<td>42.8</td>
</tr>
<tr>
<td>Dementia (n = 198)</td>
<td>85.0 (5.5)*</td>
<td>156</td>
<td>78.8</td>
<td>62</td>
<td>32.3**</td>
</tr>
<tr>
<td>Alzheimer's disease (n = 106)</td>
<td>85.0 (5.3)</td>
<td>85</td>
<td>80.2</td>
<td>38</td>
<td>37.6</td>
</tr>
</tbody>
</table>

* p < 0.05 and ** p ≤ 0.01, significantly different (Student's t or chi-square test) from nondemented.
† Three subjects with missing data among the nondemented and six among the demented (five with Alzheimer's disease) group.
‡ Numbers in parentheses, standard deviation.
prospective study, we found that smoking was negatively associated with prevalent Alzheimer’s disease and dementia in the cross-sectional phase, but this association disappeared with incident Alzheimer’s disease and dementia in the prospective phase.

These cross-sectional findings are in agreement with those of previous case-control studies showing an inverse association between smoking and prevalent Alzheimer’s disease (18–22). The hypothesis was that smoking has a protective effect on the development of Alzheimer’s disease. However, recall bias and differential survival can play a major role in such cross-sectional studies. Smoking exposure is usually assessed from two different sources, that is, the subject himself for the nondemented and an informant for the demented subjects. While assessment of exposure from nondemented subjects is by definition the gold standard, two contrasting phenomena cause great uncertainty in the assessment of exposure from demented subjects’ informants. On the one hand, the informant might not be sufficiently knowledgeable about the exposure of the proband and tend to underestimate it (40). On the other hand, the informant might be prone to identify plausible causes for the proband’s sickness, thus overestimating risky exposures (40). The net effect is hard to predict, but error variance in the assessment of exposure is doubtless increased.

Smoker mortality (age-, sex-, and education-adjusted hazard ratio = 0.8, 95 percent confidence interval 0.5–1.2), smoking in the demented group was associated with a significantly higher mortality risk (hazard ratio = 3.5, 95 percent confidence interval 1.4–8.8). The interaction effect between smoking and dementia proved significant ($p = 0.04$).

**DISCUSSION**

In this population-based cross-sectional and prospective study, we found that smoking was negatively associated with prevalent Alzheimer’s disease and dementia in the cross-sectional phase, but this association disappeared with incident Alzheimer’s disease and dementia in the prospective phase.

The prospective phase of the present study gave us the opportunity to reduce the effect of the biases illustrated above. Since only mentally intact subjects have been followed, smoking information was obtained from subjects themselves, thus avoiding the effect of informant recall bias. Moreover, the prospective design also allowed us to limit the effect of selective recall bias. The hypothesis was that smoking was significantly associated with prevalent Alzheimer’s disease ($p = 0.04$).

**TABLE 3. Relation between smoking and prevalent and incident Alzheimer’s disease and dementia, the Kungsholmen Project, Stockholm, Sweden, 1989–1992**

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dementia</td>
<td>343</td>
<td>84.0 (5.2)</td>
<td>81.3</td>
<td>182</td>
<td>53.4</td>
<td>46</td>
<td>18.7</td>
<td>34</td>
<td>0.9</td>
<td>12</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>232</td>
<td>84.3 (5.2)</td>
<td>90.1</td>
<td>137</td>
<td>59.6</td>
<td>29</td>
<td>17.9</td>
<td>24</td>
<td>10.3</td>
<td>6</td>
</tr>
<tr>
<td>Smokers</td>
<td>111</td>
<td>83.6 (5.1)</td>
<td>63.1***</td>
<td>45</td>
<td>40.5**</td>
<td>17</td>
<td>20.2</td>
<td>10</td>
<td>9.0</td>
<td>6</td>
</tr>
</tbody>
</table>

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mortality of demented smokers. A further control of this effect was provided by ascertainment of incident dementia cases also in those subjects who had died before follow-up examination. The prospective phase failed to confirm the protective effect of smoking on the occurrence of Alzheimer’s disease or dementia. These data are in agreement with those of the only other population-based prospective study in the literature concerning the topic (33). Other population-based prospective studies focusing on smoking in relation to cognitive impairment are also in line with our data (43, 44). The prospective study reporting a significantly protective effect (relative risk = 0.24) was carried out in a volunteer cohort. Such a cohort is not usually representative of the general population (30). Because of the small sample size of the present study, we cannot exclude smoking as a risk factor for Alzheimer’s disease or dementia, as Ott et al. (32) recently have reported.

In conclusion, the protective effect of smoking on Alzheimer’s disease or dementia is not confirmed by this study.

ACKNOWLEDGMENTS

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REFERENCES