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Interaction Between Genetic and Environmental Risk Factors for Alzheimer's Disease: A Reanalysis of Case-Control Studies

C.M. Van Duijn, D.G. Clayton, V. Chandra, L. Fratiglioni, A.B. Graves, A. Heyman, A.F. Jorm, E. Kokmen, K. Kondo, J.A. Mortimer, W.A. Rocca, S.L. Shalat, H. Soininen, and A. Hofman for the EURODEM Risk Factors Research Group

Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, The Netherlands (C.M.V.D., A.Ho.); MRC Biostatistics Unit, Cambridge, United Kingdom (D.G.C.); Neuroepidemiology Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland (V.C.); Departments of Neurology and Psychiatry, University of Florence and SMID Centre, Florence, Italy (L.F., W.A.R.); Battelle Research Center, Seattle, Washington (A.B.G.); Department of Neurology, Duke University, Durham, North Carolina (A.He.); Social Psychiatry Research Unit, Australian National University, Canberra, Australia (A.F.J.); Department of Neurology, Mayo Clinic, Rochester (E.K.), and Veterans Affairs Medical Center, Minneapolis (J.A.M.), Minnesota; Department of Public Health, Hokkaido University, Sapporo, Japan (K.K.); Department of Epidemiology, Yale University, New Haven, Connecticut (S.L.S.); Department of Neurology, University of Kuopio, Finland (H.S.)

To study the interaction among genetic and environmental risk factors, a reanalysis of case-control studies of Alzheimer's disease (AD) was conducted based on the original data of all studies carried out to January 1, 1990. Seven studies were included in the present analysis, comprising a total of 814 AD patients and 894 control subjects. When comparing those with a positive and negative family history of dementia, similar odds ratio were found for late maternal age [1.7; 95% confidence interval (0.6–4.8) vs. 2.0 (1.1–3.5)], head trauma [1.7 (0.7–4.2) vs. 1.9

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Address reprint requests to C.M. Van Duijn, EURODEM Risk Factors Research Group, Department of Epidemiology and Biostatistics, Erasmus University Medical School, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

(1.1–3.2)], and history of depression [2.0 (0.2–19.8) vs. 2.1 (0.8–1.7)]. This suggests a model in which these risk factors increase the risk for AD independent of family history of dementia. Among those with a positive family history of dementia, the odds ratios for family history of Down's syndrome [4.2 (0.9–20.0)] and of Parkinson's disease [3.3 (0.4–28.2)] tended to be higher than among those with a negative family history of dementia [2.6 (0.8–8.5) and 2.4 (0.8–7.0), respectively]. However, for both disorders the difference in odds ratio was not statistically significant. For history of cigarette smoking, there was no association to AD for those with no first degree relatives with dementia and an inverse relation with AD for those with a positive family history. Although in all analyses, family history of dementia remained significantly associated with AD in the absence of other factors, the odds ratio associated with family history of dementia tended to be lower for those with a positive smoking history, particularly for those with two or more affected relatives. These findings suggest that smoking may interact specifically with a genetically determined process.

Key words: Alzheimer's disease, case-control studies, heredity, risk factors

INTRODUCTION

Genetic factors play an important role in Alzheimer's disease (AD). In a considerable number of families the disease is inherited as an autosomal dominant disorder. However, AD is a disorder with a complex genetic etiology. The disease may be caused by a mutation in the amyloid precursor protein gene on chromosome 21 [Goate et al.,1991; Chartier-Harlin et al., 1991; Murrell et al.,1991; Hendriks et al., 1992; Mullan et al., 1992a], but this mutation is found in only a small proportion of all patients [Van Duijn et al., 1991a; Tanzi et al., 1992]. Genetic heterogeneity is further evidenced by studies suggesting linkage to chromosome 19 [Pericak-Vance et al., 1991] and chromosome 14 [Schellenberg et al., 1992; St. George-Hyslop et al., 1992; Van Broeckhoven et al., 1992; Mullan et al., 1992b]. Recently, a significant association was reported between familial and sporadic late-onset AD and the $\epsilon 4$ allele of the apolipoprotein E gene (APOE) localized on chromosome 19q13.2 [Strittmatter et al., 1993].

Although epidemiologic studies have shown familial aggregation of AD [Rocca et al., 1986; Jorm, 1990], the disease appears to occur sporadically in over 50% of the patients [Van Duijn et al., 1991c]. It has been suggested that sporadic AD may be attributed to environmental causes [Fitch et al., 1988; Farrer et al., 1989; Sadovnick et al., 1989]. Complex segregation analysis suggested that although there is evidence for a role of one or more major genes in AD, there is also evidence for multifactorial inheritance [Farrer et al., 1991; Van Duijn et al., 1993]. The amyloid precursor protein gene on chromosome 21 [Goate et al., 1991; Chartier-Harlin et al., 1991; Murrell et al., 1991; Hendriks et al., 1992; Mullan et al., 1992a] and the locus on chromosome 14 [Schellenberg et al., 1992; St. George-Hyslop et al., 1992; Van Broeckhoven et al., 1992; Mullan et al., 1992b] appear to be major dominant genes. For the APOE gene on chromosome 19 [Strittmatter et al., 1993; Corder et al., 1993], it remains to be determined whether it is a primary genetic cause, which by itself is sufficient to cause AD, or merely a genetic factor modulating the expression of the AD phenotype determined by an other genetic or environmental cause. Other factors that have been implicated in AD include family history of Down's syndrome, family history

of Parkinson's disease, late maternal age at birth, head trauma, depression, hyperthyroidism, smoking, aluminum, and education [Rocca et al., 1986; Jorm, 1990].

Little is known of the interaction between genetic and other putative risk factors for AD. The genotype and the risk factor may increase the risk of AD independently. It is also conceivable that the genotype may exacerbate the effect of the risk factor (or vice versa) or that the presence of both the genotype and the risk factor may be required to increase the risk of disease [Ottman, 1990]. Ottman [1990] has outlined a general epidemiologic approach to study gene-environment interaction and has suggested to use family history of disease in first degree relatives as a surrogate measure of genetic susceptibility in the absence of a genetic biologic marker. As misclassification in genetic susceptibility will occur when using family history, a large data set is required to study gene-environment interaction.

We have reanalyzed the original data of 7 case-control studies of AD to study the interaction between genetic and environmental factors using family history of dementia in first degree relatives as a measure of genetic susceptibility. The data we present here are based on a total of 814 AD patients and 894 control subjects.

MATERIALS AND METHODS

Study Population

For this study, all case-control studies of AD conducted before January 1, 1990, were traced through medline search, review papers, and personal contacts [Van Duijn et al., 1991b]. We only included studies in which the patients met the criteria for the clinical diagnosis of AD of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [McKhann et al., 1984] or the criteria of the American Psychiatric Association's [1980] Diagnostic and Statistical Manual of Mental Disorders for primary degenerative dementia. Thus, we identified 11 studies [Van Duijn et al., 1991b]. Four studies were not included in the present analysis: two studies because no data on family history of dementia were collected [French et al., 1985; Kokmen et al., 1991] and two other studies because the data had not been collected symmetrically for cases and controls, i.e., control subjects were interviewed personally, but the patient's history was obtained from an informant [Soininen and Heinonen, 1982; Kondo and Yamashita, 1990]. The 7 studies on which this analysis is based are summarized in Table I; the studies are ordered alphabetically by country and city of origin. An extensive description of the studies is given elsewhere [Van Duijn et al., 1991b].

Risk Factors

A great variety of risk factors have been studied in the 7 case-control studies. In this analysis of interaction among genetic and environmental factors we included only those factors which showed significant association with AD in the overall analysis. A second criterion to include a risk factor in the present study was that the number of exposed cases and controls should allow stratification by family history of dementia. Based on these criteria, we examined the interaction of family history of dementia with the following factors: family history of Down's syndrome and Parkinson's disease, late maternal age at birth, history of head trauma, history of depression, and history of smoking.

TABLE I. Description of Studies Included in the EURODEM Collaborative Reanalysis of Case-Control Studies of AD

Study[a]	No. cases	No. controls	Case selection; data collection
1. Australia, Sydney [Broe et al., 1990]	170	170	Hospital/GP; personal interview
2. Italy[b] [Amaducci et al., 1986]	116	97	Hospital; personal interview
3. The Netherlands, Rotterdam [Hofman et al., 1989]	198	198	Population; personal interview
4. United States, Bedford, MA [Shalat et al., 1987]	102	162	Hospital; mailed questionnaire
5. United States, Denver, CO [Chandra et al., 1987]	64	64	Hospital; personal interview
6. United States, Durham, NC [Heyman et al., 1984]	46	92	Hospital; personal interview
7. United States, Seattle, WA [Graves et al., 1990]	130	130	Hospital; telephone interview

[a]Reference of study is within brackets.
[b]Multicenter study in seven cities: Bari, Florence, Genoa, L'Aquila, Milan, Padua, Rome.

For each risk factor, we evaluated the comparability of measurement across studies as described earlier [Van Duijn et al., 1991b]. As to exposure definition, we restricted the analysis of family history to disorders in first degree relatives. For late maternal age, cases and controls in whom the mother was aged 40 years or over at birth were considered exposed. We included in the analysis of patient history only exposures occurring at least 1 year before the disease onset. For control subjects we defined the age of onset of the matched case as reference and we considered only exposure before this reference age. To reduce the possibility of recall bias, we restricted the analysis of history of head trauma to that involving loss of consciousness and of episodes of depression to that medically treated. Smoking history was analyzed as a dichotomous variable; we classified patients and controls as non-smokers if they had never smoked and as smokers if they had ever smoked before disease onset or the reference age.

Data Analysis

The raw data of all the case-control studies were available for analysis. The results we present here are based on a comparison of cases with population or neighborhood controls. The association between AD and the putative risk factors was assessed by the odds ratio as an estimate of the relative risk. All studies were matched for age and gender and we used conditional logistic regression to take the possible confounding by the matching variables into account [Schlesselman, 1982]. Although the matching varied across studies (case to control ratio: 1:2 in the United States, Durham, NC study and 1:1 in the other studies), the matched set always included only 1 AD patient. The likelihood function for conditional logistic regression analysis can then be reduced to that of the Cox proportional hazard model and we used the latter to perform the analysis [Breslow et al.,1978; SAS Institute, Inc., 1983]. To obtain conditional logistic regression coefficients from the Cox proportional hazard model, the case-control pairs/triplets were identified as one stratum and in this

stratum the case was indicated as the only failure in the matched set (event = 1 for cases; event = 0 for controls). The time variable was set at 1 for cases and at 2 for controls, thus the controls appeared to be censored at a time later than that of the cases. The 95% confidence intervals (CI) for the odds ratios are based on asymptotic standard errors (SE).

The analysis presented here differs from the analysis published earlier [Van Duijn et al., 1991b] in two aspects. First, in the earlier analysis stratification by family history was based on the family history of the case, ignoring the family history of the matched control [Van Duijn et al., 1991b]. For instance, if the family history for the case was positive, the matched case-control pair/triplet was considered to be familial even if the control subject(s) did not have any affected relatives [Van Duijn et al., 1991b]. Second, a difference with the earlier publications is that the present analysis is based on Ottman's [1990] strategy to study gene-environment interaction. According to this strategy, we defined those not exposed to the risk factor and without a history of dementia in first degree relatives as the reference category. Odds ratios were estimated 1) for those with a positive family history but not exposed to the risk factor; 2) for those exposed to the risk factor but without a family history of dementia; and 3) for those exposed to the risk factor having also a positive family history of dementia. If the genotype and the risk factor increase the risk of AD independently, the model predicts that genetic susceptibility and the risk factor will each increase the risk of AD in the absence of the other [Ottman, 1990]. If the risk factor modifies the risk of a disorder primarily of genetic origin, one would expect the risk for those exposed to the risk factor to be increased only in genetically susceptible individuals. Conversely, if the genetic factor modifies the risk of a disorder primarily of environmental origin, one would expect an increased genetic relative risk only among those exposed to the risk factor. Finally, if both the risk factor and genotype are needed to increase the risk of disease, an increased risk would be found only for those exposed to both factors.

Since family history is an imperfect measure of genetic susceptibility, we would not expect to observe such extreme results. Nevertheless, gene-environment interaction should imply *statistical* interaction between the effects of family history and risk factor, although large sample sizes may be necessary to reach statistical significance [Smith and Day, 1984]. Here we have interpreted statistical interaction in the multiplicative sense. To test for interaction, for each risk factor a single model was specified including 3 dummy variables. The first variable was set at 1 for those with a positive family history of dementia, the second was set at 1 for those exposed to the risk factor, and the third was set at 1 for those with a positive family history of dementia who were also exposed to the risk factor.

RESULTS

Of the 814 patients, 399 (49%) were men and 415 (51%) were women. The mean age at onset was 66 years [standard deviation (SD) = 11 years]. Three hundred five (38%) patients had 1 or more first degree relatives with dementia compared to 140 (16%) controls (odds ratio 3.5; 95% CI 2.6–4.6). Table II shows exposure frequencies and the odds ratios for all factors studied in this analysis. Smoking history was inversely associated with AD, whereas the other factors increased the risk of disease.

TABLE II. Overall Analysis of Risk Factors Included in the Study of Gene-Environment Interaction

Risk factor[a]	Exposure frequency Cases	Controls	Odds ratio (95% CI)[b]
Family history			
Dementia (1–7)	305/814	140/894	3.5; $P < 10^{-6}$ (2.6–4.6)
Down's syndrome (1–3,5,6)	20/588	7/615	2.7; $P = 0.003$ (1.2–5.7)
Parkinson's disease (2,3)	20/312	8/294	2.4; $P = 0.034$ (1.0–5.8)
Patient history			
Maternal age 40+ years (1–3,7)	47/446	28/446	1.7; $P = 0.051$ (1.0–2.9)
Head trauma (1–3,5,7)	60/622	35/622	1.8; $P = 0.009$ (1.1–2.7)
Depression (1,4)	15/273	12/378	1.7; $P = 0.189$[c] (0.8–3.9)
Smoking (1–7)	423/821	526/907	0.8; $P = 0.053$ (0.6–1.0)

[a]Studies (for numbers see Table I) with data available on this risk factor are within parentheses.
[b]Risk estimates may differ from estimates published earlier, since this analysis is performed within a subset of studies that have collected data on family history of dementia.
[c]Depression was significantly associated with AD in the overall analysis (odds ratio 1.8; 1.2–2.9; $P = 0.009$), when studies without family history data were included [Jorm et al., 1991].

Odds ratios for family history of Down's syndrome and family history of Parkinson's disease, stratified by family history of dementia, are given in Table III. In the absence of a family history of dementia, the odds ratio for those with a first degree relative with Down's syndrome (2.6; 0.8–8.5) and for those with a first degree relative with Parkinson's disease (2.4; 0.8–7.0) were increased although not statistically significant. For both risk factors the odds ratio tended to be higher for those with a positive family history of dementia, but there was no statistically significant evidence for interaction.

Table IV gives the odds ratios for late maternal age, history of head trauma, and history of depression, stratified by family history of dementia. The odds ratios virtually did not change when stratifying by family history of dementia, indicating that the risk for family history and these risk factors are multiplicative. For late maternal age, history of head trauma and the association to AD was statistically significant in the absence of a family history of dementia. Family history of dementia remained significantly associated with AD in the absence of the other risk factors.

Table V shows that for those with no family history of dementia there was no evidence for an association between smoking history and AD, as the odds ratio was close to unity and non-significant. For those with a positive family history, an inverse relationship was observed (0.6; 0.4–1.0). The high exposure frequency of smoking made it possible to stratify the data further by the number of affected first degree relatives (Table VI). The risk estimate for smoking history was most pronounced for those with 2 or more affected relatives. If we consider the odds ratio associated with

TABLE III. Interaction Between Family History of Dementia and Family History of Down's Syndrome and of Parkinson's Disease

Family history of		Family history of dementia −	Family history of dementia +	Test for interaction[a]
Down's syndrome	−	1[b] reference	3.3[b]; $P < 10^{-6}$ (2.4–4.4)[c]	
	+	2.6[b]; $P = 0.119$ (0.8–8.5)	13.8[b]; $P = 0.001$ (3.0–63.8)	
Odds ratio Down's syndrome within stratum of family history of dementia		2.6; $P = 0.119$ (0.8–8.5)	4.2; $P = 0.065$ (0.9–20.0)	$P = 0.620$
Parkinson's disease	−	1[b] reference	3.6[b]; $P < 10^{-6}$ (2.4–5.6)	
	+	2.4[b]; $P = 0.113$ (0.8–7.0)	12.0[b]; $P = 0.022$ (1.4–101.4)	
Odds ratio Parkinson's disease within stratum of family history of dementia		2.4; $P = 0.113$ (0.8–7.0)	3.3; $P = 0.271$ (0.4–28.2)	$P = 0.779$

[a]Comparison of odds ratio for risk factor for stratum family history − and family history +.
[b]Odds ratio derived from a single conditional logistic regression model.
[c]95% CI within parentheses.

TABLE IV. Interaction Between Family History of Dementia and Maternal Age, Head Trauma, and Depression

Risk factor		Family history of dementia −	Family history of dementia +	Test for interaction[a]
Maternal age 40+ years	−	1[b] reference	3.6[b]; $P < 10^{-6}$ (2.5–5.1)[c]	
	+	2.0[b]; $P = 0.028$ (1.1–3.5)	6.0[b]; $P = 0.001$ (2.1–16.9)	
Odds ratio maternal age 40+ years within stratum of family history of dementia		2.0; $P = 0.028$ (1.1–3.5)	1.7; $P = 0.329$ (0.6–4.8)	$P = 0.810$
Head trauma	−	1[b] reference	2.9[b]; $P < 10^{-6}$ (2.2–3.9)	
	+	1.9[b]; $P = 0.021$ (1.1–3.2)	5.0[b]; $P = 0.001$ (2.1–12.1)	
Odds ratio head trauma within stratum of family history of dementia		1.9; $P = 0.021$ (1.1–3.2)	1.7; $P = 0.223$ (0.7–4.2)	$P = 0.891$
Depression	−	1[b] reference	3.9[b]; $P < 10^{-6}$ (2.4–6.5)	
	+	2.1[b]; $P = 0.128$ (0.8–1.7)	7.9[b]; $P = 0.077$ (0.8–78.7)	
Odds ratio depression within stratum of family history of dementia		2.1; $P = 0.128$ (0.8–1.7)	2.0; $P = 0.549$ (0.2–19.8)	$P = 0.980$

[a]Comparison of odds ratio for risk factor for stratum family history − and family history +.
[b]Odds ratio derived from a single conditional logistic regression model.
[c]95% CI within parentheses.

TABLE V. Interaction Between Family History of Dementia and Smoking

Risk factor		Family history of dementia −	Family history of dementia +	Test for interaction[a]
History of smoking	−	1[b] reference	3.9[b]; $P < 10^{-6}$ (2.6–5.7)[c]	
	+	0.9[b]; $P = 0.397$ (0.7–1.2)	2.5[b]; $P < 10^{-6}$ (1.8–3.6)	
Odds ratio history of smoking within stratum of family history of dementia		0.9; $P = 0.397$ (0.7–1.2)	0.6; $P = 0.055$ (0.4–1.0)	$P = 0.228$

[a]Comparison of odds ratio for risk factor for stratum family history − and family history +.
[b]Odds ratio derived from a single conditional logistic regression model.
[c]95% CI within parentheses.

family history of dementia for those with 1 affected relative (not shown in table), the odds ratio among non-smokers was 3.0 (2.0–4.7) and among those with a positive smoking history was 2.5 (1.7–3.5). However, for those with 2 or more affected relatives, the odds ratio for family history was 1.9 times higher among non-smokers (10.9; 2.6–46.9) compared to those with a positive smoking history (6.0; 2.2–16.1).

DISCUSSION

This study shows that late maternal age at birth and a history of head trauma are associated with a statistically significant increase in the risk for AD in the absence of a family history of dementia. For those with a positive family history of dementia, an inverse association between the risk of AD and smoking history was found. There was no evidence for an association between history of smoking and AD for those with no first degree relatives with dementia. Family history of dementia remained significantly associated with AD regardless of the presence or absence of other risk factors.

The results of this reanalysis of case-control studies must be interpreted bearing the crude measurement of genetic susceptibility in mind. The use of family history of dementia as an indicator certainly incurs misclassification, which may have reduced the statistical power to show gene-environment interaction. Another issue is related to the finding that several genes may be implicated in AD. Due to genetic heterogeneity

TABLE VI. Risk for AD for Smoking Stratified by the Number of Relatives Affected With Dementia

History of smoking	No. affected relatives 0	No. affected relatives 1	No. affected relatives 2
−	1[a] reference	3.0[a]; $P < 10^{-6}$ (2.0–4.7)[b]	10.9[a]; $P = 0.001$ (2.6–46.9)
+	0.8[a]; $P = 0.227$ (0.6–1.1)	2.0[a]; $P = 0.002$ (1.3–3.0)	4.8[a]; $P = 0.002$ (1.8–13.2)
Odds ratio within stratum of family history of dementia	0.8; $P = 0.227$ (0.6–1.1)	0.7; $P = 0.066$ (0.4–1.1)	0.4; $P = 0.359$ (0.1–2.6)

[a]Odds ratio derived from a single conditional logistic regression model.
[b]95% CI within parentheses.

it is unlikely that we are able to assess a mechanism in which a gene exacerbates the effect of an environmental factor without increasing the risk for AD by itself. The predicted lack of association with AD for those with this gene but without the risk factor is likely to be blurred by the increase in risk for AD for those with a positive family history due to other genes having an independent effect. Consequently, the most important virtue of our study is perhaps the possibility to investigate the role of risk factors for AD in the absence of an increased genetic risk. Finally, despite the pooling of case-control studies, the sample size of this analysis may have been relatively small [Smith and Day, 1984], in particular for risk factors with a low exposure frequency. As loss of statistical significance within subgroups may be explained by loss of statistical power, we therefore chose to compare odds ratios in order to assess interaction rather than to test for statistical significance within or between subgroups.

For family history of Down's syndrome, family history of Parkinson's disease, late maternal age, history of head trauma, and history of depression, a consistent increase in risk for AD was observed across the individual case-control studies, although not always statistically significant [Van Duijn et al., 1991c; Mortimer et al., 1991; Jorm et al., 1991; Rocca et al., 1991]. The validity of these findings and the mechanism through which these risk factors may be implicated in AD have been discussed earlier [Van Duijn et al., 1991c; Mortimer et al., 1991; Jorm et al., 1991; Rocca et al., 1991; Clayton, 1991; Hofman, 1991]. In the analysis published previously, we did not take into account the family history of the control subject. Compared to the present analysis, the analysis published earlier showed odds ratios among those with a positive family history of dementia that were closer to unity and differed more from the odds ratios among those with a negative family history, in particular for late maternal age (1.3 and 2.7, respectively, in those with a positive and those with a negative family history) [Rocca et al., 1991] and head trauma (1.4 and 2.3, respectively) [Mortimer et al., 1991].

The present analysis showed that late maternal age and a history of head trauma are associated with a statistically significant increase in the risk for AD in the absence of a family history of dementia. For these risk factors as well as for history of depression, relative risks for those with and without a family history of dementia were very similar to each other and to those found in the overall analysis. This suggests that there is no evidence for interaction of these risk factors with the genotype, despite the loss of statistical significance within subgroups. These findings argue against the models in which 1) the risk factor merely exacerbates the genotype; and 2) the risk factor and the genotype are both required to increase the risk for AD. Since family history of dementia remained strongly associated with AD in the absence of other risk factors, the results are most consistent with a model in which the genetic factor and these risk factors increase the risk for AD independently.

The risk for AD for those with a family history of Down's syndrome as well as for those with a family history of Parkinson's disease tended to be higher when having a positive family history of dementia in addition. However, for both disorders the interaction was not statistically significant. Although risk of AD was increased for those with a positive and negative family history of dementia, none of the odds ratios was statistically significant. Due to the possibility of misclassification in genetic susceptibility and the rare occurrence of a positive family history of Down's syndrome and Parkinson's disease, no definitive conclusions can be drawn regarding the evi-

dence for gene-environment interaction and the AD risk associated with the presence of these disorders in relatives in the stratified analysis for family history of dementia.

An inverse association between AD and history of smoking was found in our data [Graves et al., 1991]. Though there is a possibility that older smokers, who eventually may have developed AD, are screened out of the case series due to conditions secondary to smoking [Van Duijn and Hofman, 1991; Graves et al., 1991], the inverse relation derives support from the finding that nicotine may improve information processing and attention in AD patients [Newhouse et al., 1988; Sahakian et al., 1989]. Two findings of our study suggest that smoking interacts specifically with a genetically determined process. First, in accordance with our earlier findings [Graves et al., 1991], for those with no family history of dementia there was no statistically significant association between smoking history and AD and the odds ratio for smoking was close to unity. Second, in the present analysis the association between history of cigarette smoking and familial AD tended be stronger with increasing number of affected first degree relatives. The odds ratio associated with family history tended to be lower in particular in those who had smoked and who had 2 or more affected relatives. The latter finding agrees with the delay in onset age observed in patients with a positive smoking history compared to non-smoking patients from families in which the disease is apparently inherited as an autosomal dominant disorder [Van Duijn and Hofman, 1991].

Our study suggests that several risk factors may increase the risk of AD independent of genetic susceptibility. These findings may have important implications for genetic-epidemiologic studies of AD. For instance, it will be important to take the influence of these factors into account in segregation and linkage studies of AD. Statistical evidence for gene-environment interaction was not obtained in our study. However, we recognize the possibility of misclassification in genetic susceptibility and in exposure to the risk factors as well as the relatively small sample size for studying interaction. These problems may be sufficient to account for our failure to find statistically significant evidence for gene-environment interaction. Prospective follow-up studies incorporating biologic markers of genetic susceptibility, such as APOE, would have a greater chance of success, but even then large studies would be required to demonstrate gene-environment interaction.

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