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Alcohol and Tobacco Consumption as Risk Factors for Alzheimer's Disease: A Collaborative Re-Analysis of Case-Control Studies

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A meta-analysis, involving the secondary analysis of original data from 11 case-control studies of Alzheimer's disease, is presented for alcohol consumption and cigarette smoking. Five studies were included in the meta-analysis of alcohol consumption. Alcohol consumption was computed in terms of average weekly intake, measured in ounces of 'pure alcohol'. This variable was categorized into tertiles to represent low, medium and high intake. Analyses showed no excess estimated risk of Alzheimer's disease for any level of alcohol intake. Smoking was analysed in three different manners: (1) lifetime prevalence of smoking (ever/never)—this included eight studies; (2) amount smoked (less than or equal to one pack per day versus more than one pack per day)—this included seven studies; and (3) pack-years—including four studies. A statistically significant inverse association between smoking and Alzheimer's disease was observed at all levels of analysis, with a trend towards decreasing risk with increasing consumption ($p_{(trend)} = 0.0003$). A propensity towards a stronger inverse relation was observed among patients with a positive family history of dementia, but the difference between this group and the group with no such history was not statistically significant. Although the observed disturbance in nicotinic receptor function in Alzheimer's disease may provide an explanation for these findings, possible biases related to the selection or survival of study subjects cannot be fully ruled out at this time. Prospective, community-based studies of incident cases of Alzheimer's disease are needed to document in detail the smoking history, age of onset of disease and survival of patients and cognitively intact people by smoking status.

INTRODUCTION

In this paper, the evidence for an association between alcohol consumption and Alzheimer's disease (AD), and cigarette smoking and AD is reviewed and a meta-analysis of original data collected from 11 case-control studies is presented.[1–11]

Alcohol

Since alcohol is a known cause of dementia,[12] heavy alcohol consumption that could result in cognitive deficits is used as an exclusionary criterion for the diagnosis of AD.[13,14] Because alcohol has neurotoxic properties[15] however, it has also been suggested as a putative risk factor for AD.[16] Furthermore, alcohol abuse has recently been associated with an accelerated rate of cognitive decline in Alzheimer patients.[17] Case-control studies have also examined the use of alcohol because of its potentially confounding effects with head trauma, a factor which has been shown to confer an increased risk for AD.[18]

Previous studies of the role of alcohol consumption in the aetiology of AD have shown no association, although one study[19] found a statistically significant inverse relation (unmatched odds ratio (OR) = 0.46,

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$0.01<p<0.025$). The Italian study[4] found matched odds ratios of 2.33 ($p = 0.34$) and 1.00 ($p = 1.00$) for drinking 0.5 litres or more of wine or spirits daily, in hospital and population controls, respectively. The USA, Durham study[2] found that patients were less likely than controls to have consumed beer (unmatched OR = 0.71) and liquor (unmatched OR = 0.54). These differences were not statistically significant. The frequency of wine drinking was similar in the two groups (unmatched OR = 1.05). No differences between cases and controls were observed in the USA, Minneapolis study[3] for items relating to alcohol consumption, which included frequency, amount and episodic drinking. Alcohol consumption was studied but the results were not reported in the USA, Denver study,[5] and thus are presented below.

Smoking

A reduced frequency of smokers among Alzheimer patients was reported as early as 1981.[20] The inverse association between smoking and Parkinson's disease (PD) is well known,[21–23] although its causal significance remains controversial.[24] Eight of the nine studies included in the current meta-analysis examined smoking as a putative risk factor for AD. The study that did not was based on a medical record review[7] which did not contain smoking histories.

Of the studies included in the meta-analysis, one found an inverse association between smoking and AD,[8] one found a positive association,[6] and the remaining seven observed no association. In the Netherlands study,[8] a strong inverse association (OR = 0.40, 95% CI: 0.20–0.80) was seen in patients with a history of familial aggregation of dementia; no association was found in those without such a history (OR = 1.2, 95% CI: 0.6–2.6). These investigators also found that the risk of AD decreased as the consumption of cigarette smoking increased.[8]

The USA, Bedford study[6] reported an odds ratio of 2.0 (95% CI: 0.9–4.3) comparing smokers to never-smokers. Here, an *increasing* estimated relative risk was noted with increasing consumption of cigarettes ($p_{(trend)} = 0.006$). This analysis of dose-response was based on categorized packs of cigarettes smoked, but did not incorporate the number of years of smoking. In this study, cases from a Veterans hospital were compared with neighbourhood controls selected from lists of registered voters. The participation rate for cases was 77%; for controls, 33%.[6] Since veterans may be expected to smoke more than the general population, and since smokers have been found to respond less frequently to questionnaires than non-smokers,[25] the positive result for smoking obtained in this study may be spurious.

Among other studies in the literature, one[26] demonstrated a greater consumption of cigarettes in cases versus controls, although these results were not statistically significant. Two studies have reported no association,[27–28] and two an inverse effect.[19,29] Jones[27] compared the medical records of 81 patients diagnosed with probable AD with interviews from 112 controls selected from a luncheon club and care home, and found no differences in the lifetime prevalence of smoking between the groups (OR = 1.58, $p = 0.75$). This finding might be due to the very different populations used for comparison and the different methods of obtaining data from cases and controls. A study by Barclay *et al*[28] found no differences in smoking habits between 39 probable AD patients and 39 spouse controls, but such small numbers lend little statistical power to detect an effect; the probability of finding an effect is further diminished by the choice of spouse controls, since couples tend to share indoor air and often, smoking habits.

Ferini-Strambi[19] recently reported an unmatched odds ratio for smoking prevalence of 0.47 (95% CI: 0.23–0.94) comparing 63 hospitalized patients with early onset AD to 126 neighbourhood controls. The methods used for control eligibility, ascertainment and data collection procedures among controls are unclear from this report. Patients hospitalized for AD may differ from neighbourhood controls in important ways. It is unclear whether an attempt was made to adjust for potential confounders, and, although each case was matched to two controls for several factors, no demographic data are given to examine the success of such matching; data were analysed without employing the 1:2 matching employed in the study design. Grossberg[29] compared the smoking histories of 144 AD patients (diagnostic criteria unspecified) with 96 controls obtained from various medical clinics (unspecified). Data for cases were obtained from surrogate respondents by telephone interview; control interviews appear to have been done in-person with the control. The (unmatched) odds ratio was 0.33 ($p<0.01$). Seventy-four per cent of the cases were female, compared with only 52% of the controls. Since men are more likely to smoke than women,[30] this finding is not unexpected. Additionally, controls may have been hospitalized for conditions related to smoking.

METHODS

Alcohol

Of the nine studies available for inclusion in the meta-analysis,[2–8,10,11] data for alcohol intake were available from six.[2–6,8] For a complete description of the methods used in each study, see van Duijn, Stijnen and Hofman

in this supplement.[31] Two of the three excluded studies did not collect data on alcohol intake; the first was a medical record review;[7] in the second,[11] a question was asked to assess alcohol problems in subjects, but no quantification of intake was sought. Data from the third study[10] were not yet available for re-analysis.

Of the six studies, one[6] was later excluded due to the lack of a reference category (non-drinkers could not be distinguished from light drinkers). Among the remaining studies, there was tremendous variability in the manner in which alcohol consumption was measured. Some of the studies had data for the amount of alcohol consumed, but not the duration of drinking. Data were gathered by grouping all alcoholic drinks as one category, or by collecting information separately for each type of alcohol (wine, beer, liquor). Several studies gathered categorical data while others obtained continuous data. The most standardized way of defining this variable that would allow the inclusion of the largest number of studies was the amount of 'pure alcohol' consumed in an average week.

The content of pure alcohol was taken to be, for beer: 5% (average 12 oz/drink), for wine: 10% (average 6 oz/drink) and for liquor 40% (average 1.5 oz/drink). Alcohol measured in millilitres was converted to ounces. For studies that did not distinguish the type of alcohol but instead asked for the number of all types of drinks, it was assumed that the 'average drink' contained 18% pure alcohol and that the size of the average drink was 6.5 oz (averages of the above figures).

For two studies,[2,4] categorical data were available on alcohol consumption, therefore, several assumptions were made. For the lowest category, it was assumed that average intake was half of the highest number of the category. For example, if the lowest category was '<3500 ml/week', this translated into less than 11.9 oz pure alcohol/week, and the value 5.95 was used. For an interval category, the midpoint was used. For the highest category, the conservative choice was made to use the lower end of the range. For example, '>one fifth'[2] translated into >10.24 ounces pure alcohol/week, and the value 10.24 was used.

For the studies[2,5,8] which asked separate questions on wine, beer and liquor intake, the pure alcohol value from each type of alcohol was summed for total average intake. In the Italian study,[4] questions were asked for all three types of alcohol, but each in a different way. Only the consumption of wine was quantified in a manner consistent with the definition employed here. Since wine is the most commonly consumed alcohol in Italy, it was thought that compatability with the other studies could be reasonably maintained if beer and liquor were not included in the analysis. An analysis was run on the liquor variable to justify such an exclusion; 7% of the cases and 5% of the controls consumed hard liquor 'very often' or 'every day'. This was not a statistically significant difference ($p>0.5$). Since the categories in the Italian data were not satisfactorily compatible with the other studies, analyses were conducted both including and excluding this study.

The studies that were included in the meta-analysis of alcohol consumption were those from Italy,[4] the Netherlands,[8] USA, Denver,[5] USA, Durham[2] and USA, Minneapolis.[3] Data were analysed in the manner described by van Duijn *et al* (this supplement[31]). For all variables, frequency distributions and contingency table analyses were conducted before performing conditional logistic regression analyses. The continuous alcohol variable that was created by conversion of the individual studies' questions to ounces of pure alcohol was categorized into a four-level variable (non-drinkers, <3.2 oz pure alcohol/week [low], 3.2–5.95 oz pure alcohol/week [moderate]; 5.96+ oz pure alcohol/week [high]) by dividing the frequencies among drinkers in the pooled control group into approximate tertiles. Each level of alcohol consumption was compared against the referent group of non-drinkers.

Analyses were conducted by computing risk estimates for each tertile of alcohol consumption; in addition, a test for trend in the three levels of alcohol consumption was performed by including the alcohol variable in the model as one parameter and testing the statistical significance of this term. Analyses were first carried out unadjusted for covariates. Regression models were then constructed which adjusted for family history of dementia, head trauma, education and smoking. All included studies were matched on age and gender, and no further adjustment was made for these factors.

Smoking

Eight studies were included in at least one of three levels of analysis for smoking. One study[7] did not collect data on smoking habits.

Information from eight studies was available on whether subjects had ever smoked in their lifetime. In general, this question was asked consistently from study to study. Data on amount smoked daily and duration of smoking was much more variable. Table 1 shows a list of data that were available from each study. Since the USA, Bedford study was the only study to find smoking to be a risk factor for AD, with increasing amount smoked conferring greater risk, analyses were conducted on the amount smoked in order to examine the effect of the USA, Bedford study on these pooled

TABLE 1 *Data on smoking available from eight studies included in the meta-analysis*

Study location	Ever smoked	Amount	Duration
Australia[10]	X		
Italy[4]	X	X (c)	X
Netherlands[8]	X	X (C)	X
USA, Bedford[6]	X	X (c)	
USA, Denver[5]	X	X (c)	
USA, Durham[2]	X	X (c)	*
USA, Minneapolis[3]	X	X (C)	X
USA, Seattle[11]	X	X (c)	X

*Duration in categorical form; duration used in pack-year meta-analysis only if collected in continuous form.
(C) Data collected in continuous form.
(c) Data collected in categorical form.

relative risks. Since the categories for the amount smoked differed from study to study, categories were collapsed at less than or equal to one pack per day versus more than one pack per day. The USA, Denver study was excluded from the analyses of amount smoked, since the lowest category of smoking was less than or equal to two packs per day.

Since the amount smoked was not considered to be a valid measure of dose, analyses were also conducted on the four studies which had continuous data on duration. The USA, Durham team[2] gathered data on duration by asking about the amount consumed at different age intervals (before age 20, between ages 20 and 39 and after age 40). Since it was not possible to compute the lifetime duration of smoking from these data, this study was excluded from the pack-years analysis. Pack-years were computed by multiplying the number of packs per day by the duration of smoking in years. This required categorizing the continuous variable for amount in two studies.[3,8] The pooled distribution of pack-years in the controls were categorized into tertiles of approximately equal frequencies. This formed a four-level variable of never-smokers, low (<15.5 pack-years), moderate (15.5–37.0 pack-years), and high (>37.0) exposure to cigarette smoking. As was done for alcohol, risk estimates were computed for each tertile of exposure, and tests for trend over exposure levels were performed. Effect modification of the relationship between smoking and AD by age of onset, education, gender and family history of dementia was explored. Analyses were conducted to examine the potential confounding effects of education, family history and previous history of head trauma.

RESULTS

Alcohol

Analyses were performed on the factored four-level variable for 'average weekly consumption of ounces of pure alcohol' for each individual study, and for the meta-analysis pooling these data. Exposure rates in cases were, for non-drinkers, 46%, for the lowest tertile, 13.2%, for moderate drinkers, 22.4%, and for the highest tertile, 18.4%. In controls, exposure rates were 45.6%, 12.5%, 24.7% and 17.2%, respectively. The conditional logistic regression results, unadjusted for covariates (Figure 1), show that for the overall estimates, the estimated relative risk is approximately 1.0 for the lowest and highest levels of consumption, with the intermediate level showing a relative risk of 0.70. All of the confidence intervals include 1.0.

Table 2 presents the results from the meta-analysis for the unadjusted alcohol variable and adjusted for different covariates. Analyses were performed including and excluding the Italian study. The inclusion of family history of dementia as a covariate changed the relative risks, but adjustment for smoking alone, education alone and both of these factors together had no effect on the relative risk estimates.

When the Italian study was excluded, a different trend in the risk gradient with increasing alcohol intake was apparent. Whereas a U-shaped curve was seen with the inclusion of this study, the estimated relative risk increased at the moderate level of alcohol intake when this study is excluded, creating the reverse effect. However, the relative risks are all fairly homogeneous in all of the analyses, and the overall conclusion must be one of no effect.

Smoking

Matched relative risks by individual study and for the pooled analysis for subjects' lifetime smoking status are presented in Table 3. With the exception of the USA, Bedford study, these results show a consistent trend towards an inverse relation between smoking and AD. The pooled analysis of these data, including the USA, Bedford data, demonstrates this effect to be statistically significant. In this latter analysis, 53% of cases and 59% of controls had smoked regularly at some time in their lives.

Table 4 presents the pooled findings for smoking at three levels of analysis. The first level (ever/never smoked) was conducted both including and excluding the USA, Bedford data, since the test for heterogeneity between studies suggested that these data were different from the rest of the studies (χ^2 for interaction term of USA, Bedford study by smoking status = 2.15, $p = 0.14$). The results show a statistically significant inverse association regardless of the inclusion of the USA, Bedford data; however, the effect is slightly stronger when those data are excluded. When the USA, Bedford data were analysed alone, the relative

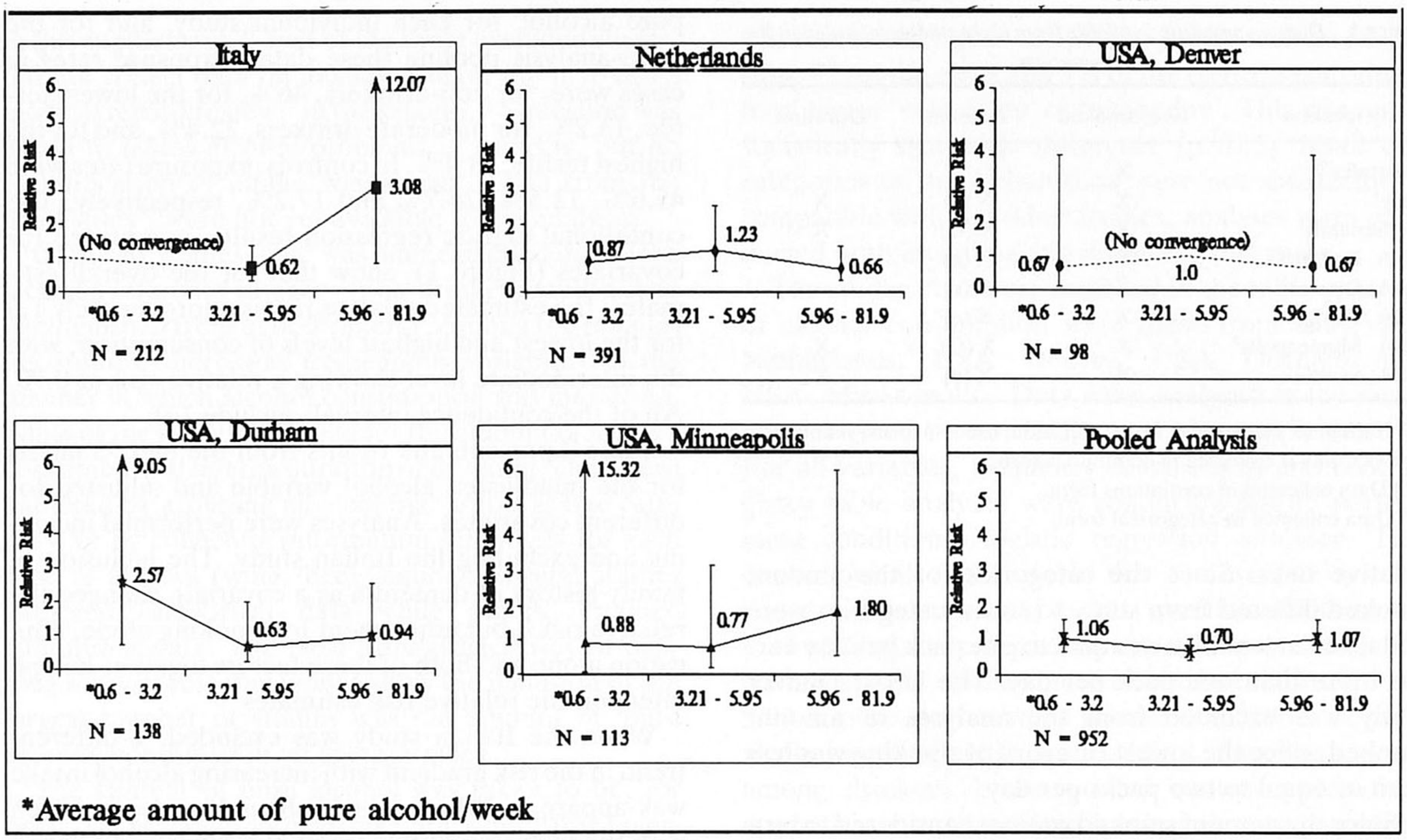

FIGURE 1 *Relative risks for average number of ounces of pure alcohol consumed per week, with 95% confidence intervals, by included study.*

risk showed the opposite association to the results from the pooled analysis. This was also true when the data were stratified on whether the case had a positive or negative family history of dementia. In the pooled analysis, smokers with a positive family history had a slightly lower estimated relative risk of AD than those without such a history (0.70 and 0.86 respectively) (Table 4), but neither of these estimates was statistically significant (although they were marginally so). When the USA, Bedford data were excluded from this stratified analysis, this effect was slightly stronger, and the relative risk for smoking given a positive family history of dementia was statistically significant (RR = 0.63, 95% CI: 0.41–0.94). It should be noted, however, that the confidence intervals in this analysis almost completely overlap and the risk estimates are not statistically different from one another.

The relative risks for the amount smoked (but not the number of years smoked) did not differ when the USA, Bedford data were included in the analysis, but a

TABLE 2 *Relative risks for meta-analysis for alcohol (in ounces pure alcohol per week), with 95% confidence intervals, unadjusted, adjusted for family history alone, and adjusted for family history, head trauma and education*

	Unadjusted	Adjusted for family history of dementia alone	Adjusted for family history of dementia, head trauma, and education
Including study numbers 3–6,8			
Low*	1.06 (0.68–1.64)	0.97 (0.59–1.60)	0.89 (0.59–1.47)
Moderate	0.70 (0.46–1.08)	0.75 (0.46–1.20)	0.82 (0.49–1.39)
High	1.07 (0.69–1.65)	0.89 (0.52–1.51)	0.95 (0.51–1.81)
Including study numbers 3,5,6,8			
Low	1.03 (0.65–1.61)	0.95 (0.56–1.61)	0.85 (0.48–1.50)
Moderate	0.98 (0.57–1.70)	1.02 (0.53–1.94)	1.48 (0.67–3.23)
High	0.80 (0.50–1.28)	0.68 (0.37–1.24)	0.68 (0.31–1.48)

*Low = 0.6–3.2 ounces pure alcohol/week; Moderate = 3.21–5.95 ounces pure alcohol/week;
High = 5.96 + ounces pure alcohol/week.

TABLE 3 *Relative risks for smoking (ever versus never) with 95% confidence intervals, unadjusted for covariates, for individual studies and for pooled analysis*

Study location	Exposure frequencies		Relative risk	95% confidence interval
	Cases	Controls		
Australia	80/168	89/169	0.79	(0.47–1.31)
Italy	51/116	52/97	0.60	(0.26–1.37)
Netherlands	99/197	110/197	0.73	(0.45–1.17)
USA, Bedford	85/102	127/161	1.53	(0.74–3.17)
USA, Denver	17/63	23/63	0.57	(0.24–1.36)
USA, Durham	25/46	50/91	0.97	(0.45–2.13)
USA, Minneapolis	54/78	37/48	0.50	(0.15–1.66)
USA, Seattle	66/129	75/129	0.73	(0.43–1.23)
Pooled analysis	477/899	563/955	0.78	(0.62–0.98)

TABLE 4 *Relative risks for smoking, and 95% confidence intervals, by three levels of analysis, including and excluding USA, Bedford study, with stratification by family history of dementia in cases for ever/never smoking status and pack-year analyses*

Unit of analysis	Study numbers included		
	2–6,8,10,11	2–5,8,10,11	6
Smoking (ever/never)*	0.78 (0.62–0.98)**	0.72 (0.56–0.92)	1.53 (0.74–3.17)
Positive family history† – cases	0.70 (0.48–1.04)	0.63 (0.41–0.94)	3.07 (0.60–15.60)
Negative family history – cases	0.86 (0.63–1.18)	0.81 (0.58–1.13)	1.24 (0.54–2.84)
Amount smoked	2–4,6,8,11	2–4,8,11	
<1 pack per day	0.84 (0.75–0.92)	0.80 (0.60–1.07)	
>1 pack per day	0.81 (0.53–1.27)	0.66 (0.44–1.00)	
p (trend)	0.11	0.02	
Pack-years	3,4,8,11		
1 <15.5	0.73 (0.50–1.09)		
2 15.5–37.0	0.63 (0.42–0.95)		
3 >37.0	0.50 (0.31–0.80)		
p (trend)	0.0003		
Postive family history – cases			
1 <15.5	0.53 (0.26–1.10)		
2 15.5–37.0	0.49 (0.24–1.02)		
3 >37.0	0.37 (0.17–0.81)		
p (trend)	0.11		
Negative family history – cases			
1 <15.5	0.85 (0.52–1.38)		
2 15.5–37.0	0.69 (0.39–1.22)		
3 >37.0	0.66 (0.33–1.34)		
p (trend)	0.11		

*Unadjusted.
**Relative risk for the specified unit of analysis and its 95% confidence interval.
†Family history of dementia.

trend was observed when these data were excluded ($p_{(trend)} = 0.02$) (Table 4).

Analyses of dose-response taking into account both the amount and the number of years smoked were carried out in four studies.[3,4,8,11] Table 5 presents the distribution of cigarette pack-years by gender and case-control status. The pack-year analyses show a decreasing trend in the estimated relative risk with increasing pack years consumed (p = 0.0003, Table 4). Additionally, the estimated relative risk of developing AD in people in the highest tertile of exposure (>37.0 pack-years) was 0.50 (95% CI: 0.31–0.80).

When the pack-year analysis was stratified by the case's family history of dementia, the inverse relation between smoking and AD was observed to be stronger among those with a positive history (Table 4). However, this trend of decreasing relative risk with increasing exposure to cigarette smoking was also evident in the stratum with a negative family history, although these estimates were no longer close to statistical significance. The strength of the trend was the same regardless of whether a family history of dementia was present or not (p = 0.11).

Analyses were conducted to examine potential effect modification by age of onset, education, gender and family history. The relative risk for the dichotomous smoking variable was, for early onset (<70) cases, 0.89 (95% CI: 0.67–1.19), and for late onset (⩾ 70) cases, 0.65 (95% CI: 0.43–0.96). These relative risks changed minimally when the USA, Bedford data were removed from the analysis (RR = 0.81, and 0.61 for early and late onset, respectively). Among early onset cases, the inverse effect of smoking was apparent only in familial cases, showing marginal statistical significance (RR = 0.60, 95% CI: 0.35–1.01); in sporadic cases, this relative risk showed no effect (RR = 0.99, 95% CI: 0.66–1.48). None of the other interaction

TABLE 5 *Distribution of smoking, in pack-years, from four studies (3, 4, 8, 11) by gender and case-control status, number and per cent*

	Males				Females			
	Cases	(%)	Controls	(%)	Cases	(%)	Controls	(%)
Never-smokers	51	(25.4)	26	(14.0)	160	(75.8)	137	(66.5)
Pack-years:								
<15.5	45	(22.4)	38	(20.6)	29	(13.8)	40	(19.4)
15.5–37.0	53	(26.3)	59	(31.9)	16	(7.6)	18	(8.8)
⩾37.0	52	(25.8)	62	(33.5)	6	(2.8)	11	(5.3)

parameters (education, gender, family history) improved the interpretation of the statistical models.

Various models were constructed for the three levels of analysis adjusting for education (family history of dementia and a history of prior head trauma were not associated with smoking). The relative risks for the pack-years analysis became somewhat stronger when adjusted for education [RR (95% CI): <15.5 pack-years: 0.68 (0.46–1.01); 15.5–3.70 pack-years: 0.58 (0.37–0.89); >37.0 pack-years: 0.49 (0.30–0.78)]. The difference between these estimates and the unadjusted figures is small, and the interpretation of the data remains the same.

DISCUSSION

Alcohol

Despite the suggestion of an inverse association noted in some studies examining the role of alcohol in the aetiology of AD,[2,19] no relation was found in the current meta-analysis. All of the studies included in the meta-analysis for alcohol consumption excluded dementia due to alcoholism in the differential diagnosis of AD[4,8] or as a specific exclusionary criterion.[2,3,5] If controls who were alcoholic were not excluded from eligibility in the same way as cases, the heaviest consumption of alcohol in cases may have been underestimated. Although the USA, Minneapolis study[3] excluded controls with alcoholism documented by previous treatment in the same way as cases were excluded, three other studies[2,6,8] do not mention specific exclusionary criteria related to alcohol consumption in potential controls. An additional two studies[4,5] chose controls with various diagnoses not likely to share risk factors with AD; the success of such selection for alcohol consumption is not known. Theoretically, the differential restriction of alcoholics in case and control selection could produce a risk estimate biased toward the null value. However, since alcoholic dementia is rare (3–4% of all dementias[14,32]), heavy alcohol consumers remain in the analysis. Thus, the potential underestimation of risk would not completely obscure an association if one existed.

The extreme variability among studies in the collection of data on alcohol intake required that the definition of alcohol intake in the pooled analysis be rather broad; this definition could not incorporate duration of drinking, binge drinking, and changes in drinking behaviour over the exposure period. The definition of intake used in the pooled analysis was able to take into account the type of alcohol consumed in those studies that discriminated between wine, beer and liquor, and the average amount and frequency of intake. Another limitation of the exposure definition was that many studies gathered categorical data, which demanded that certain assumptions be made regarding individuals' intake. The rather conservative approach of assigning the starting value for the highest category (e.g. 5.96 was assigned for the category of intake '>5.96 pure alcohol/week') may have resulted in an underestimation of the relative risk in the high exposure categories.

Smoking

In the pooled analysis of eight case-control studies, a statistically significant inverse association was observed between the lifetime prevalence of smoking and AD (RR = 0.78, 95% CI: 0.62–0.98). Analyses of dose-response, based on cigarette pack-years, were consistent with this association ($p_{(trend)} = 0.0003$). A statistically significant decreasing trend in risk with increasing amount smoked was not observed when the USA, Bedford study[6] was included in the analysis ($p_{(trend)} = 0.11$), but was observed when this study was excluded ($p_{(trend)} = 0.02$). Among early onset cases, the inverse association with smoking was evident only among those reported to have one or more relatives with dementia, and there was a suggestion of a stronger inverse trend among cases with a family history compared to those without such a history, but these relative risks were not statistically different from one another, and the statistical significance of the gradient was the same in each stratum ($p_{(trend)} = 0.11$).

The ability of meta-analysis to detect a subtle change in the estimated relative risk underscores its usefulness. While the observed inverse relation was not detectable in any one study alone, a trend is evident across studies (Table 3). Based on the observed number of discordant pairs, and assuming an alpha of 0.05 and a detectable relative risk of 0.72 (that observed in the pooled analysis), the statistical power for the pooled analysis of smoking (eight studies) was 82.6%, using the method of Schlesselman,[33] (p 162). Conversely, the individual studies' powers ranged from a low of 9% to a high of 20% to detect this relative risk, with a mean power of 14%. Although the meta-analysis affords the statistical power necessary to detect subtle changes in the relative risk, these findings should be interpreted cautiously, since the possibility that they are due to bias in subject selection or to factors related to differential survival in smokers versus non-smokers cannot, as yet, be completely ruled out.

If this association represents a veritable biological finding, mechanistic support could be found in the observed reduction in nicotinic binding site density in the cerebral cortex of AD patients.[34–36] The experimental introduction of nicotine produces an increase in

the number of nicotinic cholinergic recognition sites in the cerebral cortex.[37] Nicotine also stimulates the release of acetylcholine in the cortex.[38–39] Since the introduction of nicotine and AD have opposing effects on nicotinic receptors (nicotine upregulating these receptors and a reduction seen in AD), it could be postulated that, in smokers, the density of nicotinic binding sites may be greater than in non-smokers, thus protecting against, or retarding the onset of disease. If loss of cholinergic receptors (such as nicotinic receptors) is more severe in patients with a family history of dementia compared to those without such a history, the inverse association between smoking and AD would be stronger in this former group.

As in AD, reductions in nicotinic binding have been observed in Parkinson's disease (PD).[34] PD is frequently associated with cholinergic degeneration. An inverse association between smoking and PD has also been observed,[21,23,30,40–41] but the potential dose-response effect of smoking on the risk of PD remains unclear.[21,40,42]

Several methodological questions have been explored in further analyses in an attempt to interpret the observed inverse association between smoking and AD. First is the possibility that due to selective factors in these case-control studies, controls are more likely than cases to have smoked. Such spurious over-representation of smokers among controls in the meta-analysis is unlikely, since the analyses were limited to case-population control comparisons only, and, as pointed out earlier, such participating controls are actually *less* likely to smoke[25] than non-participating controls.

Although we cannot fully rule out the possibility of differential survival among cases and controls by smoking status, effective age matching eliminates this as a cause for concern in the interpretation of findings.[31]

An analysis examining the reported age of onset of AD in smoking versus never smoking cases revealed that smokers' onset was *earlier* than non-smokers (65.4 versus 68.4 years, respectively, $p<0.0001$). Stratification of this analysis by gender revealed no differences in males ($p = 0.33$), with the effect being limited to females ($p = 0.002$). Further analysis revealed that females who smoked were younger than females who never smoked among *both* cases and controls. Since smoking among women has become increasingly acceptable over time, the age of onset analyses among females was stratified by birth cohort (before 1900, 1900–1920, later than 1920). This resulted in the effect of age of onset washing out, indicating the probable existence of a generational effect.

Although the absence of a difference in age of onset between smoking and never-smoking male cases argues against cigarette smoking delaying disease expression, the Netherlands study[8] found that in families in which two or more AD patients were discordant for smoking, the smoking AD patient had onset an average of 4.2 years later than the non-smoking patient (personal communication, C M van Duijn). However, age of onset is known to vary within families which display autosomal dominant transmission,[43] and small numbers in the Netherlands study advise hesitation in drawing firm conclusions. This is clearly an area which merits further investigation using a prospective cohort design in which age of onset and smoking histories are more accurately documented.

The relative risk for the dichotomous lifetime prevalence of smoking stratified by age of onset (<70; 70+) was statistically significant for late onset cases (RR = 0.65, 95% CI: 0.43–0.96) but not in early onset disease (RR = 0.89, 95% CI: 0.67–1.19). Although these relative risks are not statistically different from one another, one might be tempted to imply that smoking is inversely related to AD only in late onset cases. As an alternative explanation, one should consider the possibility that older smokers who develop AD may be screened out from AD case series due to co-morbid conditions secondary to smoking. This differential process, which could operate passively (through death, through the tertiary care system and through participation procedures in epidemiological studies) or actively (though diagnostic exclusionary criteria for AD), could produce 'purified' older cases who smoke less than those who have AD but who have not been included in research studies for reasons related to their smoking. Although such a selection bias is unlikely to account entirely for the observed association between smoking and AD, it is a problem peculiar to case-control studies of AD and should be considered.

The results presented here for smoking are clearly preliminary and no conclusion can yet be drawn regarding the role that smoking may play, if any, in the aetiology of AD. Methodological issues are still at large. Even if these preliminary findings represent a valid biological phenomenon, the absolute risk incurred by smokers to develop chronic diseases such as cancer and cardiovascular disease clearly outweighs any 'advantages' of smoking.

CONCLUSION

A meta-analysis is traditionally thought of as a conglomeration of results from published reports. We have had the unique opportunity to conduct a secondary analysis of data from 11 case-control studies of

AD which examined the roles of alcohol and tobacco consumption in the aetiology of this disease. This analysis has been particularly fruitful in validating negative results from previous studies on a larger data set, in the case of alcohol consumption. An inverse association between smoking and AD has been observed for both lifetime prevalence of smoking and in dose-response analyses. While we can speculate on possible biological mechanisms for these findings, case-control studies using retrospective ascertainment procedures for gathering smoking histories and dating the onset of disease clearly leave room for a large degree of measurement error. Additionally, such studies are subject to selection biases in subject recruitment.

The conduct of prospective, population-based studies of incident AD cases will help to alleviate potential methodological deficiencies of case-control studies studying patients with prevalent AD. Such prospective investigations will be able to document patterns of survival in smokers and non-smokers who subsequently develop AD. They will increase the precision of documentation of smoking histories and the dating of the age of onset of cognitive deficits. Until prospective studies investigate the role that smoking may play, if any, in the aetiology of AD, the biological significance of the findings from the meta-analysis for smoking must be interpreted with significant caveats in mind.

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