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Occupational Exposures to Solvents and Lead 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 occupational exposures to solvents and lead. Three studies had data on occupational exposure to solvents. Among cases, 21.3% were reported to have been exposed; among controls, this figure was comparable (20.9%). This yielded a pooled matched relative risk of 0.76 (95% CI: 0.47–1.23). Four studies had data on exposure to lead. Exposure frequencies were 6.1% in cases and 8.3% in controls. This resulted in a pooled matched relative risk of 0.71 (95% CI: 0.36–1.41). The meta-analysis was particularly useful in validating negative results from individual studies and in increasing the statistical power for the analysis of lead exposure, where stratum-specific cell sizes were frequently smaller than five in individual studies. However, since exposure in the various studies was ascertained in a rather broad manner, prospective studies are recommended which focus on high-risk occupational populations and which determine the incidence of Alzheimer's disease in these and comparable unexposed populations.

INTRODUCTION

Occupational exposures to solvents and lead were one group of exposures considered in a meta-analysis of original data from 11 case-control studies of Alzheimer's disease (AD).[1–11] Exposure to occupational sources of aluminium as a specific risk factor of interest was not included in these analyses, since data for this variable were available from only one study.[2]

Solvents

Two studies[12–13] suggesting that an excess relative risk (RR) of presenile dementia is associated with industrial solvents have prompted other investigators to study this putative risk factor. A Swedish case-control study[12] selected industrial workers receiving a disability pension (151 cases receiving disability for mental or neuropsychiatric disorders, 248 controls receiving disability for reasons other than mental disorders). Exposure to 30 years or more in an occupation known to use organic solvents was five times more common in people with a diagnosis of presenile dementia in the disability record than in those without. However, the validity of the diagnosis and the general nature of exposure classification must be questioned in this study. A cohort study conducted by Mikkelsen[13] followed 2601 Danish painters and 1790 bricklayers for five years. The incidence of presenile dementia, diagnosed again from disability pensions, was 3.4 times higher in the painters, and no excess of other neuropsychiatric disease was observed. In reference to these studies, Henderson[14] has raised the issue that diagnosing physicians would probably not be blinded to exposure status. Consequently, diagnostic suspicion bias may play a role in the excess risks observed in these studies. Furthermore, the potential misclassification of

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exposure in painters, who are exposed to both solvents and lead, as well as other neurotoxic metals, advises cautious interpretation of these data.

Of the case-control studies included in the current meta-analysis, three[2,3,6] included information related to occupational solvent exposure. The USA, Bedford study[6] produced an odds ratio of 1.0 (95% CI: 0.5–1.9) for being exposed to solvents in any occupation. The USA, Durham study[2] did not find any differences between cases and controls with respect to exposure to solvents (relative risk not reported). The USA, Minneapolis study[3] reported an estimated RR for occupational solvent exposure of 1.25 (95% CI: 0.55–2.84).

Lead

The existence of neurobehavioural deficits as a consequence of exposure to inorganic lead is widely accepted.[15] In particular, heavy exposure to lead in the workplace has been associated with impaired memory, attention, concentration and psychomotor performance.[16] Due to the neurotoxicity of this metal, its ability to cause encephalopathy,[17] and case reports suggesting a neuropathological association between lead and AD,[18–19] several case-control studies have investigated it as a potential risk factor for AD.

In the USA, Bedford study,[6] the RR associated with ever working in a job involving the use of lead was 0.8 (95% CI: 0.3–2.0). In the USA, Durham and Denver studies,[2,5] no association was observed, and relative risk estimates were not reported. In the USA, Minneapolis study,[3] the estimated RR for ever being exposed to 'metals' in an occupation was 1.27 (95% CI: 0.55–3.00), comparing cases to hospital controls. Thus, no association between occupational exposure to lead and case-control status was observed in any of these studies.

METHODS

Solvents

Three studies had data available on occupational exposure to solvents.[2,3,6] In the USA, Bedford study,[6] the respondent was asked whether the subject worked in any job that involved the use of organic solvents. In the USA, Durham study,[2] respondents were asked whether the subject had ever been exposed to solvents during employment for ten hours or more per week for six months or longer. The USA, Minneapolis study[3] asked respondents whether the subjects had ever used solvents or degreasers on the job. These methods of ascertaining data on solvents were deemed to be sufficiently comparable and were thus included in the pooled analysis. No further level of detail on solvent exposure was sought. Conditional logistic regression models were used to obtain point estimates from each study separately and from the pooled data. Adjustment was made for education and smoking to test for confounding by these variables.

Lead

Four studies were included in these analyses[2,3,5,6] The question in the USA, Bedford study was the same as for the solvent question in that study. In the USA, Denver study,[5] a question on whether the subject was ever exposed to chemicals such as lead, mercury or arsenic was asked, and the specific chemicals requested. When this latter variable was coded for lead, it was used for the present analysis. The same method was used in the USA, Minneapolis study,[3] where the metal was specified and coded. In the USA, Durham study,[2] a similar question to the solvent question was asked for lead exposure. The analyses for lead were conducted in the same manner as was done for solvents.

RESULTS

Solvents

Relative risk estimates for the individual studies and pooled analysis are presented in Table 1. No association was observed between occupational exposure to solvents and AD. The frequency of exposure in cases was 21.3%; in controls, 20.9% with an unadjusted matched RR of 0.76 (95% CI: 0.47–1.23). When this estimate was adjusted for smoking and education, it was slightly higher (RR = 0.83, 95% CI: 0.50–1.39). Exposure to solvents was unrelated to a history of head trauma or family history of dementia.

Lead

Table 2 presents the findings for the analyses of occupational exposure to lead. Again, no association was observed. Exposure frequencies for lead were, for cases, 6.1%; in controls, 8.3%. The RR from the pooled analysis was 0.71 (95% CI: 0.36–1.41). This RR remained unchanged when adjusted for smoking and education (RR = 0.74, 95% CI: 0.37–1.47).

TABLE 1 *Relative risks for occupational solvent exposure (ever versus never), with 95% confidence intervals, for individual studies and for pooled analysis*

Study location	Exposure frequencies		Relative risk	95% confidence interval
	Cases	Controls		
USA, Bedford[6]	22/102	39/162	0.83	(0.44–1.55)
USA, Durham[2]	0/41	6/77	—*	
USA, Minneapolis[3]	25/78	15/48	0.92	(0.40–2.09)
Pooled analysis	47/221	60/287	0.76	(0.47–1.23)

*O cases exposed—model did not converge.

TABLE 2 *Relative risks for occupational lead exposure (ever versus never), with 95% confidence intervals, unadjusted, for individual studies and for pooled analysis*

Study location	Exposure frequencies		Relative risk	95% confidence interval
	Cases	Controls		
USA, Bedford[6]	18/101	16/161	0.72	(0.28–1.85)
USA, Denver[5]	1/42	5/50	0.25*	(0.03–2.24)
USA, Durham[2]	2/40	4/78	0.78*	(0.14–4.36)
USA, Minneapolis[3]	5/78	3/48	1.50	(0.25–8.98)
Pooled analysis	16/261	28/337	0.71	(0.36–1.41)

*Only one case exposed.

DISCUSSION

We have compared and combined data from case-control studies examining occupational exposures to solvents and lead as risk factors for AD, and have found no association for either factor. The meta-analysis was particularly useful for studying lead exposure, where the number of subjects in individual exposure strata was frequently smaller than five. Despite the fact that the occupational exposure questions were asked rather consistently between studies, how well these questions actually measure exposure (given that they are asked of a surrogate respondent and entail an 'ever/never exposed in any job' response) is not known. This method of exposure ascertainment may be subject to misclassification, most likely in the form of underestimation of exposure. Therefore, a negative finding for occupational exposures in AD from this meta-analysis does not confirm the absence of an association. For this reason, prospective studies are recommended which examine the incidence of AD in high-risk occupational populations exposed to various neurotoxins (e.g. solvents, lead, aluminium).

Some of the estimated relative risks reported from published papers differ from the figures presented here. Among these are the relative risks for solvent and lead exposure in the USA, Bedford study.[6] These differences are due to different ways of handling the varied number of controls per case in this study. Readers are referred to the paper on Methods[20] in this Supplement for an explanation on how this was done for the meta-analysis. The results of the USA, Minneapolis study[3] differ from the RRs presented here for solvents because the former comparison was made with hospital controls; the meta-analysis used only community-based population controls in those studies with two control groups. Additionally, the USA, Minneapolis study[3] reported results for all metals combined, whereas for the meta-analysis, data were made available for a specific analysis of lead exposure.

Finally, although many of the studies included occupation in their questionnaires, the degree of detail was so varied so as to exclude most of these studies from specific exposure comparison. Several studies, for instance, only included broad classification of occupation by industry type. The more detailed ascertainment of exposures of specific compounds in individual jobs would enhance the ability to compare results across studies and would facilitate pooling of data in future collaborative studies.

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