American Journal of Epidemiology

Vol. 135, No. 7
Printed in U.S.A.

Head Trauma and the Risk of Alzheimer's Disease

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A population-based case-control study of the association between head trauma and Alzheimer's disease was conducted in the Netherlands from 1980 to 1987. The study comprised 198 patients with clinically diagnosed early onset Alzheimer's disease and 198 age- and sex-matched population controls. Adjusted for sex, age, family history of dementia, and education, the odds ratio of a history of head trauma with loss of consciousness was 1.6 (95% confidence interval (CI) 0.8–3.4). The odds ratio for men was 2.5 (95% CI 0.9–7.0), and that for women was 0.9 (95% CI 0.3–2.8). The increase in odds ratio was limited to head trauma that occurred within the period of 10 years prior to the onset of dementia (odds ratio = 10.0; 95% CI 1.0–96.8). There was no evidence of effect modification by family history of dementia as measured on a multiplicative scale. However, the power to show interaction may have been low in this study. The authors' findings are compatible with the view that head trauma may be implicated in Alzheimer's disease, with a short lag time between the head trauma and the first symptoms of disease. The association needs to be confirmed in a prospective follow-up study to fully exclude the possibility of recall bias. *Am J Epidemiol* 1992;135:775–82.

Alzheimer's disease; case-control studies; dementia; head injuries

Repeated head trauma in boxers has been linked to dementia pugilistica (punch drunk syndrome) (1). In patients with this syndrome, neurofibrillary tangles, indistinguishable from those seen in Alzheimer's disease, are found (2). These findings have led to the hypothesis that head trauma may be implicated in Alzheimer's disease. In four case-control studies, a significant increase in the risk of Alzheimer's disease was observed for those with a history of head trauma (3–6). With the exception of two small studies (7, 8), each of the previous studies reported an excess of head trauma in patients with Alzheimer's disease, although no significant association could be established (9–14). Little is known of the mechanism through which head trauma may be implicated in Alzheimer's disease. Graves et al. (5) reported that the risk of Alzheimer's disease increased when the period between head trauma and the onset of disease decreased. Since other studies have been too small to consider the timing of the head trauma relative to the onset of disease, this inverse trend remains to be confirmed. Another issue to resolve is the interaction of head

Received for publication June 10, 1991, and in final form September 27, 1991.

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

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Supported by the Steering Committee for Research on Aging foundation, the Netherlands Organisation for Scientific Research, and the Eurodem European Community Concerted Action on Dementia.

The authors gratefully acknowledge the contribution of Prof. Dr. H. A. Valkenburg, Dr. W. A. Rocca, and Dr. H. W. ter Haar.

trauma with other risk factors for Alzheimer's disease, in particular, genetic factors.

The emphasis of this study on the relation between head trauma and Alzheimer's disease was on the lag time between the head trauma and disease onset and on the interaction of head trauma with other risk factors, i.e., family history of dementia, sex, and education.

MATERIALS AND METHODS

We studied 198 patients with Alzheimer's disease clinically diagnosed before age 70 years and 198 randomly selected healthy population controls matched for age and sex. Head trauma and other putative risk factors for Alzheimer's disease were assessed by a structured interview of the next of kin of the patient or control. Details of the study design have been published previously (15).

Patients and controls

For this study, patients in whom the diagnosis of Alzheimer's disease was made in the period January 1980 to July 1987 were eligible. The study was population based and was aimed at a complete case ascertainment in the two study areas, the four northern provinces of the Netherlands and the region of the city of Rotterdam. To obtain a full ascertainment of patients, we asked all nursing homes, psychiatric institutions, social-geriatric services, neurologists, and facilities for computed tomography in the specified areas for patients with dementia. The patients were seen by three of us (T. A. T., R. H., and W. S.), who independently confirmed the diagnosis of probable Alzheimer's disease by a standard protocol similar to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (16). Dementias other than Alzheimer's disease (e.g., multi-infarct dementia and dementia secondary to alcoholism, depression, metabolic disorder, and other conditions) were excluded on the basis of the clinical history, neurologic examination, and neuropsychologic and laboratory tests. All patients had a typically slow progressive decline of intellectual function (16), a score of more than 0.5 on the Clinical Dementia Rating scale (17), a score of less than 20 (out of 30) on the Short Portable Mental Status Questionnaire (18), and a score of seven or less on the Hachinski scale (19). None of the patients had evidence of abnormalities on computed tomography other than cerebral atrophy or of focal dysfunction on electroencephalography. Information was available for 198 patients, that is, 98 percent of the 201 patients eligible for this study.

For each patient, a reference subject was selected, matched for age (within 5-year age groups), sex, and place of residence. These controls were drawn randomly from the population register of the municipality of the patient at the time of diagnosis. None of the controls showed evidence of dementia as defined by a Short Portable Mental Status Questionnaire score of 20 or lower. For controls, the first person asked consented in 103 cases (52 percent), in 68 (34 percent) the second person selected consented, in 23 (12 percent) the third, and in four (2 percent) the fourth.

Data collection

We assessed data on head trauma and other putative risk factors for Alzheimer's disease by a structured interview. Because of the cognitive decline of the patients, the history was taken from the next of kin of the patient. To assure symmetry in data collection, we also interviewed next of kin for the controls. For 174 cases (88 percent) and 188 controls (95 percent), the informant was the spouse or an adult child. As etiologic factors were studied, questions referred to exposure of the patient before the age of onset of dementia. Age of onset of Alzheimer's disease was estimated as the age at which memory loss or change in behavior was first noted by the next of kin or any other relative. For controls, a "reference age" was defined based on the age of onset of Alzheimer's disease in the matched case. Head trauma was assessed in closed ques-

tions with additional open-ended questions about 1) loss of consciousness and duration of unconsciousness; 2) age at the time of the head trauma; 3) circumstances surrounding the event; and 4) medical treatment.

Full pedigree information on dementia was obtained as part of the structured interview (15). To increase the validity of these data, we verified the information about the family history through an additional interview with a first-degree relative. If the patient had been admitted to the hospital, the diagnosis was checked in independent medical records. Patients were considered to have a positive family history of dementia when there was at least one first-degree relative with dementia.

Data analysis

We have restricted the analysis to head injuries with loss of consciousness. The duration of the unconsciousness varied from 1 minute to 2 hours. According to the informants, all patients had regained normal intellectual cognitive function after the head trauma. We assessed the strength of the association between head trauma and Alzheimer's disease by the odds ratio as an estimate of the relative risk. Conditional logistic regression analysis was used to take the matched design into account (20). The odds ratio was estimated by maximum likelihood, and the 95 percent confidence interval was based on the asymptotic standard error. Possible confounding by family history of dementia and education was adjusted for by adding these variables to the conditional logistic regression model. To control for bias which may result from the fact that cases and controls were not matched for informant, we performed a separate analysis based on the 111 matched case-control pairs that were concordant for informant. The results of this analysis were very similar to those of the overall analysis and did not change any of the conclusions. Modification of the relation between head trauma and Alzheimer's disease by sex and education was studied by stratified analysis. For family history of dementia, interaction was tested as described by Ottman (21). Those without a head trauma and without a family history of dementia were taken as a reference category. Risks were then estimated simultaneously for those with a head trauma but without a family history of dementia, those with a positive family history but without a head trauma, and those with a head trauma as well as a positive family history.

RESULTS

Of the 198 patients, 74 were male and 124 were female. The mean age at onset was 56.8 years (standard deviation (SD) = 5.3), and the mean age at diagnosis was 61.1 years (SD = 4.5). Table 1 shows that 96 patients (48 percent) had one or more first-degree relatives with dementia compared with 37 controls (19 percent) (15). The odds ratio adjusted for education was 4.9 (95 percent confidence interval (CI) 2.8–8.4). Adjusted for family history of dementia, the odds ratio for those with less than 7 years of education was 1.7 (95 percent CI 1.1–2.7).

There was a nonsignificant increase in risk (odds ratio (OR) = 1.3; 95 percent CI 0.7–

TABLE 1. Family history of dementia* and education in 198 patients with clinically diagnosed Alzheimer's disease and 198 age- and sex-matched controls, the Netherlands, 1980–1987

Variable	Yes	No	OR†	95% CI†	OR‡	95% CI
Family history						
Cases	96	102	4.5	2.7–7.7	4.9	2.8–8.4
Controls	37	161				
<7 years education						
Cases	112	86	1.4	0.9–2.1	1.7	1.1–2.7
Controls	88	110				

* In first-degree relatives.
† Odds ratio (OR) with 95% confidence interval (CI).
‡ OR adjusted for dementia in first-degree relatives and education.

2.6) for those with a history of head trauma with loss of consciousness (table 2). When we restricted the analysis to case-control pairs that were concordant for informant, the risk estimate was virtually unchanged (OR = 1.4; 95 percent CI 0.5–4.1). In the overall analysis, the odds ratio for head trauma adjusted for family history of dementia and education was 1.6 (95 percent CI 0.8–3.4). When the data were stratified according to sex, an increase in risk was observed only in men (p value for interaction = 0.17). There was no evidence of effect modification by education (p value for interaction = 0.56).

The mean period of time between the occurrence of the head trauma and the onset of dementia or the reference age was 16.8 years (SD = 16.3) for patients and 29.9 years (SD = 12.9) for controls. Stratification for the time lag until the onset of Alzheimer's disease showed that those with a head trauma within 10 years before the occurrence of Alzheimer's disease had eight times the chance of having Alzheimer's disease (table 3). The odds ratio was 3.0 (95 percent CI 0.3–28.8) in women. In men, five cases and no controls had a head trauma within 10 years before disease onset (p = 0.03). There was no significant increase in odds ratio for head trauma that occurred more than 10 years before the disease onset or the reference age in men (OR = 1.2; 95 percent CI 0.3–4.7) or in women (OR = 0.4; 95 percent CI 0.1–1.7).

Table 4 shows the interaction with family history of dementia. For those with a head trauma and a first-degree relative with dementia, there was a ninefold risk of Alzheimer's disease. On a multiplicative scale, there was no evidence of effect modification by family history (p = 0.90). The odds ratio for head trauma was 1.7 (95 percent CI 0.8–4.0) for those without a first-degree relative

TABLE 2. Head trauma with loss of consciousness in 198 patients with clinically diagnosed Alzheimer's disease and 198 age- and sex-matched controls, the Netherlands, 1980–1987

	Head trauma		OR*	95% CI*	OR†	95% CI	OR‡	95% CI
	Yes	No						
All (n = 198)								
Cases	22	176	1.3	0.7–2.6	1.8	0.8–3.8	1.6	0.8–3.4
Controls	17	181						
Men (n = 74)								
Cases	16	58	2.0	0.8–5.0	2.7	1.0–7.4	2.5	0.9–7.0
Controls	9	65						
Women (n = 124)								
Cases	6	118	0.8	0.3–2.2	1.0	0.3–3.2	0.9	0.3–2.8
Controls	8	116						

* Odds ratio (OR) with 95% confidence interval (CI).
† OR adjusted for dementia in first-degree relatives.
‡ OR adjusted for dementia in first-degree relatives and education.

TABLE 3. Timing of head trauma with loss of consciousness relative to onset of dementia in 198 patients with clinically diagnosed Alzheimer's disease and 198 age- and sex-matched controls, the Netherlands, 1980–1987

Timing of head trauma relative to onset*	No. of		OR†	95% CI†	OR‡	95% CI	OR§	95% CI
	Cases	Controls						
No head trauma	176	181	1.0	Reference	1.0	Reference	1.0	Reference
Head trauma ≤10 years before	8	1	8.0	1.0–64.0	8.8	1.0–76.9	10.0	1.0–96.8
Head trauma >10 years before	12	15	0.8	0.3–1.8	1.0	0.4–2.6	0.9	0.4–2.2

* Data are missing for two cases and one control.
† Odds ratio (OR) with 95% confidence interval (CI).
‡ OR adjusted for dementia in first-degree relatives.
§ OR adjusted for dementia in first-degree relatives and education.

TABLE 4. Head trauma with loss of consciousness and Alzheimer's disease, effect modification by family history of dementia in first-degree relatives, the Netherlands, 1980–1987

Component	No. of		OR*	95% CI*	OR†	95% CI
	Cases	Controls				
Head trauma – Family history –	89	147	1.0	Reference	1.0	Reference
Head trauma – Family history +	87	34	4.7	2.7–8.1	4.9	2.8–8.6
Head trauma + Family history –	13	14	1.7	0.8–4.0	1.5	0.6–3.6
Head trauma + Family history +	9	3	9.2	1.8–48.3	9.5	1.8–48.8

* Odds ratio (OR) with 95% confidence interval (CI).
† OR adjusted for education.

with dementia and 2.0 (95 percent CI 0.4–10.0) for those with a positive family history. The risk estimates did not change materially when adjusted for education.

DISCUSSION

In this study, the association between Alzheimer's disease and head trauma with loss of consciousness was confined to head trauma that occurred within a period of 10 years before the onset of dementia. Although overall no relation could be established in women, there was an excess of head trauma among female patients within this 10-year period compared with controls. The association was not modified by family history of dementia, as measured on a multiplicative scale.

Ten previous studies consistently showed a higher frequency of head trauma in patients with Alzheimer's disease than in controls (3–6, 9–14). Four studies reported the risk of Alzheimer's disease to be significantly elevated (3–6). Pooling of the data from all formal case-control studies of head trauma with loss of consciousness showed a significant association (OR = 1.8, 95 percent CI 1.3–2.7) (4, 5, 9, 10, 12, 13, 15, 22). It is important to note that in the only prospective follow-up study based on data obtained from medical records of the Rochester register (12) a slight elevation in risk of 1.3 ($p = 0.70$) was reported, similar to the unadjusted risk observed in our study. Family history of dementia, however, was not assessed as a putative confounder in the Rochester study, and the data did not allow stratification by timing of the head trauma relative to the onset of disease. In the reanalysis of case-control studies, the association between Alzheimer's disease and head trauma could be established only in men (22). Although the association was strongest for head trauma that occurred within 10 years before disease onset, a significant elevation in risk (OR = 1.6; 95 percent CI 1.0–2.6) was also observed for head trauma that occurred more than 10 years before the onset of disease (22). Such an inverse trend had been shown earlier by Graves et al. (5), who reported an association between Alzheimer's disease and head trauma (with or without loss of consciousness) that occurred 1–9 years (OR = 9.7; 95 percent CI 1.1–83.3) and 10–29 years (OR = 5.0; 95 percent CI 1.3–9.8) before the onset of disease. In contrast, our study of head trauma with loss of consciousness suggests that the risk of Alzheimer's disease was increased only within the 10-year period before the onset of disease. The finding of this association in men and women argues against effect modification by sex. Regarding the interaction with family history of dementia, it has been suggested that head trauma plays a role only in those who are genetically susceptible (23), while others have reported that environmental factors such as head trauma may be associated with sporadic Alzheimer's disease

rather than with the familial form of the disease (22, 24). Using family history of dementia as an indicator for genetic susceptibility (21), we observed a similar odds ratio for Alzheimer's disease in those with and those without an increased genetic risk. This suggests that head trauma may influence the risk of Alzheimer's disease in those who are not genetically susceptible and that there is no evidence for synergy or antagonism in a multiplicative model. One may argue, however, that the power to show interaction in our study has been low.

The type of study reported here may suffer from bias. A first problem to be discussed is recall bias. Since relatives of patients may be eager to find an explanation for the disease of the patient, they may overreport the exposure to factors, such as head trauma, that are thought to be associated with the disease. We have therefore restricted the analyses to severe head trauma with loss of consciousness. These events are less vulnerable to recall bias since it is unlikely that relatives of patients report serious events that did not occur and that relatives of controls have forgotten such a severe head trauma. A second methodological problem to be discussed concerns the diagnosis of Alzheimer's disease, which in most cases was based on clinical data. Although we firmly applied the criteria for the clinical diagnosis of Alzheimer's disease and the diagnosis was confirmed in all 10 cases on whom an autopsy was performed (15), misclassification may have occurred in disease status in some cases. This type of misclassification tends to diminish a true association. Misclassification may also bias the comparison of sporadic and familial Alzheimer's disease. In the absence of a genetic marker for population studies (25), we have classified the patients on the basis of their family history of dementia, assuming that Alzheimer's disease in those with a positive history is most likely of primarily genetic origin and that the disease in those with no first-degree relatives with dementia is most likely of primarily environmental origin. Indeed, relatives of patients without a family history may carry the gene and express the disease later in life, whereas familial aggregation of Alzheimer's disease may be due to clustering of nongenetic disease. This has perhaps led to nondifferential misclassification (21), which may have reduced the power to show effect modification. To avoid the possibility of selection bias, we endeavored to make case selection population-based in the two study areas. Although selection may have occurred in the control series because of the higher nonresponse compared with cases, it is unlikely that this was associated with a history of head trauma.

Two interpretations of a relation between recent head trauma and Alzheimer's disease are possible: 1) the head trauma may be a consequence of an early stage of the dementia; and 2) head trauma may be implicated in the pathogenesis of Alzheimer's disease. To validate the first explanation, there is evidence of an increase in risk of head trauma and falls for Alzheimer patients compared with subjects who were not demented (26–28). It is difficult in a case-control study to distinguish events preceding or following the onset of disease, in particular when studying a disorder such as Alzheimer's disease in which the age at onset is not easily assessed. However, we questioned relatives extensively about symptoms of the disease prior to the occurrence of the head trauma and excluded those patients with changes in behavior or memory loss before the head trauma occurred.

The second explanation, that head trauma may lead to Alzheimer's disease, is supported by the finding of the Alzheimer-type neurofibrillary degeneration in patients with dementia pugilistica (2, 29). This type of pathology has been associated with repeated head trauma in boxers (1, 30). Recent studies of patients with dementia pugilistica have also shown diffuse cortical plaques identical to those found in Alzheimer's disease (31–33). Because of the similarity in pathology, a common pathogenesis of Alzheimer's disease and dementia pugilistica has been suggested (1, 2). The mechanism through which head trauma may be implicated in dementia is still unclear. Head trauma may induce changes in the blood-brain barrier, which

may lead to Alzheimer's disease (1, 3). On the other hand, it is conceivable that head trauma may cause rupture of brain vessels, which are already weakened by amyloid deposits (1). Thus, the trauma may trigger a subclinical pathologic process and provoke early onset of dementia. This hypothesis is supported by the finding of an earlier onset of disease in patients with a history of head trauma (34, 35) and by the short lag time between the head trauma and disease onset observed in the present study.

Although the findings of our study are compatible with a role of head trauma in early onset Alzheimer's disease, we interpret our results with caution. Despite the apparently consistent findings of case-control studies (22), we cannot exclude the possibility that all studies may have been biased in a similar way. The validity of case-control studies of Alzheimer's disease conducted to date is limited by the possibility of confounding by recall bias and selection bias. For determination of the etiologic significance of the relation between head trauma and Alzheimer's disease, the association needs to be confirmed in a prospective follow-up study.

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