

Head Trauma as a Risk Factor for Alzheimer's Disease: A Collaborative Re-Analysis of Case-Control Studies

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A re-analysis of the data from 11 case-control studies was performed to investigate the association between head trauma and Alzheimer's disease (AD). To increase comparability of studies, exposures were limited to head trauma with loss of consciousness (hereafter referred to as 'head trauma') and comparisons were restricted to community (versus hospital) controls. Test for heterogeneity across studies was negative; consequently, data were pooled in subsequent analyses. The pooled relative risk for head trauma was 1.82 (95% confidence interval: 1.26–2.67). Stratified analyses showed stronger associations in cases without a positive family history of dementia and in males (versus females). Adjustment of the pooled relative risk for family history of dementia, education and alcohol consumption did not alter significantly the association between head trauma and AD. There was no interaction effect between head trauma and family history of dementia, suggesting that these risk factors operate independently. Mean age of onset was not significantly different in cases with a history of head trauma compared to cases without such a history. The findings of the pooled analysis support an association between reported head trauma and AD.

INTRODUCTION

Several exposures are known to be capable by themselves of precipitating dementia syndromes. These include severe head trauma, acute infections, and excessive use of alcohol and drugs. Although we know that these factors can cause irreversible cognitive deficits, their role in the aetiology of Alzheimer's disease (AD) is less clear. In this paper, we review the evidence for an association between head trauma and AD, and present findings from a meta-analysis of original data collected in 11 case-control studies of AD.^{1–11}

Head trauma has been linked with pathologically-confirmed AD in several individual case reports.^{12–16} The degree to which these associations can be explained as chance coincidences is unknown. The

case of a steelworker who developed Alzheimer's disease eight years after a severe head trauma at age 22¹⁶ is perhaps the most difficult to dismiss. The extremely low incidence of AD at age 30 and the absence of a family history of dementia in this case increases the likelihood that trauma may have played a significant aetiological role.

The most well-established association between head trauma and degenerative neurological disease is the syndrome of dementia pugilistica that can follow a career of professional or amateur boxing.¹⁷ This syndrome, which usually is only mildly progressive following cessation of boxing,¹⁸ is associated pathologically with an accumulation of neurofibrillary tangles in the cerebral cortex and brainstem.¹⁹ The other primary lesion of AD, the senile plaque, had been considered to be absent in this condition. However, a recent paper by Roberts *et al*,²⁰ in which they re-analysed slides from dementia pugilistica cases using modern immunocytochemical methods, demonstrated an accumulation of beta amyloid protein comparable to that seen in AD, accompanied by the formation of

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diffuse senile plaques. Other similarities between dementia pugilistica and AD include atrophy of cells in the nucleus basalis of Meynert and loss of cortical cholinergic markers.²¹ Thus, these two conditions appear to have more similarities than believed previously.

Table 1 summarizes the findings of eight published, pair-matched case-control studies of AD^{2-6,9,22,23} for which data on head trauma exposure were available. Three of these studies found a significant positive association with head trauma, two for comparisons with community control subjects,^{2,9} and one for comparisons with hospital controls, but not commonly controls.³ All but one of these studies reported odds ratios in excess of 1.0; none demonstrated an inverse association.

In addition to the studies listed in Table 1, two studies in which cases and controls were frequency-matched by age and sex have been reported. Soininen and Heinonen¹ compared 63 institutionalized patients with AD with a mixed control group of 33 individuals residing in institutions and 58 living in the community. They reported that 6 cases and 13 controls had a history of head injury (odds ratio = 0.6). Paschalis *et al*²⁴ reported the findings of a case-control study with 103 AD patients and 90 community controls. The odds

TABLE 1 Odds ratios, statistical significance ($p < 0.05$) and power for head trauma in previously published, matched case-control studies of Alzheimer's disease

Study	Matching	Odds ratio	Statistical significance	Power*
Heyman <i>et al</i> 1984	gender, age	5.3	S	0.155
Mortimer <i>et al</i> 1985	gender, age, race, residence	2.8 (4.5)**	NS (S)**	0.296
Amaducci <i>et al</i> 1986	gender, age, residence	2.0 (3.5)**	NS (NS)**	0.155
Chandra <i>et al</i> 1987	gender, age, race, informant relationship	6.0	NS	0.127
Shalat <i>et al</i> 1987	gender, age, residence	2.4	NS	0.127
Chandra <i>et al</i> 1989	gender, age, race, residence	1.2	NS	0.155
Graves <i>et al</i> 1990	gender, age, informant relationship	3.0	S	0.405
Ferini-Strambi <i>et al</i> 1990	gender, age, residence, education	1.0	NS	0.140
Mean Power*				0.195

*Power to detect an odds ratio of 2.0 with an alpha level of 0.05.

**Items in parentheses are for case-hospital control comparisons. All other comparisons are with community controls.

ratio for prior head trauma was 2.7, which was not statistically significant.

A major concern in interpreting the findings of the existing case-control studies is their low statistical power to demonstrate an association with head trauma. The last column of Table 1 gives the probability that individual studies would detect an odds ratio of 2.0 with an alpha of 0.05, based on the number of discordant pairs identified.²⁵ None of the published studies had more than a 41% chance of detecting an odds ratio of 2.0. Indeed, the average statistical power was less than 20%. Thus, for a true association with an odds ratio of 2.0, only one in five studies might be expected to demonstrate this association. This frequency is very similar to the proportion of studies in Table 1 that demonstrated a significant association (two out of eight) for case-community control comparisons.

The use of meta-analytical techniques is especially appropriate for studying relatively rare exposures such as a history of head injury, which is generally reported to have occurred in only 5–10% of elderly individuals without AD (Table 2). The principal considerations in applying this technique are comparability of exposure ascertainment and heterogeneity across studies. In the meta-analysis presented below, these issues are addressed.

Other questions considered in this paper include the role of genetic susceptibility and gender in modifying the risk of AD following a head trauma episode and the issue of whether head trauma constitutes a risk factor selectively for early or late onset dementia.

METHODS

A general description of the methods used in the collaborative re-analysis is given in van Duijn *et al*.²⁶ In order to provide a comparable exposure measure for

TABLE 2 Estimated relative risks (RR) for head trauma with loss of consciousness for individual studies and pooled analysis

Study	RR	95% CI	Exposure frequency		Exposure rate (%)
			Cases	Controls	
Australia ¹⁰	1.17	0.34–4.20	7/152	6/152	3.9
Italy ⁴	2.00	0.43–12.37	6/95	3/95	3.2
Netherlands ⁸	1.33	0.65–2.80	22/197	17/197	8.6
USA, Denver ⁵	6.00	0.73–276.01	6/48	1/48	2.1
USA, Minneapolis ³	2.80	0.95–9.93	16/45	7/45	15.6
USA, Rochester ⁷	1.43	0.49–4.42	11/392	8/392	2.0
USA, Seattle ⁹	2.38	0.99–6.28	19/130	8/130	6.2
Pooled Analysis	1.82	1.26–2.67	87/1059	50/1059	4.7

the 11 studies included in the analysis, we decided to focus on head injury with loss of consciousness of any duration. Data on such an exposure were available for seven studies, which constituted the basis for the pooled analyses. Estimates of relative risk (RR) and 95% confidence intervals (CI) for three other studies in which the severity of head trauma could not be determined in individual cases^{2,6,11} are reported separately. A further restriction imposed to increase comparability across studies was to limit comparisons of cases to controls identified from the community. We report RR estimates and 95% CI for comparisons with hospital controls for two studies.^{3,4} However, these data are not included in the pooled analyses.

Although most studies ascertained head trauma with loss of consciousness in a similar manner, some used stricter definitions. Broe *et al*¹⁰ required a minimum period of unconsciousness of 15 minutes. Kokmen *et al*⁷ counted only those cases admitted to hospitals with loss of consciousness or amnesia. Amaducci *et al*⁴ ascertained episodes of head trauma that caused memory loss, confusion or coma. Although the latter investigators did not require loss of consciousness for an episode to be counted, head injuries fulfilling these criteria are likely to have been more severe than those determined by a simple loss of consciousness.

Family history of dementing illness was defined by having at least one affected first order relative (van Duijn *et al*²⁶). A dichotomous variable for education was created, categorizing individuals into those with 12 or more years of education versus those with less education. Finally, a three-level categorical variable was used to identify people with low, medium or high pure alcohol consumption per week, as described by Graves *et al*.²⁷

Analyses were performed using a mainframe version of SAS at the Department of Epidemiology and Biostatistics at Erasmus University in Rotterdam, the Netherlands. Frequency distributions were obtained for all variables to be used in the analyses. Contingency tables were developed for associations between covariates as well as for case-control comparisons of the head trauma-disease associations in individual studies. The odds ratio was used to estimate relative risk (RR).²⁶ For individual pair-matched studies, 95% CI for RR were estimated from confidence intervals of a binomial parameter representing the proportion of the total discordant pairs in which the case was exposed and the control not exposed²⁸ (p 378). Because various test-based methods of estimating confidence intervals have been used in published studies, the 95% CI for individual studies reported in this paper may differ somewhat from published values. Confidence intervals

in unmatched studies were estimated by Woolf's Method²⁵ (p 176). Finally, 95% CI for RR in the conditional logistic regressions were estimated from maximum likelihood determined parameters.²⁵

Statistical power of individual and pooled matched studies was estimated using the procedure outlined in Schlesselman²⁵ (p 162). Differences in RR for subgroups defined by family history, gender and age at onset were assessed by Woolf's test for heterogeneity²⁵ (p 194). Conditional logistic regression analyses for head trauma with loss of consciousness were carried out on pooled data adjusted for family history, education and alcohol consumption. Interaction effects were studied for the matching variables, age and gender.

RESULTS

Estimated RR for Head Trauma in Individual Studies

Estimated RR for head trauma with loss of consciousness in individual studies and their associated 95% CI are presented in Table 2. Two observations are noteworthy. First, despite considerable variation in the estimated RR among studies, all RR exceeded 1.0. Second, in all studies, the 95% CI included 1.0. The relatively large size of the confidence intervals is consistent with the low statistical power of individual studies, evident in Table 1.

Table 3 lists the RR and associated CI for the three studies in which head trauma was not defined by loss of consciousness, as well as the two comparisons with hospital controls. Estimated RR ranged from 2.4 to 18.0, and in three out of the five comparisons the 95% CI included 1.0. Again, confidence intervals were very large, and despite substantial differences in estimated RR, there was considerable overlap.

Heterogeneity across Studies

A series of seven conditional logistic regressions adjusted for the interaction between each individual study and head trauma were performed. None of the interaction terms were significant, suggesting absence of heterogeneity across studies in the association between head trauma and Alzheimer's disease. The lack of heterogeneity can be appreciated from an inspection of the confidence intervals of individual studies in Table 2, which display a large degree of overlap.

Unadjusted RR for Head Trauma with Loss of Consciousness

Given the lack of heterogeneity, data from the seven studies in Table 2 were pooled for further analyses. The resulting pooled RR estimate for these studies was

TABLE 3 Estimated relative risks for head trauma for comparisons not included in the pooled analysis

Study	RR	95% CI	Exposure frequency	
			Cases	Controls
Head trauma, severity unknown				
Japan* ¹¹	18.00	3.73–86.76	12/34	2/68
USA, Bedford ⁶	2.67	0.64–15.6	5/98	4/162
USA, Durham ²	2.40	0.49– 9.10	5/40	3/80
Comparisons with hospital controls				
Italy ⁴	3.50	0.67–34.52	7/113	2/113
USA, Minneapolis ³	4.50	1.48–18.29	20/78	4/76
Unmatched analysis				
Finland ¹	0.63	0.23– 1.76	6/63	13/91

*Unmatched analysis

1.82 (95% CI: 1.26–2.67). In contrast to the low power of individual studies (Table 1), the pooled data provided a power of 0.97 to identify an odds ratio of 2.0 with an alpha of 0.05.

When cases were stratified into those with and without a family history of dementia (Table 4), a stronger association was evident for those cases without a positive family history ('sporadic cases') in comparison to those with such a history ('familial cases'). However, the difference in estimated RR for these two strata was not statistically significant ($\chi^2 = 1.17$, $p = 0.30$).

Stratification of cases by age of onset ($< \text{age } 70$, $\geq \text{age } 70$) demonstrated no effect of this variable on the RR or 95% CI, which were very similar (Table 4). As expected, the difference in estimated RR for these strata was not statistically significant ($\chi^2 = 0.039$, $p = 0.86$).

When cases were stratified by gender (Table 4), large differences were evident. Female gender was associated with a small and non-significant inverse association, while male gender was associated with an elevation of the RR. Ninety five per cent CI for the two genders had little overlap, and the difference in estimated RR between strata was statistically significant ($\chi^2 = 8.03$, $p = 0.005$).

TABLE 4 Estimated relative risks and 95% confidence intervals for head trauma with unconsciousness for strata defined by familial/sporadic status, age of onset and gender

Stratum	RR	95% CI	Exposure frequency	
			Cases	Controls
Sporadic cases	2.31	1.17–4.84	31/304	14/304
Familial cases	1.42	0.76–2.71	28/236	20/236
Age of onset < 70 yrs	1.95	1.12–3.48	43/359	23/359
Age of onset ≥ 70 yrs	1.81	1.03–3.25	41/670	24/670
Males	2.67	1.64–4.41	69/409	29/409
Females	0.85	0.43–1.70	18/650	21/650

Adjusted RR for Head Trauma

Table 5 presents the results from a series of conditional logistic regression models on the pooled data, adjusted for family history, gender and age of onset. Although adjustment for family history resulted in a slight decrease in the estimated RR and adjustment for the interaction effect of gender and head trauma a small increase, the 95% CI for head trauma in the different models had considerable overlap. In all models, the association between head trauma and AD remained significant.

As described above, stratification of cases into those with and without a family history of dementia demonstrated a lower RR for familial cases and their matched controls. However, this analysis neglected family history of dementia in the controls. The possibility that a family history of dementia may increase or decrease the susceptibility to AD following a head trauma episode was investigated by including the interaction effect, family history X head trauma, in a conditional logistic regression model together with main effects for family history and head trauma. This inclusion resulted in no further explained variance ($\chi^2 = 0.00$, $R^2 = 0.00$, $p = 0.979$).

Table 6 presents findings from a second series of regression models adjusted for education, family history and alcohol consumption. As before, these adjustments had little effect on either the pooled head trauma RR or the associated 95% CI.

Graves *et al*⁹ reported that the estimated RR of AD increased as the time between the last head trauma and disease onset diminished. This trend was also evident in the pooled data (Table 7). When head traumas were dichotomized into those occurring more than 10 years prior to the age of disease onset and those occurring within 10 years of onset and these two predictors were included in a single conditional logistic regression model, the estimated RR for head trauma within 10 years of disease onset (5.53) was more than three times that for head trauma occurring more than 10 years prior to onset (1.63). However, both RRs were statis-

TABLE 5 Estimated relative risks and 95% confidence intervals for head trauma with unconsciousness adjusting for family history of dementia, and gender and age of onset interaction effects

Adjustment	RR	95% CI
None	1.70	1.13–2.56
Family history of dementia	1.64	1.02–2.64
Family history of dementia, Gender X head trauma	2.30	1.27–4.18
Family history of dementia, Gender X head trauma, Age of onset X head trauma	2.30	1.04–5.07

TABLE 6 Estimated relative risks and 95% confidence intervals for head trauma with unconsciousness adjusting for education, family history of dementia, and alcohol consumption

Adjustments	RR	95% CI
None	1.70	1.13–2.56
Education	2.01	1.31–3.07
Education, Family history of dementia	1.91	1.16–3.13
Education Family history of dementia		
Alcohol consumption	2.20	1.14–4.22

tically significant, and the 95% CI exhibited considerable overlap.

Timing of the Head Injury and Age at Onset

Cases and controls did not differ significantly in mean age at the time of head trauma ($t = 1.27$, $p = 0.21$). For both cases and controls, the mean age of reported head traumas was in the mid to late 30s.

To determine whether head trauma accelerates onset of the disease, the age of onset in cases with a history of head trauma was compared to that of cases without such a history. Because of the possibility that the age of onset in familial cases may be genetically determined, comparisons were carried out for sporadic and familial cases separately. In neither group was there a significant difference in age of onset by exposure status. For familial cases, mean age of onset was slightly higher for cases with head trauma than without (67.3 versus 66.1 years). This difference was not statistically significant ($t = 0.52$, $p = 0.60$). For sporadic cases, the mean age of onset also was higher in those with a history of head injury (66.6 versus 64.5 years), but again this difference was not significant ($t = 1.14$, $p = 0.25$).

Finally, given the finding of a larger RR for head traumas occurring closer to the time of disease onset, we examined the predictors of the lag time in cases (time between head injury and disease onset). As shown in Table 8, neither gender nor family history of dementia were significant predictors of the lag time. However, a relatively strong effect of education was found, individuals with lower education being more likely to report head injuries with shorter lag times.

TABLE 7 Estimated relative risks for head trauma occurring more and less than 10 years prior to disease onset

Variable	RR	95% CI
Head trauma ≤10 years	5.33	1.55–18.30
Head trauma >10 years	1.63	1.04–2.57

DISCUSSION

The findings of the meta-analysis provide support for an association between reported head trauma with loss of consciousness and Alzheimer's disease. In all seven pair-matched case-control studies, estimated RRs for severe head trauma exceeded 1.0. The low statistical power of such studies to identify odds ratios of 2.0 is evident in the large confidence intervals, which in all studies included 1.0.

For previously-reported significant odds ratios for head trauma^{2,3,9} either the severity of head trauma was not specified,² comparisons were reported with hospital controls,³ or data were analysed in a different manner than in the present study.⁹ Graves *et al*⁹ excluded pairs concordant for head injury with or without loss of consciousness in their analysis of the effect of head trauma with loss of consciousness. This convention led to a somewhat higher estimated RR (RR = 3.0, $p < 0.05$) than that found in the present analysis in which pairs including head injury with and without loss of consciousness were retained as discordant for head injury with loss of consciousness.

In the pooled analyses reported here, we have taken a conservative approach of including only those head traumas which involved loss of consciousness or equivalent indicators of severity. Mild head traumas were excluded, because of the likelihood that they would be susceptible to greater recall bias. Some support for this possibility is provided by Graves *et al*⁹ who reported a higher odds ratio for episodes of head trauma without loss of consciousness than for those episodes that involved a period of unconsciousness.

To avoid the possible confounding with other diseases that accompanies the use of hospital controls, the meta-analysis was restricted to case-community control comparisons. In both studies in which hospital controls were studied,^{3,4} the odds ratios for head trauma exceeded those seen in all but one of the case-community control comparisons. Thus, selection of community versus hospital controls led to a more conservative estimate of the head trauma RR.

Although the estimated RRs in the seven studies ranged from 1.17 to 6.0, all of the 95% CI included the pooled estimate of RR (1.82) and there was no evidence for heterogeneity. Adjustment for family history

TABLE 8 Predictors of lag time between head injury and onset of disease in cases*

Predictor	Slope	t	p
Gender	0.743	0.11	0.92
Education	16.91	2.51	0.02
Family history of dementia	-2.59	-0.37	0.71

*Based on 39 cases. Average lag time = 29.1 years

of dementing illness, gender, age, education and alcohol consumption resulted in small increases and decreases in the pooled head trauma RR. However, there was little indication that any of these factors constituted significant confounders.

Stratified analyses were performed to assess the role of familial/sporadic case status, age-at-onset (early, late), and gender as effect modifiers. Although head trauma appeared to be as strong a risk factor for late-onset as early-onset AD, the estimated RR for sporadic cases was higher (though not significantly so) than that for familial cases. The definition of sporadic and familial cases, while conforming to that in previous studies, does not take into account the chance occurrence of secondary cases of dementia in 'familial' families or the number and age of relatives at risk in 'sporadic' families. Misclassification of genetic and non-genetic cases, which is very likely, would tend to reduce the difference in estimated RRs between these groups. Thus, the difference between sporadic and familial cases in this analysis probably represents an underestimate of the true difference.

An unexpected finding was the very strong effect modification of gender. In stratified analyses, the estimated RR for males was 2.67, while for females the RR was less than 1.0. The 95% CI for these strata showed very little overlap. Overall, male controls were 2.2 times as likely to have been reported to have had a head trauma as female controls (exposure rates; male: 7.1%, female: 3.2%). This ratio is very similar to that reported in a large scale community survey of head trauma²⁹ suggesting that ascertainment of head trauma in male and female controls was probably unbiased by gender. However, in that study, cumulative incidence rates for males were 20% by age 75 and 8% for females by the same age. Most of the rates in Table 2 (with the exception of the study by Mortimer *et al*³) were considerably lower, suggesting a substantial degree of underascertainment. To have an effect on the estimated RR in the direction observed, the underascertainment of head trauma exposure would need to be greater for female cases as compared to female controls. Alternatively, underascertainment of head trauma in male controls could be partly responsible. It is also conceivable that gender may play a significant role in modifying the effect of severe head trauma through an as yet unknown mechanism.

The possibility that head trauma causes AD in genetically susceptible individuals was not supported by the pooled analysis, which demonstrated no interaction effect between family history of dementia and head trauma. This finding suggests that family history of dementia and head trauma explain individual com-

ponents of the variance and represent independent causal pathways.

The fact that the estimated RR for head injuries occurring within 10 years of disease onset was more than three times as large as that for head injuries occurring prior to that time is consistent with two explanations: (1) there is a tendency for informants for cases to associate disease onset with recent episodes of head trauma, which therefore are recalled better than those occurring recently in controls; and (2) the ability of the brain to recover from damage resulting from a head injury may be greater at younger ages. The first explanation requires the additional assumption that enhanced recall by case informants would not operate for head injuries occurring many years prior to disease onset. There is no a priori reason to believe that this is true. Furthermore, the mean age at which head injuries were reported to occur was not significantly different between cases and controls, making this explanation unlikely. The second explanation, reduced or slowed recovery of brain tissue following injury with advancing age, is consistent with the findings of studies in both animals and humans.³⁰

The finding of a significant association between lower education level and a shorter duration of time from head trauma to disease onset may reflect either a decreased reserve capacity or a reporting bias. Low education level has recently been implicated as a risk factor for Alzheimer's disease.^{31,32} Individuals with lower education level may be less able to compensate for damage to functioning brain tissue that follows head trauma, accelerating the onset of clinically diagnosable dementia. However, the possibility that informants for people of lower education level have poorer recall of head trauma occurring many years prior to disease onset cannot be discounted. Although we found that education predicted lag time, inclusion of interaction terms for education X head trauma in a number of logistic models failed to demonstrate modification of the head trauma effect by education.

Finally, the possibility of differential recall between informants for cases and controls as an explanation for the association with head trauma across studies needs to be considered. Because it is highly unlikely that informants for cases would report serious head trauma that did not occur, it is necessary to posit that control informants failed to recall similar episodes. Unfortunately, it is impossible to determine the degree of agreement between cases' informants and cases (who by virtue of their memory impairment are not reliable reporters), so that the degree of underascertainment of head trauma in cases is unknown in retrospective studies. In most studies no attempt was made to blind inter-

viewers or informants to the purpose of the study. Mortimer *et al*³ did blind both interviewers and informants and reported an odds ratio of 2.8 for head trauma with loss of consciousness (Table 2). In Kokmen's study,⁷ medical records were used to ascertain episodes of head trauma. Therefore, recall bias was not an issue. This study found an estimated RR for head trauma of 1.43.

One other issue relevant to recall bias is the role of differences in the informants used for cases and controls. To control for this possible source of bias, case/control pairs for which the type of informant (spouse, sibling, etc.) was not matched were excluded. The pooled head trauma RR for the remaining case/control pairs matched by type of informant was slightly higher than that for the entire sample [2.13, 95% CI: 1.37–3.42].

If head trauma constitutes a true risk factor for AD, it is necessary to explain how a head injury decades prior to disease onset can influence the occurrence of the disease. In previous publications,^{3,18} we have suggested two explanations. First, head trauma may damage the blood brain barrier, resulting in loss of immunological protection of brain tissue and/or entry of viruses and toxins that could produce damage many years later. Second, head injuries may lead to loss of functioning brain tissue, but not enough to cause a readily detectable cognitive loss. It is well known that the brain possesses a large degree of redundancy and that substantial neuronal damage can occur before clinical symptoms emerge.¹⁸ The gradual loss of functioning brain tissue during ageing coupled with the damage sustained during a head injury earlier in life could accelerate the time at which a critical threshold is reached, resulting in clinically-diagnosable dementia. Although two studies have reported that Alzheimer patients with severe head injuries experience an earlier onset of disease^{33,34} this finding was not confirmed by the pooled analysis, in which no difference in onset age was found between those patients with a history of head trauma and those without such a history.

CONCLUSIONS

Whether head trauma constitutes a significant risk factor for AD has been a hotly-debated issue. One assumption underlying this debate is that studies performed following the original publication of this finding³⁵ provided an opportunity to systematically test the hypothesis. If this had been the case, one might have concluded from the relatively small number of significant associations reported in subsequent studies that head trauma was not a consistent risk factor. However, examination of the power of such studies to detect a

significant odds ratio (Table 1) provides an alternative explanation: that in itself, no study had sufficient power to address the hypothesis.

Meta-analysis provides a powerful tool to examine risk factors like head trauma that occur with low frequency in the general population. Furthermore, it provides sufficient power to examine more complex statistical models and to identify subtle and previously unappreciated associations, such as the effect modification by gender observed in the present analysis. One important implication of this work is that the value of small case-control studies of AD lies in their ability to be combined with other studies to uncover weak associations. A strong argument can be made for standardizing data collection procedures to enhance the utility of this effort.

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