Head injury as a risk factor for Alzheimer’s disease: the evidence 10 years on; a partial replication

S Fleminger, D L Oliver, S Lovestone, S Rabe-Hesketh, A Giora

Objective: To determine, using a systematic review of case-control studies, whether head injury is a significant risk factor for Alzheimer’s disease. We sought to replicate the findings of the meta-analysis of Mortimer et al (1991).

Methods: A predefined inclusion criterion specified case-control studies eligible for inclusion. A comprehensive and systematic search of various electronic databases, up to August 2001, was undertaken. Two independent reviewers screened studies for eligibility. Fifteen case-control studies were identified that met the inclusion criteria, of which seven postdated the study of Mortimer et al.

Results: We partially replicated the results of Mortimer et al. The meta-analysis of the seven studies conducted since 1991 did not reach significance. However, analysis of all 15 case-control studies was significant (OR 1.58, 95% CI 1.21 to 2.06), indicating an excess history of head injury in those with Alzheimer’s disease. The finding of Mortimer et al that head injury is a risk factor for Alzheimer’s disease only in males was replicated. The excess risk of head injury in those with Alzheimer’s disease is only found in males (males: OR 2.29, 95% CI 1.47 to 2.06; females: OR 0.91, 95% CI 0.56 to 1.47).

Conclusions: This study provides support for an association between a history of previous head injury and the risk of developing Alzheimer’s disease.
control. To exclude this potential confound we required that data regarding previous head injury were collected from informants, both for the cases and controls.

(6) Recruitment of controls: Studies were excluded where controls were selected from psychiatric departments. The use of psychiatric controls addresses an alternative research question—does head injury specifically increase the risk of Alzheimer's disease rather than, for example, depression?

(7) Head injury occurred prior to the onset of Alzheimer's disease: It is essential that incidents of head injury in case subjects occurred before the onset of Alzheimer's disease and therefore we required studies to have explicitly stated that this was the case.

In addition to the inclusion criteria, we also noted whether studies fulfilled two further criteria, although these were not necessary for inclusion. Studies that met each criterion were collated and analysed in a sensitivity analysis to examine how the odds ratio was affected by imposing more stringent requirements.

(8) Head injury occurred at least X years prior to the onset of Alzheimer's disease: Head injuries occurring close to the onset of Alzheimer's disease may have occurred before the Alzheimer's disease was formally diagnosed but after significant cognitive and behavioural decline had occurred; the head injury may have been a result of the Alzheimer's disease. Therefore, it was important to note whether each study indicated that the head injury occurred prior to the onset of Alzheimer's disease by a period of at least X years. The duration, X years, was not specified.

(9) Matched relationship of informant: Information bias may stem from the differential recall of case informants and control informants if they have a different relationship to the subject. To avoid this source of bias we demanded that the relationship of the informant interviewed on behalf of the case was the same as the relationship of the informant interviewed on behalf of the control. For example, if the informant for the case was the spouse, then the informant for the matched control was also the spouse.

**Identification of studies**

Searches were undertaken in Medline (1966 to August 2001), Embase (1980 to August 2001), and PsycINFO (1998 to August 2001) using a comprehensive search strategy. The strategy was divided into two components; component A identified papers relating to “Alzheimer’s disease” or “apolipoprotein E”. This was combined, using the Boolean operator AND, with component B, which identified papers relating to “head injury” or “risk factors”. As an indication of quality, we required that the search strategy successfully retrieved the 11 “head injury” or “risk factors”. As an indication of quality, we required that the search strategy successfully retrieved the 11 “head injury” or “risk factors” papers. As an indication of quality, we required that the search strategy successfully retrieved the 11 “head injury” or “risk factors” papers.

The meta-analyses were based on the log-odds ratios and their standard errors as determined from the logarithms of the upper and lower bounds of the confidence intervals. After testing for heterogeneity in effect sizes between studies using a χ² test, fixed effects meta-analysis was carried out unless there was significant heterogeneity at the 5% level, in which case random effects meta-analysis was used. All analyses were carried out in Stata 7.

**RESULTS**

The odds ratios and their 95% confidence intervals are given in table 1 for all subjects and by sex in table 3. There was no significant heterogeneity between odds ratios for all subjects (Q = 12.39, df = 14, p = 0.58), or for females (Q = 1.88, df = 6, p = 0.93) or males (Q = 4.54, df = 7, p = 0.72). The results of the meta-analyses for all subjects, females and males, are given in table 2, where sensitivity analyses and separate meta-analyses for the post-Mortimer and pre-Mortimer studies are also reported. Figure 2 shows the individual and combined odds ratios for all studies.

Only two studies examined the interaction between head injury and APOE status as risk factors of Alzheimer’s disease, and therefore meta-analysis of this data was not possible.

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![Flow chart depicting identification of case-control studies.](http://jnnp.bmj.com/)

**Figure 1** Flow chart depicting identification of case-control studies.
The meta-analyses of all 15 studies and all subjects gave an odds ratio estimate of 1.58 (95% CI 1.21 to 2.06). The first sensitivity analysis considered only those 10 studies that required head injury to have occurred X years prior to onset of Alzheimer's disease (labelled P in table 1). The pooled odds ratio was estimated as 1.56 (95% CI 1.12 to 2.18), which was similar to the odds ratio for all 15 studies. The second sensitivity analysis considered only those studies where cases and controls were matched for informant type. The combined odds ratio was estimated as 1.42 (95% CI 0.75 to 2.67) which was somewhat lower than that for all studies. When we analysed only the seven post-Mortimer studies, the odds ratio fell to 1.35 (95% CI 0.94 to 1.94) and was no longer significant (table 2).

Finally, we have looked at the odds ratio for men and women (table 3). This analysis confirmed the findings of Mortimer et al that the odds ratio for head injury is only increased in men (OR 2.26; 95% CI 1.13 to 4.53) and not in women (OR 0.92; 95% CI 0.53 to 1.59) (table 2).

### Table 1 Odds ratios for each of the 15 studies data

<table>
<thead>
<tr>
<th>1st author</th>
<th>Quality*</th>
<th>Cs+†</th>
<th>Cs−‡</th>
<th>Cnt+†</th>
<th>Cnt−‡</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Mortimer studies</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortimer (1985)</td>
<td>P</td>
<td>20</td>
<td>54</td>
<td>11</td>
<td>108</td>
<td>3.64</td>
<td>1.52 to 8.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Amaducci (1986)</td>
<td>P</td>
<td>7</td>
<td>106</td>
<td>5</td>
<td>203</td>
<td>2.68</td>
<td>0.71 to 10.95</td>
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</tr>
<tr>
<td>Chandra (1987)</td>
<td>Q</td>
<td>6</td>
<td>51</td>
<td>1</td>
<td>56</td>
<td>6.00</td>
<td>0.73 to 276.02</td>
<td></td>
</tr>
<tr>
<td>Chandra (1989)</td>
<td>P, Q</td>
<td>5</td>
<td>269</td>
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<td>270</td>
<td>1.25</td>
<td>0.27 to 6.30</td>
<td>0.01</td>
</tr>
<tr>
<td>Broe (1990)</td>
<td>P</td>
<td>8</td>
<td>162</td>
<td>6</td>
<td>164</td>
<td>1.33</td>
<td>0.41 to 4.66</td>
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</tr>
<tr>
<td>Ferini-Stambi (1990)</td>
<td>P</td>
<td>5</td>
<td>58</td>
<td>10</td>
<td>116</td>
<td>1.00</td>
<td>0.26 to 3.39</td>
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<tr>
<td>Graves (1990)</td>
<td>P, Q</td>
<td>19</td>
<td>111</td>
<td>8</td>
<td>122</td>
<td>2.61</td>
<td>1.04 to 7.13</td>
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<tr>
<td>van Duin (1992)</td>
<td>P</td>
<td>22</td>
<td>176</td>
<td>18</td>
<td>181</td>
<td>1.33</td>
<td>0.65 to 2.77</td>
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<td><strong>Post-Mortimer studies</strong></td>
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<td></td>
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<tr>
<td>Li (1992)</td>
<td>Q</td>
<td>1</td>
<td>69</td>
<td>2</td>
<td>138</td>
<td>1.00</td>
<td>0.09 to 11.03</td>
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<tr>
<td>Fratiglioni (1993)</td>
<td>P, Q</td>
<td>4</td>
<td>84</td>
<td>25</td>
<td>232</td>
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<td>0.11 to 1.34</td>
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<tr>
<td>CSHA (1994)</td>
<td>P</td>
<td>13</td>
<td>149</td>
<td>27</td>
<td>393</td>
<td>1.27</td>
<td>0.58 to 2.63</td>
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<tr>
<td>Forster (1995)</td>
<td>P</td>
<td>22</td>
<td>87</td>
<td>16</td>
<td>93</td>
<td>1.50</td>
<td>0.68 to 3.41</td>
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<td>Rasmusson (1995)</td>
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<td>64</td>
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<td>2.06</td>
<td>0.19 to 104.59</td>
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<tr>
<td>O'Meara (1997)</td>
<td></td>
<td>32</td>
<td>317</td>
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<td>326</td>
<td>2.06</td>
<td>1.07 to 4.09</td>
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<tr>
<td>Tsolaki (1997)</td>
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<td>15</td>
<td>54</td>
<td>1.07</td>
<td>0.43 to 2.66</td>
<td></td>
</tr>
</tbody>
</table>

*P, studies with head injury X years prior to Alzheimer's onset; Q, studies with matched informant type.
†Cs+/Cnt+, number of cases/controls who had sustained a head injury with loss of consciousness.
‡Cs−/Cnt−, number of cases/controls who had not sustained a head injury with loss of consciousness.

### Table 2 Results of fixed effects meta-analyses

<table>
<thead>
<tr>
<th></th>
<th>Number of studies</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
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<tr>
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<td>15</td>
<td>1.58</td>
<td>1.21 to 2.06</td>
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<tr>
<td>P only</td>
<td>10</td>
<td>1.56</td>
<td>1.12 to 2.18</td>
<td>0.01</td>
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<tr>
<td>Q only</td>
<td>6</td>
<td>1.42</td>
<td>0.75 to 2.67</td>
<td>0.28</td>
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<tr>
<td>Post-Mortimer</td>
<td>7</td>
<td>1.35</td>
<td>0.94 to 1.94</td>
<td>0.10</td>
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<tr>
<td>Pre-Mortimer Females*</td>
<td>8</td>
<td>1.90</td>
<td>1.29 to 2.81</td>
<td>0.0001</td>
</tr>
<tr>
<td>All studies</td>
<td>7</td>
<td>0.91</td>
<td>0.56 to 1.47</td>
<td>0.69</td>
</tr>
<tr>
<td>Post-Mortimer</td>
<td>4</td>
<td>0.92</td>
<td>0.53 to 1.59</td>
<td>0.75</td>
</tr>
<tr>
<td>Males†</td>
<td>8</td>
<td>2.29</td>
<td>1.47 to 3.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-Mortimer</td>
<td>4</td>
<td>2.26</td>
<td>1.13 to 4.53</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Female data: in Rasmusson (1995) neither cases nor controls had a head injury so the odds ratio cannot be computed.
†Male data: Fratiglioni (1993) had an estimated odds ratio of 0 and could therefore not contribute to the meta-analysis.
DISCUSSION

This study has partially replicated the main findings of Mortimer et al. There was no significant association between head injury and Alzheimer's disease in the seven studies conducted after Mortimer et al., in contrast to the eight studies included in the Mortimer et al meta-analysis. However, overall the 15 studies showed a significant association with an odds ratio of 1.58 (95% CI 1.21 to 2.06), somewhat lower than the relative risk of 1.82 (95% CI 1.26 to 2.67) reported by Mortimer et al. On the other hand, Mortimer et al’s finding that the association between head injury and Alzheimer’s disease was present only in males, was replicated. For males we observed an odds ratio of 2.26 and for females an odds ratio of 0.92. These findings are very similar to Mortimer et al’s study, which reported an estimated relative risk of 2.67 for males and a relative risk less than 1 for females.

A possible explanation for the gender difference in the risk of Alzheimer’s disease following head injury is the role of the female hormones, oestrogen and progesterone. Animal models of stroke and traumatic brain injury (TBI) have provided evidence to suggest that these hormones may confer a neuroprotective and neuroregenerative effect. For example, Bramlett and Dietrich, using an animal model of TBI, found contusion volume was significantly smaller in adult female rats than in male and ovariectomised female rats. The variation in circulating endogenous hormones was provided as an explanation for the observed differences in the extent of brain damage. Also, oestrogen has been implicated as a protective factor in the development of Alzheimer’s disease. Therefore, it is possible that females are protected from Alzheimer’s disease after head injury due to the protective effects of the female hormones.

This study was unable to review the relation between head injury and APOE gene status as risk factors for Alzheimer’s disease. Only two studies that investigated this relation using a case-control design were identified. Mayeux et al found that patients with at least one APOE e4 allele and a history of head injury had a 10-fold increased risk of developing Alzheimer’s disease. No association was found between head injury and Alzheimer’s disease in the absence of APOE e4 allele. In contrast, O’Meara et al found that APOE e4 allele had little effect on the observed association between head injury and risk of Alzheimer’s disease. However, O’Meara et al noted that the low rate of head injury reported by control subjects might have hindered the study’s power to detect an interaction between head injury and APOE e4.

The relation between head injury and Alzheimer’s disease has also been examined through population based cohort studies that prospectively assess the risk of Alzheimer’s disease following head injury. The historical cohort study of Plassman et al found an increased risk of Alzheimer’s disease in World War II veterans who had sustained either a moderate (hazard ratio (HR) 2.32; 95% CI 1.04 to 5.17) or severe head injury (HR 4.51; 95% CI 1.77 to 11.47) but not a mild head injury. The absolute rate of dementia observed in the sample as a whole, mean age at follow up of 75.8 years, was low at less than 5%. In contrast, other cohort studies have failed to find evidence for an increased risk of Alzheimer’s disease following head trauma. Nemetz et al identified people who had sustained a head injury during the period 1935–84 and used the resources of the Rochester Epidemiology Project, a computerised medical linkage system, to identify those who developed Alzheimer’s disease prior to 1 June 1988, last contact, or death. Nemetz et al found that the number of individuals with head injury who later developed Alzheimer’s disease was not significantly higher than the incidence of Alzheimer’s disease in Rochester, Minnesota.

An advantage of the cohort design is that it removes many of the biases that plague case-control studies. The use of medical records to document the occurrence of head injury removes the need to rely on retrospective informant reports, and thus the data for case and control subjects is more likely to be of equal accuracy and precision. On the other hand, there are several biases that may be present using case-control methods. For example, recall bias may arise because the informants of Alzheimer’s patients may more readily recall a previous head injury than informants of control subjects, due to a need to account for their loved one’s illness, or as a result of cues within the hospital environment. Further, the recall of a spouse informant may be more precise than that of other family members due to the duration and quality. These issues are further exacerbated by differing definitions of head injury, the lack of a standard method for assessing the severity of head injuries, the potential for the misclassification of Alzheimer’s disease, and the fact that many case-control studies lack the statistical power necessary to detect an association with head injury.

The potential for bias to confound interpretation of the results of individual case-control studies is of major concern. This is illustrated by the study of Niino et al which explored the association between a large number of potential risk factors and Alzheimer’s disease. Nearly all of the factors investigated were found to be more common in patients with Alzheimer’s disease, suggesting reporter bias may have confounded the results. In Mortimer et al’s review, relative risks for studies of head injury with loss of consciousness compared to those for head injury of any severity were in the opposite direction to what one would predict. In the latter case, relative risk ranged from 2.40 to 18.0 and in the former,

### Table 3 Odds ratios for female and male data

<table>
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<tr>
<th>1st author</th>
<th>Female</th>
<th>Male</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
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<td>Pre-Mortimer studies</td>
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<td></td>
</tr>
<tr>
<td>Mortimer (1985)</td>
<td>–*</td>
<td>–</td>
<td>3.64</td>
<td>1.52 to 9.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broe (1990)</td>
<td>0.50</td>
<td>0.01 to 9.60</td>
<td>1.75</td>
<td>0.44 to 6.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fermini-Strambi (1990)</td>
<td>1.54</td>
<td>0.21 to 9.63</td>
<td>0.64</td>
<td>0.06 to 3.96</td>
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<td></td>
</tr>
<tr>
<td>Post-Mortimer studies</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>van Duijn (1992)</td>
<td>0.74</td>
<td>0.20 to 2.51</td>
<td>1.99</td>
<td>0.76 to 5.51</td>
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<tr>
<td>Fratiglioni (1993)</td>
<td>0.58</td>
<td>0.14 to 1.83</td>
<td>0.00</td>
<td>0.00 to 1.93</td>
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<td></td>
</tr>
<tr>
<td>CSHA (1994)</td>
<td>1.26</td>
<td>0.42 to 3.45</td>
<td>1.35</td>
<td>0.39 to 4.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasmussen (1995)</td>
<td>–†</td>
<td>–</td>
<td>1.76</td>
<td>0.16 to 9.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Meara (1997)</td>
<td>1.11</td>
<td>0.44 to 2.85</td>
<td>4.18</td>
<td>1.45 to 14.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsolaki (1997)</td>
<td>0.62</td>
<td>0.17 to 2.20</td>
<td>2.01</td>
<td>0.49 to 8.40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No female data.
†Neither cases nor controls had a head injury so that the odds ratio could not be computed.
from 1.17 to 6.01. These findings are compatible with reporting bias (mild injuries are probably more prone to reporter bias) or Alzheimer’s disease playing a causative role in the occurrence of head injury.

In order to explore the effects of bias, we conducted a sensitivity analysis to examine whether imposing more stringent inclusion requirements, and thus minimising the possibility of bias still further, had the predicted affect on the odds ratio. The first restriction required studies to have recruited subjects with a head injury that occurred a specified period before the onset of Alzheimer’s disease—that is, the injury was sustained at least X years before the onset of Alzheimer’s disease. The purpose of this analysis was to minimise the artefact from Alzheimer’s disease causing the head injury. A reduction in the odds ratio on exclusion of these studies would be compatible with the findings being due to this artefact. In fact, exclusion of these studies was found to have little effect on the odds ratio.

The other restriction, relating to recall bias, required studies to have matched, either individually or by group, the relationship of the informant to the case and control subject. One possible hypothesis is that Alzheimer’s patients tend to be accompanied by their spouse, whereas the control subjects bring all comers to act as their informant. This would mean Alzheimer’s patients would be more likely to have an informant who is better able to remember what happened many years ago. This artefact would therefore increase the odds ratio. However, Mortimer et al. found that the relative risk for head trauma increased slightly when studies that had not matched informant type were excluded (RR 2.13, 95% CI 1.37 to 3.42). In the present study, analysis after removal of studies exposed to this bias, showed a reduction in odds ratio to a non-significant level. Unfortunately, when we attempted to perform sensitivity analyses of the male data, only two studies were left, one of which found a substantially increased and one a substantially decreased odds ratio.

In summary, the findings of the present study provide support for an association between head injury and the risk of Alzheimer’s disease only in males. In light of the inherent complications in conducting case-control studies, future work should consider the use of population based cohort designs that rely on medical records to document head injury history.

**APPENDIX: EXCLUDED STUDIES**

Reasons for exclusion detailed in square parentheses [ ]


2. Bidzan L, Ussorowska D. Risk factors for dementia of Alzheimer type. Psychiatriszczna Polska 1995;29(3, suppl.):147–52. [Unable to establish the severity of the head injury, whether head injury in the cases occurred prior to the onset of AD, and if data collection was symmetrical]


5. Guo Z, Cupples LA, Kurz A, et al. Head injury and the risk of AD in the MIRAGE study. Neurology 2000;54:1316–23. [Unable to establish whether head injury in the cases occurred prior to the onset of AD. Case and control subjects were not matched (spouse controls)]


12. Kondo K, Nimo M, Shido K. A case-control study of Alzheimer’s disease in Japan—significance of life-styles. Dementia 1994;5:314–26. [Data collection was not symmetrical. Unable to establish whether there was a formal examination of the controls to rule out dementia]


21. Salib E, Hillier V. Head injury and the risk of Alzheimer’s disease: a case control study. Int J Geriatr Psychiatry 1997;12:363–8. [Case and control subjects were not matched. Controls were recruited from a psychiatric department]

severe head trauma but did not require a loss of consciousness. No formal examination of the controls to rule out dementia.)


24. Soininen H, Heinonen OP. Clinical and etiological aspects of senile dementia. Eur Neurol 1982;21:401–10. [Data collection was not symmetrical. Unable to establish the severity of the head injury, diagnostic criteria, and whether head injury in the cases occurred prior to the onset of AD]

25. Sullivan P, Petitti D, Barbaccia J. Head trauma and age of onset of dementia of the Alzheimer type. JAMA 1987;257:2289–90. [Unable to establish the severity of the head injury or whether there was a formal examination of the controls to rule out dementia]


27. Tang M, Liu X, Yunyang. Risk factors for Alzheimer’s disease in community: a population-based case control study. [Chinese]. Chinese Mental Health Journal 2001;15:22–5. [Data collection was not symmetrical. Did not exclude head injury that occurred after the onset of AD. Set “age periods” to provide a time frame within which incidents of head injury occurred for both cases and controls]


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REFERENCES
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