Environmental differences in twin pairs discordant for Alzheimer’s disease

I Räihä, J Kaprio, M Koskenvuo, T Rajala, L Sourander

Abstract
The aim of this study was to examine the contribution of environmental factors to the pathogenesis of Alzheimer’s disease by comparing environmental differences in twin pairs discordant for Alzheimer’s disease. Seventy four twin pairs discordant for Alzheimer’s disease were found by linking the Finnish twin cohort and the Hospital Discharge Register from years 1972–91. In 50 pairs (25 monozygotic and 25 dizygotic pairs), both co-twins had responded to a questionnaire survey in 1975. Exposure differences were compared between these pairs. A reduced risk of Alzheimer’s disease was significantly associated with a higher level of schooling (relative risk 0.3; 95% confidence interval 0.1–0.9, p=0.029). In addition, a reduced risk was suggestively associated with ambidextrousness or left handedness (p=0.083) and an increased risk with marriage (p=0.052), widowhood (p=0.074), and a history of cholelithiasis (p=0.071). In conclusion, a reduced risk of Alzheimer’s disease was associated with a higher level of schooling.

Subjects and methods
FINNISH TWIN COHORT
The Finnish twin cohort was compiled from the Central Population Registry of Finland using selection procedures described in detail elsewhere. Briefly, all sets of persons with the same birth date, same sex, same surname at birth, and same local community of birth were identified from the Central Population Registry of Finland. This yielded all the pairs (n=17 357) of same sex adult twins born in Finland before 1958 with both co-twins alive in 1967, as well as a few subjects who satisfied these criteria but who were not biological twins. A baseline questionnaire, administered in 1975, asked whether the subjects were twins and included questions for zygosity classification. The questionnaire also contained medical and psychosocial questions (97 items). The overall response rate was 89%. Further inquiries from local parish records were made on all non-respondents and conflicting responses to determine twinship. The validity of zygosity questions was confirmed by blood typing a subsample of 104 twin pairs living in the Helsinki area. About 93% of all responding pairs were classified as monozygotic or dizygotic with only 1.7% probability of misclassification. A total of 2489 pairs was left unclassified by zygosity. These consisted of pairs with an unknown address or with non-response to the 1975 questionnaire. The algorithm for classifying zygosity left 7% of respondent pairs unclassified because of conflicting responses to the items. A total of 13 888 (4307 monozygotic and 9581 dizygotic) twin pairs, who were 18 years of age or older at baseline were identified.

COLLECTION OF TWINS WITH ALZHEIMER’S DISEASE
The collection of twin pairs with Alzheimer’s disease is also described in detail elsewhere. The linkage of a national registry of hospital discharges from the period 1972 to 1991 with the Finnish Twin Cohort yielded 285 twin subjects who had dementia as a discharge diagnosis. The medical records of these twin individuals and their co-twins were reviewed to confirm and classify dementia. The diagnosis

Correspondence to:
Dr I Räihä, Department of Geriatrics, University of Turku, Kunnallismiehentie 20, FIN-20700 Turku, Finland. Telephone 00 358 21 2692060; fax 00358 21 2692107.

Received 23 April 1997 and in final form 20 January 1998
Accepted 3 April 1998
Distribution of twin pairs discordant for Alzheimer’s disease (n=50) according to their discordance for the risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Case with trait/control without</th>
<th>Control with trait/case without</th>
<th>Relative risk (95% CI)</th>
<th>χ² p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social factors:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever or never married</td>
<td>10 3</td>
<td>3.33 (0.86–18.9)</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>Widowed or not</td>
<td>14 6</td>
<td>2.33 (0.84–7.41)</td>
<td>0.074</td>
<td></td>
</tr>
<tr>
<td>Schooling (more or less)</td>
<td>4 13</td>
<td>0.31 (0.073–0.996)</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>Lifestyle:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever or never smoker</td>
<td>2 5</td>
<td>0.40 (0.038–2.44)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>1 5</td>
<td>0.20 (0.004–1.79)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Abstainer</td>
<td>9 7</td>
<td>1.29 (0.43–4.06)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Medical and biological:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambidextrous or left or right handed</td>
<td>3 9</td>
<td>0.33 (0.58–1.34)</td>
<td>0.083</td>
<td></td>
</tr>
<tr>
<td>Analgesics (more or less use)</td>
<td>8 14</td>
<td>0.57 (0.21–1.46)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Analgesics (any or none)</td>
<td>3 8</td>
<td>0.38 (0.06–1.56)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Antacid (any or none)</td>
<td>6 5</td>
<td>1.20 (0.31–4.97)</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>5 5</td>
<td>1.00 (0.23–4.35)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>History of urticaria</td>
<td>3 3</td>
<td>1.00 (0.13–7.47)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>History of allergic exema</td>
<td>7 7</td>
<td>1.00 (0.30–3.34)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>History of cholelithiasis</td>
<td>11 4</td>
<td>2.75 (0.82–11.9)</td>
<td>0.071</td>
<td></td>
</tr>
</tbody>
</table>

Results
The table shows the distribution of twin pairs according to their discordance for the categorical risk factors included in the analysis. Longer schooling, when categories of more or less were used, was associated with a reduced risk of nearly 70% (p=0.029), which was similar both in monozygotic and dizygotic twins. The mean education level of the twins with Alzheimer’s disease (mean 6.1 (SD 1.9) years) was significantly less than that of their co-twins without Alzheimer’s disease (mean 6.8 (SD 2.5) years) (paired t test: t=2.35, p=0.023). The mean difference was equally large among monozygotic (0.6 years) and dizygotic (0.8 years) pairs. In addition to the significant association between schooling and Alzheimer’s disease, there were several suggestive associations between putative exposure factors and Alzheimer’s disease, in which the level of the significance was >0.05 but <0.1 (an inverse association for ambidextrousness or left handedness and positive associations for marriage, widowhood, and a history of cholelithiasis). The occurrence of other disease histories and putative risk factors were similar among the affected and unaffected co-twins. Of the continuous variables, neuroticism (p=0.48), extroversion (p=0.63), body mass index (p=0.94), and alcohol consumption (g/month; p=0.53) were not associated with Alzheimer’s disease.

Discussion
Several studies have found an association between limited educational attainment and Alzheimer’s disease. In addition, in the American Nun study, low linguistic ability in early life was a strong predictor of poor cognitive function and Alzheimer’s disease in late life. Our study provides more evidence for the relation between low educational attainment and increased risk of Alzheimer’s disease. The similar risk in monozygotic and dizygotic twins suggests that the association was unrelated to genetic factors. It has been proposed in the threshold model of dementia that neurocognitive capacity, when reduced below a specific threshold, accelerates the development of neuropathological lesions and cognitive impairment. A higher educational level may reflect a higher neurocognitive reserve developed in early life and may thus provide a protective effect against Alzheimer’s disease. The important question to be answered is whether education increases neocortical synaptic density. On the other hand, there has been concern that the screening instruments used to identify subjects for cognitive decline may be subject to educational bias. In the present study, the effect of education on diagnosing Alzheimer’s disease may be less significant, because, due to the linkage method, dementia was already clinically evident and mostly moderate or severe at the ascertainment of disease. In addition to the theory of premorbid vulnerability of the brain, lifestyle differences associated with a
Environmental differences in twin pairs discordant for Alzheimer’s disease

A low level of low education, such as nutrition, alcohol consumption, and occupational exposure, may explain the higher risk of Alzheimer’s disease. Low educational level is related to manual work, which has been found to be a predictor for Alzheimer’s disease. Manual workers are at greater risk of exposure to toxic agents than other workers. Occupational solvents have been found to be associated with impaired cognition. In our study, data on possible occupational exposure were not systematically available.

In addition to the association between the level of schooling and Alzheimer’s disease, there were associations which did not quite reach the level of significance. The suggestive inverse association between ambidextrousness or left handedness is potentially interesting, because lateralized abnormalities have been found to be an important feature of dementia of the Alzheimer’s type. A selective vulnerability of the left hemisphere has been found in dementia of the Alzheimer’s type. In a study by Seltzer et al., left handedness was underrepresented in late onset Alzheimer’s disease compared with the general population. However, further studies are needed to confirm whether right hemispheric dominance might provide protective traits against Alzheimer’s disease.

The co-twin control design is a sensitive method, and it may achieve up to twice the power of conventional case-control studies. The advantage of the record linkage method, in addition to the nationwide cohort of twins, is the long follow up time of the twin pairs. The long follow up is essential to exclude the concordance for Alzheimer’s disease, as a variation in the disease expression between co-twins may be up to 15 years. As the questionnaire exposure data were collected with few exceptions before the manifestation of Alzheimer’s disease, recall bias or other effects of dementia on reporting of exposures are unlikely to account for the differences between cases and their co-twins.

We thank Mr Kauko Heikinä for statistical help and Ms Pirjo Pielika for secretarial assistance. The study was supported by the Academy of Finland and the Turku University Foundation.

Environmental differences in twin pairs discordant for Alzheimer's disease

I Räihä, J Kaprio, M Koskenvuo, T Rajala and L Sourander

J Neurol Neurosurg Psychiatry 1998 65: 785-787
doi: 10.1136/jnnp.65.5.785

Updated information and services can be found at:
http://jnnp.bmj.com/content/65/5/785

These include:

References
This article cites 14 articles, 6 of which you can access for free at:
http://jnnp.bmj.com/content/65/5/785#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Dementia (1020)
Drugs: CNS (not psychiatric) (1945)
Memory disorders (psychiatry) (1390)
Psychiatry of old age (338)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/