International Journal of Epidemiology
© International Epidemiological Association 1991

Vol. 20, No. 2 (Suppl. 2)
Printed in Great Britain

Psychiatric History and Related Exposures as Risk Factors for Alzheimer's Disease: A Collaborative Re-Analysis of Case-Control Studies

A F JORM,* C M VAN DUIJN,† V CHANDRA, L FRATIGLIONI, A B GRAVES, A HEYMAN, E KOKMEN, K KONDO, J A MORTIMER, W A ROCCA, S L SHALAT, H SOININEN, A HOFMAN FOR THE EURODEM RISK FACTORS RESEARCH GROUP†

Jorm A F (NH and MRC Social Psychiatry Research Unit, The Australian National University, Canberra, Australia), van Duijn C M, Chandra V, Fratiglioni L, Graves A B, Heyman A, Kokmen E, Kondo K, Mortimer J A, Rocca W A, Shalat S L, Soininen H, Hofman A for the EURODEM Risk Factors Research Group. Psychiatric history and related exposures as risk factors for Alzheimer's Disease: A collaborative re-analysis of case-control studies. *International Journal of Epidemiology* 1991; **20 (Suppl 2)**: S43–S47.

Data from case-control studies of Alzheimer's disease (AD) were pooled to examine the possible roles of history of depression, anti-depressant treatment and adverse life events as risk factors. History of depression was found to be associated with AD, although the effect was confined to late onset cases. The association held for episodes of depression more than 10 years before AD onset, as well as for episodes occurring within a decade of onset. No association was found with anti-depressant treatment. However, data were only available from two studies, limiting the power of the analysis. Also, no association was found with the three major life events considered in the pooled analysis: death of spouse, death of a child and divorce.

INTRODUCTION

This paper considers whether individuals who have a history of psychiatric disorder are more likely to develop Alzheimer's disease (AD). While there is a potentially large number of psychiatric disorders which could be investigated as risk factors for AD, many of these present severe methodological problems. In making a clinical diagnosis of AD, it is necessary to exclude disorders which could provide an alternative explanation of the dementia. In practice, this means that subjects with a range of psychiatric disorders, including psychotic disorders, mental retardation and alcohol abuse, may be excluded. Because of the exclusion procedure involved in making a clinical diagnosis of AD, such disorders cannot be easily researched as potential risk factors. In practice, the major psychiatric disorders which can be investigated by the case-control method are those involving anxiety and depression. However, depression is the only disorder which has been systematically investigated in case-control studies. History of depression has been considered in a number of studies, with four of these reporting this exposure to be significantly more common in cases than controls.[1–4] However, this difference could be due to depression being an early manifestation of AD. It has been reported in clinical studies that elderly patients thought to be suffering from depression can progress to clear dementia over a period of a few years.[5] In order to allow for this possibility, studies of history of depression need to pay close attention to the timing of depressive episodes.

There are other exposures related to psychiatric history which are of interest as potential risk factors, in particular psychiatric treatments and adverse life events. Treatments of psychiatric disorders are of interest as potential risk factors because they alter neurotransmitter functioning and have been implicated in other neurological disorders viz. Parkinsonism and tardive dyskinesia. Among the treatments which could be

*NH&MRC Social Psychiatry Research Unit, The Australian National University, Canberra, Australia.
†EURODEM, Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, The Netherlands.
Reprint requests: EURODEM, Department of Epidemiology and Biostatistics, Erasmus University Medical School, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

TABLE 1 *Results from case-control studies examining history of depression as a risk factor for AD*

Study	Exposure frequency: Cases	Controls	RR	95% CI
Studies which assessed depression before AD onset:				
Australia[2]	11/170	4/170	2.75	0.88–8.56
USA, Bedford[4]	4/103	8/208	0.83	0.22–3.14
USA, Minneapolis[3]	4/78	1/48	3.00	0.32–28.62
USA, Rochester[13]	36/392	21/392	1.84	1.04–3.25
All studies	55/743	34/818	1.82	1.16–2.86
Studies which assessed depression at any time during life:				
Finland[6]	0/62	2/53	0.00	0.01–3.65
USA, Durham[11]	7/45	6/92	2.86	0.82–10.02

considered are electroconvulsive therapy, lithium, anti-depressants and major and minor tranquillizers. Treatments such as lithium and ECT have seldom been assessed in case-control studies, perhaps because they are fairly rare in the population. Major tranquillizers are difficult to assess as a risk factor for two reasons. Firstly, they are used to treat psychotic disorders which may be an exclusion factor in diagnosing AD. Secondly, they may be associated with AD because major tranquillizers are sometimes used to control behaviour problems which accompany the disease. Minor tranquillizers and anti-depressants could potentially be investigated in case-control studies, but have been assessed in relatively few studies. Only one study collected data on both minor tranquillizers and anti-depressants, one collected data on anti-depressants only and another on minor tranquillizers only. None of these studies reported significant associations.[2,3,6] Nevertheless, these exposures merit further investigation. Unfortunately, one of the studies examining minor tranquillizers used a different method for assessing this exposure in cases compared to controls and is therefore not comparable with the other study. The studies examining anti-depressants are, however, comparable and were included in the present re-analysis. Anti-depressant treatment may be a risk factor for AD because of the anti-cholinergic effect of many anti-depressants and the role of this transmitter system in the disease.

TABLE 3 *Time at which depression occurred in relation to AD onset*

Group	Exposure frequency: Cases	Controls	RR	95% CI
Depression up to 10 years before AD onset:				
All subjects	19/742	13/818	1.60	0.77–3.30
Early onset	7/203	10/275	0.71	0.25–1.98
Late onset	12/523	3/509	4.46	1.24–16.02
Depression more than 10 years before AD onset:				
All subjects	35/742	21/818	1.92	1.11–3.32
Early onset	7/203	6/275	1.70	0.51–5.65
Late onset	28/523	15/509	2.01	1.06–3.80

TABLE 2 *History of depression as a risk factor in subgroups of cases*

Subgroup	Exposure frequency: Cases	Controls	RR	95% CI
Familial*	4/79	3/93	1.34	0.30–5.93
Sporadic*	9/149	9/206	1.54	0.55–4.26
Female	34/377	19/377	1.93	1.05–3.55
Male	21/366	15/441	1.68	0.83–3.41
Early onset	14/203	16/275	1.01	0.45–2.26
Late onset	41/524	18/509	2.44	1.36–4.36

*Data available only from Australia and USA, Bedford

Adverse life events have been investigated as triggers for many psychiatric disorders and have also been assessed in several case-control studies of AD. A small early study found more stressful life events in cases of 'organic brain syndrome' during the five years before onset.[7] However, larger case-control studies of AD have been negative.[2,8,9] The major problem in assessing life events in AD is that it necessarily has to be via informants and involves recalling events which may have occurred in the distant past. The accuracy of the data may sometimes be doubtful and informants of cases may be more likely to recall events in line with their preconceptions about possible links. A solution is to consider only clearly-defined major life events which would presumably always be known to an informant e.g. death of a spouse, death of a child, divorce. Such life events have been researched in a number of case-control studies and are the focus of analysis here.

To summarize, history of psychiatric disorders, psychiatric treatments and severe life events have all been considered as potential risk factors for AD. However, either because of methodological problems in collecting the relevant data or because too few data are available, only a subset of these exposures were included in the collaborative re-analysis reported here. The specific exposures considered in the re-analysis were history of depression, treatment with anti-depressants and severe well-defined life events viz. death of a spouse, death of a child and divorce.

TABLE 4 *Results from case-control studies examining anti-depressant treatment as a risk factor for AD*

Study	Exposure frequency: Cases	Controls	RR	95% CI
Australia	14/151	13/167	1.22	0.51–2.95
USA, Minneapolis	3/74	1/48	1.00	0.06–15.86
All studies	17/225	14/215	1.20	0.52–2.78

TABLE 5 *Results from case-control studies examining death of a spouse as a risk factor*

Study	Exposure frequency		RR	95% CI
	Cases	Controls		
Australia[2]	85/170	86/170	0.97	0.58–1.62
Finland*[6]	27/63	21/53	1.14	0.54–2.40
Italy[8]	18/116	21/97	0.45	0.16–1.31
Netherlands[12]	44/198	21/198	2.36	1.34–4.17
USA, Denver[9]	36/61	39/61	0.63	0.20–1.91
USA, Durham[11]	7/46	15/92	0.91	0.32–2.58
USA, Minneapolis[3]	8/78	6/48	0.40	0.08–2.07
All matched studies	198/669	188/666	1.12	0.83–1.51
All matched studies—excluding Netherlands	154/471	167/468	0.78	0.54–1.14

*Unmatched study

METHODS

Data from 11 case-control studies were considered for inclusion in the present re-analysis.[2–4,6,8–14] Data on history of depression were collected in six of the studies.[2–4,6,11,13] In all of these studies only medically-treated depression was considered. In four of these studies, this exposure was assessed through an interview with an informant, in one study it was assessed from medical records[13] and in another from subject and informant interviews checked from medical records.[6] Four of the six studies also collected data on when the depression was diagnosed.[2–4,13] Two studies recorded age at diagnosis while the other two recorded the date of diagnosis. In the present re-analysis, only episodes of depression which occurred more than one year before onset of AD were considered.

Two studies collected data on use of anti-depressants.[2,3] Both relied on informants' reports of this exposure. Anti-depressant use was considered as an exposure if it occurred at any time over a subject's life.

TABLE 7 *Results from case-control studies examining divorce as a risk factor*

Study	Exposure frequency		RR	95% CI
	Cases	Controls		
Australia	5/170	9/170	0.50	0.15–1.66
Finland	3/63	3/53	0.83	0.16–4.31
Italy	2/116	3/97	0.33	0.03–3.17
Netherlands	23/198	12/198	2.10	1.00–4.41
USA, Denver	17/63	18/60	0.92	0.40–2.08
USA, Durham	0/46	0/92	—	—
USA, Minneapolis	1/78	0/48	—	—
All matched studies	48/671	42/665	1.15	0.72–1.84
All matched studies—excluding Netherlands	25/473	30/467	0.74	0.39–1.38

TABLE 6 *Results from case-control studies examining death of a child as a risk factor*

Study	Exposure frequency		RR	95% CI
	Cases	Controls		
Australia	33/170	34/170	0.96	0.55–1.66
Italy	24/116	14/96	1.34	0.63–2.81
Netherlands	27/198	19/198	1.45	0.79–2.66
USA, Denver	20/63	17/60	1.30	0.57–2.97
USA, Minneapolis	9/78	6/48	1.00	0.25–4.02
All studies	113/625	90/572	1.20	0.87–1.65

Five of the 11 case-control studies collected at least some data on life events.[2,3,8,9,12] The range of life events covered varied considerably from study to study. The only events recorded with any consistency were death of a spouse, death of a child and divorce. Data on death of a spouse and divorce were collected in four studies,[3,8,9,12] while data on death of a child were collected in five.[2,3,8,9,12] However, in three other studies, death of a spouse or divorce could be inferred through data on current marital status.[2,6,11] It is possible that some subjects re-married after being widowed or divorced, in which case the frequency of these exposures would be underestimated. However, in most cases current marital status would be a good indicator of these life events. In all studies, the data on life events were collected through interviews with informants. In the present re-analysis, the life events were included as an exposure if they occurred at any time over a subject's life.

The data from the case-control studies were pooled using the methods described in a companion paper.[15]

RESULTS

Table 1 shows the results from the four studies which provided data on episodes of depression which occurred before onset of AD, together with the results from pooling their data. Data on history of depression

TABLE 8 *Results from case-control studies examining any of the three life events (death of spouse, death of child, divorce)*

Study	Exposure frequency		RR	95% CI
	Cases	Controls		
Australia	99/170	94/170	1.16	0.73–1.86
Italy	38/116	31/96	0.84	0.38–1.88
Netherlands	81/198	47/198	2.32	1.48–3.64
USA, Denver	50/61	45/58	1.50	0.53–4.21
USA, Minneapolis	16/78	12/48	0.63	0.20–1.91
All studies	284/623	229/570	1.43	1.09–1.89
All studies—excluding Netherlands	203/425	182/372	1.05	0.74–1.50

TABLE 9 *Death of a spouse as a risk factor in subgroups of cases*

Subgroup	Exposure frequency		RR	95% CI
	Cases	Controls		
All matched studies:				
Familial	71/227	61/250	1.48	0.92–2.39
Sporadic	86/307	87/309	0.98	0.63–1.51
Female	164/382	149/401	1.37	0.96–1.95
Male	34/287	39/265	0.63	0.34–1.16
Early onset	73/415	58/425	1.47	0.98–2.19
Late onset	122/236	128/216	0.71	0.43–1.16
All matched studies—excluding Netherlands				
Familial	49/131	49/154	1.19	0.65–2.19
Sporadic	64/205	78/207	0.57	0.32–1.01
Female	123/258	135/277	0.82	0.52–1.28
Male	31/213	32/191	0.70	0.35–1.38
Early onset	31/228	38/238	0.86	0.48–1.55
Late onset	122/236	128/216	0.71	0.43–1.16

were also available from two other studies, but age at which depression occurred was not determined. Nevertheless, the results from these studies are worthy of mention and are shown in the lower part of Table 1. Overall, the data indicate that there is an association between history of depression and AD.

The data on history of depression were analysed separately for various subgroups of cases, giving the results shown in Table 2. The RRs are similar for familial and sporadic cases and for males and females, but late onset cases ($\geq$ 70 years) have a larger RR than early onset cases. However, this difference only approaches statistical significance ($p = 0.08$).

To assess whether depression may have been associated with AD as a prodromal feature, separate analyses were carried out for episodes up to 10 years before AD onset and more than 10 years before onset. The results of these analyses are shown in Table 3. It appears that AD is associated with depression in both periods.

The results from the two studies of anti-depressant use are shown in Table 4. When the results were pooled, there was no association. Because of the small number of studies involved, it was not feasible to do an analysis by subgroups.

The results from studies examining life events are shown in Tables 5–8. These Tables give the RRs for particular life events as well as for experiencing any of the three major events analysed here. It can be seen that only the Netherlands study found any association. The results from this study were found to differ significantly from other studies for death of a spouse, divorce and for experiencing any of the three events. The bottom of Tables 5, 7 and 8 shows the pooled analyses when all studies with matched designs are included and also when the Netherlands study is excluded. When all studies are included there are associations between AD and having experienced any of the three life events. However, once the Netherlands study is excluded, no association remains.

Tables 9–12 shows the results of pooled analyses of life events with various subgroups. Again, a number of

TABLE 10 *Death of a child as a risk factor in subgroups of cases*

Subgroup	Exposure frequency		RR	95% CI
	Cases	Controls		
Familial	30/204	31/199	0.96	0.56–1.66
Sporadic	59/288	41/271	1.39	0.87–2.20
Female	74/353	62/339	1.15	0.78–1.71
Male	39/272	28/233	1.29	0.76–2.20
Early onset	61/376	34/346	1.65	1.05–2.57
Late onset	52/238	55/215	0.87	0.54–1.38

TABLE 11 *Divorce as a risk factor in subgroups of cases*

Subgroup	Exposure frequency		RR	95% CI
	Cases	Controls		
All matched studies:				
Familial	14/229	23/250	0.53	0.24–1.13
Sporadic	27/307	16/308	1.83	0.91–3.70
Female	32/384	30/401	1.09	0.62–1.91
Male	16/287	12/264	1.30	0.57–2.97
Early onset	25/415	16/425	1.57	0.80–3.07
Late onset	20/238	26/215	0.68	0.34–1.39
All matched studies—excluding Netherlands				
Familial	7/133	15/154	0.27	0.08–0.98
Sporadic	11/205	12/206	0.80	0.32–2.03
Female	16/260	23/277	0.59	0.27–1.29
Male	9/213	7/190	1.17	0.39–3.47
Early onset	5/228	4/238	1.00	0.25–4.00
Late onset	20/238	26/215	0.68	0.34–1.39

TABLE 12 *Any of the three life events in subgroups of cases*

Subgroup	Exposure frequency		RR	95% CI
	Cases	Controls		
All studies:				
Familial	88/202	76/198	1.33	0.85–2.09
Sporadic	139/288	109/270	1.53	1.02–2.27
Female	208/351	165/338	1.73	1.22–2.46
Male	76/272	64/232	1.03	0.65–1.63
Early onset	132/376	81/346	1.93	1.34–2.78
Late onset	148/236	146/213	0.85	0.54–1.34
All studies—excluding Netherlands				
Familial	54/106	51/102	1.11	0.59–2.10
Sporadic	92/186	87/168	0.86	0.51–1.47
Female	144/227	134/214	1.09	0.68–1.74
Male	59/198	48/158	1.00	0.57–1.74
Early onset	55/189	36/159	1.47	0.82–2.64
Late onset	148/236	146/213	0.85	0.54–1.34

associations are present when the Netherlands study is included, but these disappear when it is excluded.

DISCUSSION

Of the three types of exposures considered here, only history of depression emerged as a risk factor for AD. This association was confined to late onset cases. Depression was found to be more common, not only in the decade before onset of AD, but also earlier in life, implying that it is not simply a prodromal feature of AD. Recall bias on the part of informants is not a plausible explanation of this association, because it was also observed in the one case-control study which used medical records to determine exposures.[13] While the evidence for an association appears convincing, the findings require replication in prospective studies involving confirmed cases of depression and controls. It would be particularly interesting to know whether one type of depression (e.g. bipolar, unipolar) specifically confers risk.

What explanations might be given for an association with history of depression? One possibility, considered in the present analysis, is that anti-depressant treatment is responsible, perhaps because of the anti-cholinergic effects of many anti-depressants. While the present data did not support a role for anti-depressants they came from only two studies and these studies did not specifically examine anti-depressants which have anti-cholinergic effects. Another possibility is that the neurotransmitter systems disrupted in depression also have some involvement in AD. For example, the noradrenergic system has been implicated in depression and is sometimes found to be abnormal in AD. However, noradrenergic abnormalities have been reported as confined to early onset cases,[16] whereas the present data show that history of depression is associated with late onset AD. A third explanation, not necessarily incompatible with the previous one, is that individuals with a history of depression already have a subtle cognitive deficit,[17] so that they more quickly reach the threshold for the appearance of dementia in old age.

When adverse life events were examined, no association with AD was found except in the Netherlands study. The results from this study were not homogeneous with those from other studies. When the Netherlands results were excluded, no association was found in the pooled data. The anomalous results from the Netherlands may have been due to the method of control selection. Matched controls were selected randomly from the general population, but only 61% of the selected individuals agreed to participate, requiring the selection of substitutes. The controls included in the study may have been a biased sample with respect to life events. Given the overall negative results in the pooled analyses, further research on life events as a risk factor for AD would not seem profitable.

The pooled analyses reported here cover only a small number of exposures from the domain of psychiatric history. There is still a need for data to be gathered on history of psychiatric disorders other than depression and on history of psychiatric treatments.

REFERENCES

[1] Barclay L L, Kheyfets S, Zemcov A, Blass J P, McDowell F H. Risk factors in Alzheimer's Disease. In: Fisher A, Hanin I, Lachman C, eds. *Alzheimer's and Parkinson's diseases*. New York: Plenum, 1985 pp. 141–6.

[2] Broe G A, Henderson A S, Creasey H, *et al.* A case-control study of Alzheimer's disease in Australia. *Neurology* 1990; **40:** 1698–1707.

[3] French L R, Schuman L M, Mortimer J A, Hutton J T, Boatman R A, Christians B. A case-control study of dementia of the Alzheimer type. *Am J Epidemiol* 1985; **121:** 414–21.

[4] Shalat S L, Seltzer B, Pidcock C, Baker E L. Risk factors for Alzheimer's disease: A case-control study. *Neurology* 1987; **37:** 1630–3.

[5] Reding M J, Haycox J, Blass J P. Depression in patients referred to a dementia clinic: A three-year prospective study. *Arch Neurol* 1985; **42:** 894–6.

[6] Soininen H, Heinonen O P. Clinical and etiological aspects of senile dementia. *Eur Neurol* 1982; **21:** 401–10.

[7] Amster L E, Krauss H H. The relationship between life crises and mental deterioration in old age. *Int J Aging Hum Dev* 1974; **5:** 51–5.

[8] Amaducci L A, Fratiglioni L, Rocca W A, *et al.* Risk factors for clinically diagnosed Alzheimer's disease: A case-control study of an Italian population. *Neurology* 1986; **36:** 922–31.

[9] Chandra V, Philipose V, Bell P A, Lazaroff A, Schoenberg B S. Case-control study of late onset 'probable Alzheimer's disease'. *Neurology* 1987; **37:** 1295–300.

[10] Graves A B, White E, Koepsell T, *et al.* A case-control study of Alzheimer's disease. *Ann Neurol* 1990; **28:** 766–74.

[11] Heyman A, Wilkinson W E, Stafford J A, Helms M J, Sigmon A H, Weinberg T. Alzheimer's disease: A study of epidemiological aspects. *Ann Neurol* 1984; **15:** 335–41.

[12] Hofman A, Schulte W, Tanja T A, *et al.* History of dementia and Parkinson's disease in 1st-degree relatives of patients with Alzheimer's disease. *Neurology* 1989; **39:** 1589–92.

[13] Kokmen E, Beard C M, Chandra V, Offord K P, Schoenberg B S, Ballard D J. Clinical risk factors for Alzheimer's disease: A population-based case-control study. *Neurology* 1991, In press.

[14] Kondo K, Yamashita I. A case control study of Alzheimer's disease in Japan; association with inactive psychosocial behaviors. In: Hasegawa K, Homma A, eds. *Psychogeriatrics: Biomedical and Social Advances*. Amsterdam: Exerpta Medica, 1990, pp. 49–53.

[15] van Duijn C M, Stijnen T, Hofman A. Risk factors for Alzheimer's disease: Overview of the EURODEM collaborative re-analysis of case-control studies. *Int J Epidemiol,* 1991; **20 (Suppl 2):** S4–S12.

[16] Rossor M N, Iversen L L, Reynolds G P, Mountjoy C R, Roth M. Neurochemical characteristics of early and late onset types of Alzheimer's disease. *Brit Med J* 1984; **288:** 961–4.

[17] Miller W R. Psychological deficit in depression. *Psychol Bull* 1975; **82:** 238–60.