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Familial Aggregation of Alzheimer's Disease and Related Disorders: A Collaborative Re-Analysis of Case-Control Studies

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Case-control studies of Alzheimer's disease were re-analysed to examine the association of Alzheimer's disease with family history in first degree relatives of dementia, Down's syndrome and Parkinson's disease. Overall, the relative risk of Alzheimer's disease for those with at least one first degree relative with dementia was 3.5 (95% confidence interval 2.6–4.6). Stratification according to age of onset of Alzheimer's disease showed that the relative risk decreased with increasing onset age. However, among patients with an onset of disease after 80 years, there were still significantly more subjects with one or more first degree relatives with dementia as compared to controls (relative risk 2.6; 95% confidence interval 1.3–5.2). The relative risk of Alzheimer's disease was significantly lower in patients who had one first degree relative with dementia (relative risk 2.6; 95% confidence interval 2.0–3.5) as compared to those who had two or more affected relatives (relative risk 7.5; 95% confidence interval 3.3–16.7). Furthermore, the re-analysis showed a significant association between Alzheimer's disease and family history of Down's syndrome (relative risk 2.7; 95% confidence interval 1.2–5.7), which was strongest in those patients who had a positive family history of dementia. The relative risk of Alzheimer's disease for those with a positive family history of Parkinson's disease was 2.4 (95% confidence interval 1.0–5.8).

INTRODUCTION

Although the cause of Alzheimer's disease (AD) is still unknown, genetic factors seem to play an important role in its aetiology.[1,2,3–5] Together with age, a positive family history of dementia is one of the few established risk factors of AD.[6] AD has also been linked with a family history of Down's syndrome and of Parkinson's disease.[6,7] In this paper we present a re-analysis of case-control studies that examined familial aggregation of AD and other disorders.[7–16] The aims of this analysis were to compare risk estimates from the individual studies, to analyse the pooled data in order to obtain stable risk estimates, and to study subgroups in the pooled data set, based on gender, onset age and family history of dementia. First, we will briefly review the evidence for an association of AD with family history of dementia, Down's syndrome and Parkinson's disease.

Familial aggregation of Alzheimer's disease has been long recognised.[17,18] In a number of families the disease is apparently inherited as an autosomal dominant disorder.[2] It has been suggested that all cases of AD may be due to autosomal dominant inheritance.[1,19–22] Other studies have suggested a more complex mechanism, in which genetic as well as environmental factors may be implicated.[2,23–25] There is some evidence from genetic studies that the strength of familial aggregation of AD may vary with age of onset. Heston has suggested that familial aggregation of AD may be specific to early

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onset patients.[26] In his study, familial aggregation was observed only in early onset patients. The risk in relatives of autopsy-proven patients diagnosed after the age of 70 years was not statistically different from the risk in the general population. Thal and coworkers reported that nearly 50% of the patients with early onset of disease (<55 years) had a positive family history of dementia, as compared to only 25% of those with a late onset.[27] Although several studies have also supported this hypothesis,[12,28,32,34] modification of the association between AD and family history of dementia by age of onset was not observed in other studies.[29–31]

Family history of dementia has been studied in a variety of case-control studies.[7–9,11–13,15,16,35–36] Nine studies reported a significantly higher risk of AD for relatives of patients with dementia. The only study that failed to show familial aggregation of AD was of late onset patients.[12] In studies that comprised only early onset cases, an increase in risk of AD for subjects with a positive family history of dementia was consistently reported.[7,9,35]

Family history of Down's syndrome has been associated with AD. There is much evidence for a link between AD and Down's syndrome. The Alzheimer type neuropathological changes have been shown in patients with Down's syndrome[37–39] and genetic linkage to chromosome 21 has been reported in a number of families in which AD was apparently inherited as an autosomal dominant disorder.[3–5] These observations have led to the hypothesis of familial aggregation of AD with Down's syndrome. A higher frequency of presenile AD than expected has been observed in relatives of patients with Down's syndrome,[40] but this finding was not confirmed by a study of the family history of dementia of 188 patients with trisomy 21 and 185 controls.[41] It cannot be excluded, however, that AD is associated with family history of Down's syndrome due to translocations on chromosome 21.[41] Studies of the family history of Down's syndrome of patients with AD have also yielded equivocal results. Family history of Down's syndrome has been studied in ten studies.[9,11,12,16,19,20,26,31,32,42] Although seven studies observed more patients with a positive family history of Down's syndrome as compared to controls,[9,11,12,16,26,31,32] a significant association was established in only three studies.[9,16,26] The study of Heston suggested that the risk was only increased for early onset AD.[26] In three studies that have examined family history of Down's syndrome, no patients or controls with a positive family history were found.[19,20,42] So far it has not been possible to discern whether the negative findings of these studies reflect the low rate of occurrence of Down's syndrome (1 in 700 in the general population) or a true lack of association. Another issue to resolve is whether familial aggregation of AD with Down's syndrome is found more in familial cases specifically, as would be predicted by a genetic link between AD and Down's syndrome.

Parkinson's disease is a neurological disorder that has been associated with AD. AD and Parkinson's disease share several neuropathological characteristics[43] and it has been suggested that AD and Parkinson's disease may have a common aetiology.[44] Two case-control studies of AD have investigated family history of Parkinson's disease.[7,11] In both studies there were more Alzheimer patients with a first degree relative with Parkinson's disease as compared to age- and sex-matched population controls. In the largest study, a significant increase in risk was observed, particularly in men with early onset of AD.[7]

METHODS

Family history data have been assessed in seven case-control studies in this re-analysis[45] in which the data had been collected symmetrically for patients and controls (Table 1).[7,9,11–13,15,16] Family history was obtained in five studies by a personal interview,[7,9,11,12,16] in one study by telephone interview[15] and in one study by a questionnaire mailed to the informant.[13] In the Dutch study family history data were always verified by a second informant who was a first degree relative of the participant. The analysis was restricted to disorders in first degree relatives. To increase comparability, we restricted the case-control comparisons to control subjects derived from the population.

All seven studies collected data on family history of dementia. The analysis included all first degree relatives with a history of dementia, not AD specifically, because anamnestic information on the cause of dementia is not likely to be reliable. In addition, affected relatives may have been diagnosed years before, when the diagnosis of AD may have been less accurate. Family history of Down's syndrome has been assessed in seven studies.[7,9,11,12,16] In two studies, no distinction was made between Down's syndrome and mental retardation.[9,12] Family history of Parkinson's disease has been studied in two investigations.[7,11] Both studies have excluded patients with a history of Parkinson's disease before the onset of AD. In the Dutch study the diagnosis of Parkinson's disease was checked with independent medical records.[7] The number of first degree relatives, a putative confounder, was available in six of the seven eligible studies (Table 1).

The strength of the association was assessed by computing the odds ratio as an estimate of the relative risk

TABLE 1 *Studies of the EURODEM collaborative analysis of case-control studies that assessed family history of dementia, Down's syndrome or Parkinson's disease*

	Cases	Controls	Dementia	Down's syndrome	Parkinson's disease	Number siblings
Australia[16]	170	170	+	+	–	+
Italy[11]	116	97	+	+	+	+
Netherlands[7]	198	198	+	+	+	+
USA, Bedford[13]	102	162	+	–	–	–
USA, Denver[12]	64	64	+	+	–	+
USA, Durham[9]	46	92	+	+	–	+
USA, Seattle[15]	130	130	+	–	–	+

(RR). Conditional logistic regression analysis was used to take the effects of education, the number of siblings and the matching variables age and gender into account.[45] In this paper, we present the adjusted relative risks with 95% confidence intervals (95% CI). Stratified analyses were conducted based on gender, onset age and family history of dementia. For the latter subgroup, the family history was considered positive for those who had at least one first degree relative with dementia.

RESULTS

Family history of dementia

Table 2 shows the relative risks of AD for first degree relatives of patients with dementia in the seven individual studies and in the pooled analysis. Overall, the relative risk of AD for those with at least one first degree relative with dementia was 3.5 (95% CI 2.6–4.6). The test for heterogeneity indicated no evidence for heterogeneity in relative risks, except for the risk observed in the Denver study.[12] The latter study of late onset AD (onset age 70 years or over) deviated significantly ($p = 0.01$) from the other studies in the overall analysis as well as in a subgroup analysis of late onset Alzheimer patients. In the present study, the relative risks were similar for men (RR 3.9; 95% CI 2.5–6.5) and women (RR 3.3; 95% CI 2.3–4.6). Stratification according to age of onset of AD showed that the relative risk decreased with increasing onset age (Table 3). Although there were still significantly more late onset patients with a positive family history of dementia than controls, the relative risk differed significantly from the risk of early onset patients (onset before the age of 70 years). Table 4 shows that this finding was due to a lower relative risk for late onset AD for subjects with a demented parent. The percentage of patients of whom one of the parents was affected with dementia decreased with increasing onset age (Figure 1). The prevalence of dementia in parents of control subjects did not show a trend across the age strata. Figure 2 shows that the percentage of patients with one or more affected siblings increased with increasing onset age. Table 5 gives the relative risk for AD according to the number of first degree relatives with a history of dementia. There were 49 patients with two or more first degree relatives as compared to seven controls (RR 7.5; 95% CI 3.3–16.7). The risk of AD increased with the number of affected relatives (p-value for trend = 0.008). This trend was observed in early onset patients ($p = 0.013$) as well as late onset patients ($p = 0.005$).

TABLE 2 *Family history of dementia and the relative risk of Alzheimer's disease*

	Exposure frequency			
Study	Cases	Controls	RR*	95% CI
Australia	58/170	21/170	3.8	2.1–6.9
Italy	29/116	12/97	2.6	1.0–7.5
Netherlands	96/198	37/198	4.8	2.8–8.1
USA, Bedford	21/103	9/162	4.4	1.8–10.7
USA, Denver	21/54	18/50	1.0	0.5–2.2
USA, Durham	25/44	14/87	7.2	2.7–19.1
USA, Seattle	55/129	29/130	2.5	1.4–4.4
Overall analysis	305/814	140/894	3.5	2.6–4.6
Excluding USA, Denver	284/760	122/844	3.6	2.7–4.9

*Adjusted for age, gender, number of siblings and education

Family History of Down's Syndrome

In all studies included in the re-analysis there were

TABLE 3 *Family history of dementia and the relative risk of Alzheimer's disease by onset age*

	Exposure frequency			
Onset age (years)	Cases	Controls	RR*	95% CI
⩽59	97/272	37/327	4.0	2.4–6.1
60–69	76/183	31/205	5.3	2.8–10.0
70–79	72/196	43/198	2.3	1.4–3.6
80+	41/122	20/123	2.6	1.3–5.2

*Adjusted for age, gender, number of siblings and education

TABLE 4 *Family history of dementia and the relative risk of Alzheimer's disease by relationship*

Family history Dementia	Exposure frequency Cases	Controls	RR*	95% CI
Parents	190/814	95/894	2.3	1.8–3.1
Siblings	101/814	23/894	4.8	2.9–7.8
Onset patient before the age of 70 years:				
Parents	115/453	43/528	3.5	2.3–5.2
Siblings	40/453	9/528	4.4	2.1–9.0
Onset patient at age of 70 years or over:				
Parents	63/308	47/307	1.4	0.9–2.1
Siblings	57/308	14/307	4.7	2.5–9.0

*Adjusted for age, gender, numbers of siblings and education

more patients with a positive family history of Down's syndrome as compared to controls (Table 6). The test for heterogeneity indicated that there was no evidence for heterogeneity across studies. Overall, the relative risk of AD was 2.7 (95% CI 1.2–5.7) for first degree relatives of patients with Down's syndrome. Similar risks were observed for men and women and for early onset and late onset patients (Table 7). The relative risk tended to be higher for patients with a positive family history of dementia as compared to patients with no family history of dementia. However, the difference did not reach statistical significance.

Family History of Parkinson's Disease

Family history of Parkinson's disease was assessed in two studies (Table 8). In both studies, there were more patients with a positive family history of Parkinson's disease as compared to controls. Pooling of the studies yielded a relative risk for AD of 2.4 (95% CI 1.0–5.8) for those with a first degree relative with Parkinson's disease. No significant differences in relative risks were observed comparing men versus women, patients with a positive family history of dementia versus patients with no family history and early onset versus late onset patients (Table 9). However, relative risks tended to be higher for men and for patients with no family history of dementia.

DISCUSSION

This re-analysis of case-control studies of AD showed familial aggregation of dementia in both early onset and late onset AD. Significantly more Alzheimer patients than controls had a first degree relative with Down's syndrome. Furthermore the re-analysis supported a higher frequency of Parkinson's disease in first degree relatives of patients with AD.

These findings must be interpreted in light of the various problems encountered in case-control studies of AD. As the majority of studies were hospital-based for case selection, selection bias may result from differential referral of patients according to family history of dementia.[45] The pooled risk estimate, however, was very similar to the relative risks observed in the population-based studies of Hofman *et al.*[7] and Broe *et al.*[16] Another issue related to selection bias is that all studies included prevalent patients.[45] Observed associations may therefore relate to predictors of survival rather than to the risk of AD. However, in a sub-analysis of incident patients, i.e. patients included in the study within one year of diagnosis, risk estimates remained

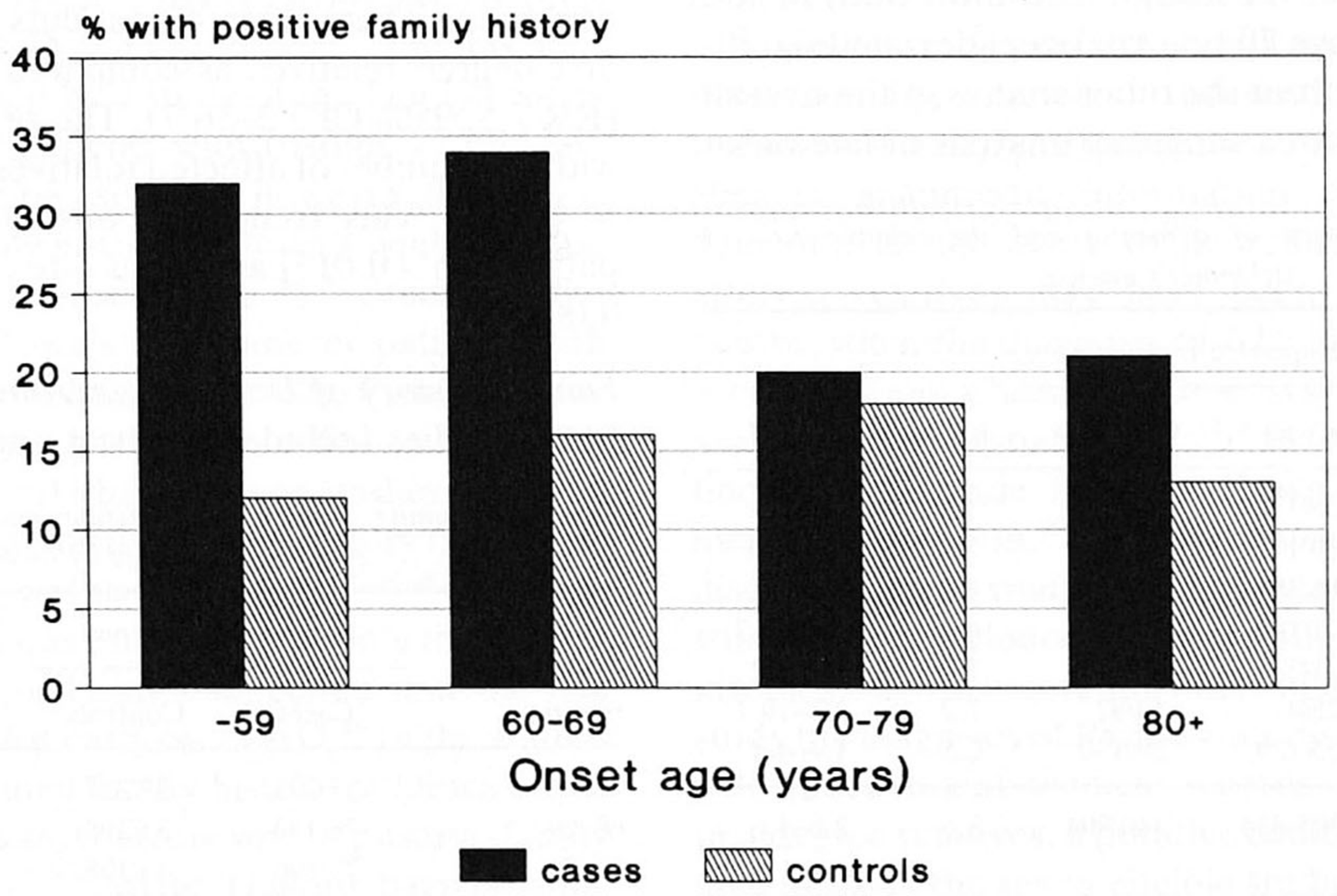

FIGURE 1 *Percentage of Alzheimer cases and controls with a positive family history of dementia in the parents.*

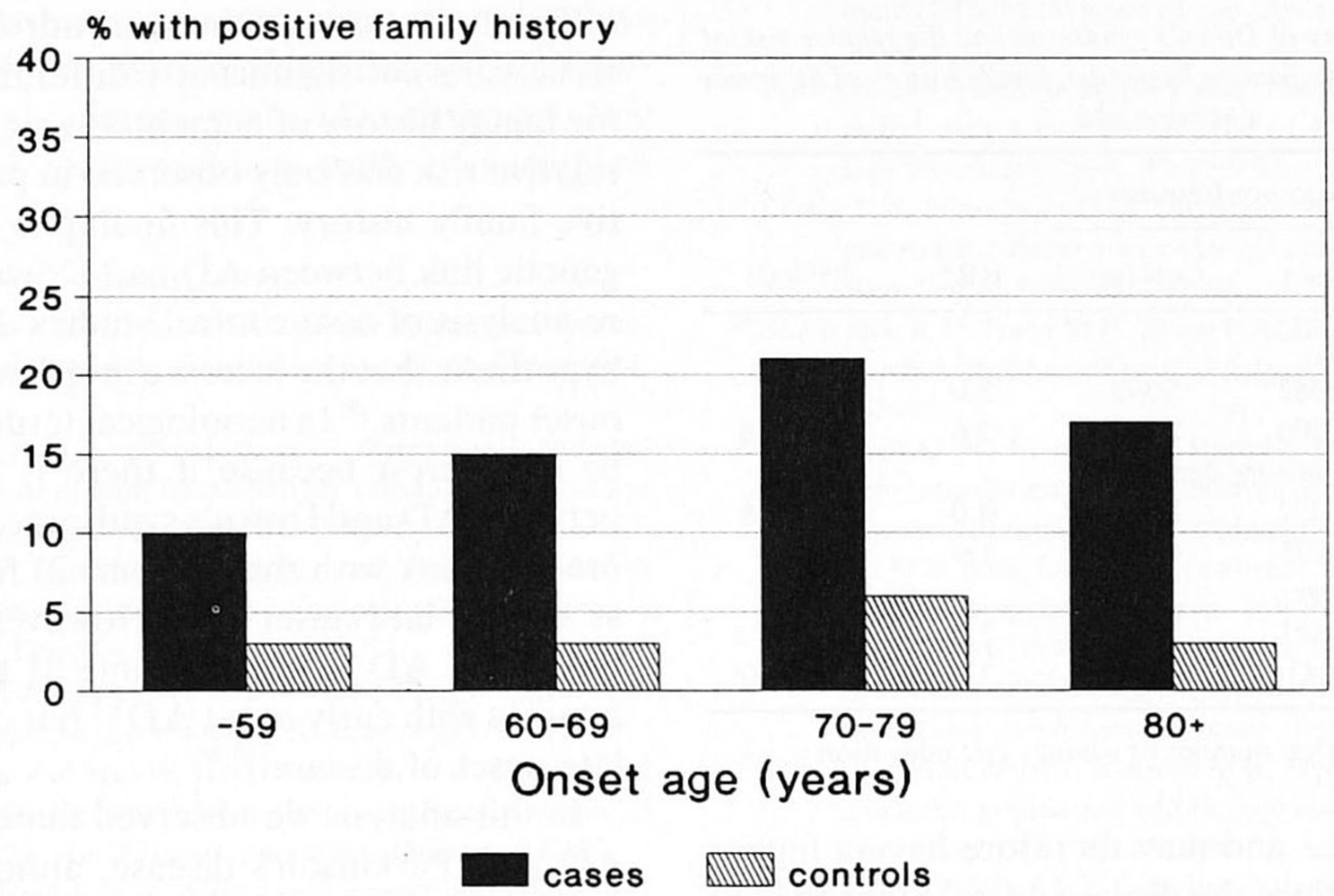

FIGURE 2 *Percentage of Alzheimer cases and controls with a positive family history of dementia in the siblings.*

virtually the same. As to information bias, non-differential misclassification may occur when assessing disease history in first degree relatives. A related issue is that we did not distinguish the type of dementia in relatives, which may not always have been of the Alzheimer type. Similarly, for Down's syndrome no distinction was made between Down's syndrome and mental retardation in two studies.[9,12] This has most likely led to an underestimate of the strength of association between AD and these disorders. Another problem in assessing family history of late onset disorders such as AD and Parkinson's disease is that misclassification may also occur because relatives are still at risk of the disease after the study or may have died before the expression of the disease. Assuming that such a censoring mechanism has been similar for first degree relatives of patients and controls, this type of bias can also be considered unlikely to affect the relative risk. Recall bias may be another important source of bias in these studies. Spurious associations may occur if relatives of patients pay more attention to the occurrence of other diseases in their family than relatives of control subjects. This is more likely to occur in assessment of disease in relatives who are more distantly related. We have therefore restricted the re-analysis to first degree relatives.

In this analysis of 814 patients with clinically diagnosed AD[46] and 894 age- and gender-matched control subjects we observed aggregation of dementia in the families of patients with early onset as well as those with late onset AD. For early onset AD, the risk was about four times elevated, which was significantly higher than the 2.5 elevation in risk for AD after the age of 70 years. The lower relative risk resulted from a lower prevalence of dementia in parents of late onset patients. No difference was observed in risks for early onset and late onset AD for history of dementia in siblings. An explanation for these findings may be related to the clustering of onset age within families.[2,47] Relatives of late onset patients are more likely to have a late

TABLE 5 *Family history of dementia and the relative risk of Alzheimer's disease by number of affected first degree relatives*

Number of relatives with dementia	Exposure frequency			
	Cases	Controls	RR*	95% CI
0	509	709	1	reference
1	206	103	2.6	2.0–3.5
2+	49	7	7.5	3.3–16.7

*Adjusted for age, gender, number of siblings and education

TABLE 6 *Number of subjects with a positive family history of Down's syndrome in Alzheimer cases and controls*

	Exposure frequency			
	Cases	Controls	RR*	95% CI
Australia	5/165	0/165	—	—
Italy	1/116	0/97	—	—
Netherlands	5/198	3/198	1.7	0.3–13.0
USA, Denver	2/64	0/64	—	—
USA, Durham	7/45	4/91	3.5	1.2–5.7
Overall analysis	20/588	7/615	2.7	1.2–5.7

*Adjusted for age, gender, number of siblings and education

TABLE 7 *Family history of Down's syndrome and the relative risk of Alzheimer's disease: stratification by gender, family history of dementia and onset age*

	Exposure frequency			
	Cases	Controls	RR*	95% CI
Stratification by gender:				
Women	15/382	5/398	3.0	1.2–7.3
Men	5/206	2/216	2.6	0.6–10.5
Stratification by family history dementia:				
Positive	12/227	3/248	4.0	1.3–12.5
Negative	7/275	4/275	1.9	0.6–6.0
Stratification by onset age:				
Before 65 years	9/327	3/348	2.8	1.1–7.5
65 years or over	9/243	4/241	2.6	0.7–10.0

*Adjusted for age, gender, number of siblings and education

onset of the disease and may therefore have a higher chance of dying before the disease onset. Since the life expectancy has most likely been higher for siblings than for parents, the chance of expressing the disease may have been higher in siblings of late onset patients. Alternatively, if there is a true difference in relative risk for late onset AD between those who have an affected sibling and those who have an affected parent, this would suggest that familial aggregation of late onset AD may be of non-genetic or multifactorial origin. This finding is also compatible with a recessive disorder. A second finding which may point to heterogeneity is that the risk of AD was significantly different for those with two or more first degree relatives with dementia as compared to those with one.

There were significantly more patients with a first degree relative with Down's syndrome than control subjects. Although each of the individual studies showed a higher frequency of Down's syndrome in the family of patients, a significant increase in risk of AD for subjects with a positive family history of Down's syndrome could only be shown after pooling of the data. This may be explained by the fact that Down's syndrome is a relatively rare disorder and large numbers of relatives are therefore needed to establish an increase in risk. Our findings confirm earlier studies of family history of Down's syndrome.[9,16,26] Although risks were not significantly different when stratifying for family history of dementia, a significant increase in relative risk was only observed in patients with a positive family history. This finding is compatible with a genetic link between AD and Down's syndrome. The re-analysis of case-control studies did not confirm the hypothesis that the increase in risk was specific to early onset patients.[26] In aetiological terms, this finding may be of interest because if there is a true association between AD and Down's syndrome, our finding would predict a link with chromosome 21 for both early onset as well as late onset AD. However, to date, genetic linkage of AD to chromosome 21 has been shown in families with early onset AD[3–5] but not in families with late onset of disease.[48,49]

In this analysis we observed familial aggregation of AD with Parkinson's disease, although patients with Parkinson's disease before the onset of AD were excluded in the case selection. The relative risk tended to be higher in men as compared to women. In the interpretation of these findings it is important to note that the diagnosis of AD was clinically assessed. Since the type of dementia was not confirmed pathologically, we cannot exclude the possibility that the higher frequency of Parkinson's disease has occurred specifically in the family of patients who suffered from dementia caused by parkinsonism or Lewy body disease.

In conclusion, this re-analysis confirmed earlier studies that reported familial aggregation of early onset AD. In contrast to earlier studies, the re-analysis also showed familial aggregation of late onset AD. The association between AD and family history of dementia, however, was weaker in late onset patients. Pooling of the data showed a significant increase in relative risk of AD for subjects with a first degree relative with Down's syndrome. Individual studies may have lacked

TABLE 8 *Number of subjects with a positive family history of Parkinson's disease in Alzheimer cases and controls*

	Exposure frequency			
	Cases	Controls	RR*	95% CI
Italy	6/114	3/96	2.0	0.4–14.8
Netherlands	14/198	5/198	2.8	1.0–10.8
Overall analysis	20/312	8/294	2.4	1.0–5.8

*Adjusted for age, gender, number of siblings and education

TABLE 9 *Family history of Parkinson's disease and the relative risk of Alzheimer's disease: stratification by gender, family history of dementia, and onset age*

	Exposure frequency			
	Cases	Controls	RR*	95% CI
Stratification by gender:				
Women	11/198	6/186	1.6	0.5–4.9
Men	9/114	2/108	4.4	0.9–20.9
Stratification by family history dementia:				
Positive	7/124	4/121	1.8	0.5–6.1
Negative	13/188	4/173	3.2	0.9–11.5
Stratification by onset age:				
Before 65 years	16/272	8/258	2.4	1.0–5.8
65 years or over	4/29	0/25	—	—

*Adjusted for age, gender, number of siblings and education

statistical power to assess an association. The re-analysis also supported the hypothesis of familial aggregation of Parkinson's disease with AD. However, this finding should be confirmed in a study of autopsied patients.

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