

# Risk Factors for Alzheimer's Disease: Overview of the EURODEM Collaborative Re-Analysis of Case- Control Studies

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Studies of risk factors for Alzheimer's disease have been hampered by low statistical power. The data from 11 case-control studies were pooled and re-analysed to evaluate the evidence for the association of Alzheimer's disease with family history of dementia and related disorders, parental age, medical history, and environmental factors. This paper gives a brief description of the participating studies and discusses the strategy that has been followed in the collaborative analysis.

## INTRODUCTION

Case-control studies have yielded few leads about the aetiology of Alzheimer's disease (AD).<sup>1,2</sup> Although advanced age and a positive family history of dementia have been consistently associated with AD, studies on the role of other putative risk factors have yielded contradicting results. A major concern in the interpretation of these findings is the low statistical power of the individual case-control studies. Although the largest study comprised 392 cases and 392 age- and gender-matched controls, the size of the other studies varied from 34 to 198 cases.<sup>3-13</sup> Given an exposure frequency of 0.10 in controls, a significance level of 0.05 (two-sided) and a power of 0.90, the largest detectable relative risk is 3.4 in a study of 100 cases and 100 controls and 2.5 in a study of 200 cases and 200 controls.<sup>14</sup> The relatively small sample size of the individual studies may therefore explain some of the apparently conflicting results.

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In a collaborative re-analysis based on raw data of 11 case-control studies, we evaluated the evidence for the association of AD with family history of dementia and related disorders, parental age, head trauma, medical and psychiatric history, and environmental factors. The aim of the analysis was to study risk factors for AD, with sufficient power to detect associations with relatively rare exposures and with specific subgroups of AD. In addition, individual studies were re-analysed to see whether associations were consistently found across studies. In this paper, we will give a brief overview of the case-control studies that contributed data to the re-analysis and discuss the strategy that has been followed in the analysis.

## DESCRIPTION OF THE INDIVIDUAL STUDIES

All case-control studies of AD conducted before 1 January 1990, were traced through medline search, review papers, and personal contacts. Studies in which the patients did not meet the NINCDS-ADRDA or DSM III criteria for the clinical diagnosis of AD were excluded.<sup>15,16</sup> Thus, 11 studies were identified as eligible for the re-analysis. Table 1 gives an overview of the selection of cases in the individual studies. The selection of control subjects in each study is described in Table 2. In the tables, the studies are ordered alphabetically by country and city of origin.

TABLE 1 Selection of cases in the 11 case-control studies

Country, Principal Investigator	Number of		Eligibility criteria					Response rate	Informant	Data collection
	cases	controls	Age onset	Gender†	Period of diagnosis	Exclusion criteria**				
Australia Broe, Henderson, Creasey, Jorm	170	170	all	M&F	1986- 1988	Not English speaking No suitable informant	—	Next of kin	Structured interview at home	
Finland Soininen	63	91	>65	M&F	1979	Oligophrenia Chromosomal abnormality MID (H.I.S. >7) Other secondary dementias	61%	Next of kin Parish records	Structured interview	
Italy Amaducci, Fratiglioni	116	213	40-80	M&F	1982- 1983	No next of kin available Residence outside regions of participating centers	79%	Next of kin	Structured interview at home	
Japan Kondo	34	68	all	M&F	—	No suitable informant Cerebrovascular lesions	—	Spouse	Structured interview	
The Netherlands Hofman	198	198	<65	M&F	1980- 1987	MID (H.I.S. >7) Parkinson's disease Other secondary dementias	99%	Next of kin	Structured interview at home	
USA—Bedford Shalat	106	214	all	M	1975- 1982	History of alcoholism History of severe head trauma Residence outside Eastern Massachusetts	77%	Next of kin	Mailed questionnaire with additional phone calls	
USA—Denver Chandra	64	64	>70	M&F	1975- 1985	No suitable informant	100%	Next of kin	Structured interview	
USA—Durham Heyman	46	92	<67	M&F	—	History of stroke History of alcoholism Parkinson's disease	100%	Next of kin	Structured interview	
USA—Minneapolis Schuman, Mortimer	78	124	all	M	1979- 1982	Secondary dementias	98%	Informant who lived >5 years with patient	Structured interview	
USA—Rochester Kokmen	392	392	all	M&F	onset 1960- 1974	Residence outside Rochester Other dementias	not applicable	Medical records		
USA—Seattle Graves	130	130	all	M&F	1980- 1985	MMSE >26 Parkinson's disease Major affective disorder Hypothyroidism History of stroke No suitable informant	69%	Next of kin	Structured interview by telephone	

\*NINCDS-ADRDA denotes the criteria for Alzheimer's disease from the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association;<sup>15</sup> DSM-III denotes the criteria for Alzheimer's disease from the Diagnostic and Statistical Manual for mental disorders, 3rd edition;<sup>16</sup> \*\*MID denotes Multi-Infarct Dementia; HIS denotes Hachinski Ischemic Score;<sup>17</sup> MMSE denotes Mini-Mental State Examination;<sup>18</sup> †M denotes Males, F denotes Females.

TABLE 2 Selection of controls in the 11 case-control studies

Country, Principal Investigator	Number of		Origin of controls	Matching variables	Eligibility criteria*	Exclusion criteria	Response rate	Informant	Data collection
	cases	controls							
Australia Broe, Henderson, Creasey, Jorm	170	170	Population	Gender Age ( $\pm 3$ years) GP practice	MMSE > 26	Not English speaking No suitable informant	—	As for cases	As for cases
Finland Soinenen	63	91	Nursing home Population	Gender Age Institutionalizing period	Age > 65 No dementia	As for cases Encephalitis Meningitis	$\pm 50\%$	Subject	As for cases
Italy Amaducci, Fratiglioni	116	213	Hospital: 116 Neighbourhood/ friend: 97	Gender Age ( $\pm 3$ years) Residence Hospital (if applicable)	No dementia (Blessed)	As for cases Relative of case	—	As for cases	As for cases
Japan Kondo	34	68	Neighbourhood	Gender Age ( $\pm 5$ years) Residence			—	Subject	As for cases
The Netherlands Hofman	198	198	Population	Gender Age ( $\pm 5$ years) Residence	No dementia (SPMSQ)		61%	As for cases	As for cases
USA—Bedford Shalat	106	214	Neighbourhood	Gender Age Residence		Household < 2 registered voters	31%	As for cases	As for cases
USA—Denver Chandra	64	64	Hospital	Gender Age ( $\pm 3$ years) Relationship Race	No dementia (SPMSQ)	As for cases	100%	As for cases matched for relationship	As for cases
USA—Durham Heyman	46	92	Population random-digit dialing	Gender Age ( $\pm 5$ years)	MMSE > 21		100%	As for cases	As for cases
USA—Minneapolis Schumann, Mortimer	78	124	Hospital: 76 Neighbourhood 48	Gender Age ( $\pm 3$ years) Race, Residence	No dementia	As for cases	Hospital: 84% Neighbour- hood: 64%	As for cases	As for cases
USA—Rochester Kokmen	392	392	Register	Gender Age ( $\pm 3$ years)	No dementia through index year	Symptoms of dementia	Not applicable	As for cases	As for cases
USA—Seattle Graves	130	130	Friend or non- blood relative of case	Gender Age ( $\pm 10$ years)	No memory loss	As for cases	—	As for cases matched for relationship	As for cases

\*MMSE denotes Mini-Mental State Examination;<sup>18</sup> Blessed denotes Blessed information, memory and concentration test;<sup>19</sup> SPMSQ denotes Short Portable Mental Status Questionnaire.<sup>20</sup>

In 9 of the 11 studies data collection has been symmetrical for cases and controls. In most studies, data were collected by interviewing a next of kin in person. There were three studies that differed in this respect. In the study conducted in Bedford, USA<sup>8</sup> data were collected by mailed questionnaires, in the Rochester study<sup>9</sup> only medical records were used and in the Seattle study<sup>12</sup> the data were collected by telephone interview. Four studies (Australia, Finland, The Netherlands, USA Rochester) can be considered as population based, i.e. they aimed at a full ascertainment of cases with AD in a defined geographical area.<sup>4,9,10,11</sup> An important feature of all 11 case-control studies is that each is based on prevalent cases, who may have been diagnosed with AD for several years, as well as incident or newly diagnosed cases.

#### *Australia*

This study was conducted by Broe, Henderson, Creasey, Jorm *et al.* and comprised 170 cases and 170 population controls.<sup>11</sup> The study aimed at a complete ascertainment of Alzheimer cases in a series of general practices in Sydney. Ascertainment was carried out through dementia clinics at two hospitals and the general practitioners in the catchment area of these hospitals. For cases, there were no inclusion criteria for onset age, but the large majority was of late onset. Cases were diagnosed between 1986 and 1988. Controls were matched for age, gender and general practice. Data collection was completely symmetrical for cases and controls, i.e. for both cases and controls data were obtained by a structured interview of a next of kin.

#### *Finland*

The study of Soininen *et al.* comprised 63 Alzheimer cases with an onset of disease of 65 years or older.<sup>3</sup> This study was conducted in 1979 and aimed to ascertain all patients with the diagnosis of dementia in a defined geographical area of eastern Finland. The response rate for cases was 61%. Controls (N = 91) were randomly drawn from nursing homes and the general population. Cases and controls were matched for gender, age and institutionalization and length of stay. Data collection was not symmetrical for cases and controls: control subjects were interviewed directly whereas the information of the cases was obtained by interviewing an informant.

#### *Italy*

Amaducci, Fratiglioni *et al.* conducted a hospital based multi-centre study of 116 Alzheimer cases.<sup>6</sup> Cases were diagnosed in 1982 and 1983. Patients with a disease

onset between 40 and 80 years were eligible. Most cases were of early onset: the onset of 91% of the sample was before 70 years. The response rate for cases was 79%. There were two control populations in this study: 116 hospital controls and 97 neighbourhood controls. Cases and controls were matched for gender, age, area of residence and hospital. Response rates for controls were unknown. For both cases and controls an informant was interviewed.

#### *Japan*

The study of Kondo *et al.* comprised 34 cases and 68 neighbourhood controls.<sup>13</sup> Case selection was hospital based and there were no inclusion criteria for onset age. Information for the cases was obtained from the spouse. Cases and controls were matched for age and gender. Data collection was not symmetrical for cases and controls. For cases an informant was interviewed whereas control subjects were interviewed directly.

#### *The Netherlands*

The study of Hofman *et al.* comprised 198 cases with early onset AD and 198 population controls.<sup>10</sup> The study aimed at a complete ascertainment of Alzheimer patients in whom the diagnosis was made before the age of 70 years in four Northern provinces of the Netherlands and the area of metropolitan Rotterdam. Ascertainment was carried out through all neurological, psychiatric and geriatric services in the study areas. All cases were diagnosed between 1980 and 1987 and the response rate for cases was 99%. Control subjects were drawn randomly from the same municipality as the cases. Cases and controls were matched for age, gender and area of residence. The response rate for control subjects was 61%. For both cases and controls an informant was interviewed.

#### *USA, Bedford, Massachusetts*

The study of Shalat *et al.* comprised 106 Alzheimer patients diagnosed between 1975 and 1982.<sup>8</sup> Since the cases were derived from a Veterans hospital, all cases were male. Although there were no restrictions for age of onset, the onset of disease of the majority (61%) of the patients was before the age of 65 years. Neighbourhood controls (n = 214) were drawn from lists of registered voters. The cases could be matched for gender and age to 162 controls. The response rate was 77% for cases and 31% for controls. Data were collected by self-administered questionnaires, mailed to a next of kin of cases and controls. Additional phone calls were made for verification and clarification of incomplete questionnaires. The study aimed to collect the data symmetrically for cases and controls in that informants

of control subjects were asked not to consult the study subject for information.

#### *USA, Denver, Colorado*

Chandra *et al.* have studied 64 cases with late onset AD, i.e. onset age after 70 years.<sup>7</sup> Cases were diagnosed in the period 1975–1985. This hospital based study was conducted in a geriatric outpatient clinic. Cases were compared to hospital controls, matched for gender, age and race. In addition, cases and controls were matched for relationship to informant. Information was collected symmetrically for cases and controls. The response rate was 100% for cases as well as controls.

#### *USA, Durham, North Carolina*

The study of Heyman *et al.* included 46 cases with early onset AD and 92 population controls.<sup>4</sup> Case selection was hospital based. The response rate for patients was 100%. Controls were selected from the population by random-digit dialing. Cases and controls were matched for gender and age. The response rate was 100% for controls. For cases as well as controls, data were collected by a structured personal interview with a next of kin.

#### *USA, Minneapolis, Minnesota*

The study of Schuman, Mortimer *et al.* was conducted in a Veterans hospital.<sup>5</sup> The study comprised 78 male cases, diagnosed between 1979 and 1982. There were two control populations in this study: 76 hospital controls and 48 neighbourhood controls. Cases and controls were matched for gender, age and race. For both cases and controls an informant was interviewed. The response rate for cases was 98%. For hospital controls and neighbourhood controls, the response rates were 84% and 64% respectively.

#### *USA, Rochester, Minnesota*

The study of Kokmen *et al.* was based on the Rochester register.<sup>9</sup> The study included all patients with AD with an onset of disease between 1960 and 1974. The register is considered to give a nearly complete ascertainment of Alzheimer patients admitted to hospitals and outpatient facilities in the Rochester area. Control subjects were also drawn from the register. However, since the register has been shown to cover over 95% of the Rochester population, the control subjects may be considered population based. This is the largest case-control study conducted to date. The study comprised 392 cases and 392 control subjects. Since the data collection was completely based on medical records, this study only yielded information on medical history.

#### *USA, Seattle, Washington*

The study of Graves *et al.* was a hospital based study of 130 cases diagnosed between 1980 and 1985.<sup>12</sup> For cases, there were no exclusion criteria for onset age. The response rate was 69%. Cases were compared to 130 neighbourhood controls, matched for gender and age. Furthermore, cases and controls were matched for relationship to informant. Data were collected by telephone interview. Information was collected symmetrically for cases and controls.

#### STRATEGY OF ANALYSIS

The raw data of all 11 studies were centralized at the Department of Epidemiology and Biostatistics of the Erasmus University Medical School, Rotterdam, The Netherlands. The principal investigators of the studies were invited to a first workshop on the collaborative re-analysis and they all attended this meeting. During this workshop, the strategy of analysis was discussed with other invited epidemiologists and biostatisticians. In working groups, the analyses for the putative risk factors were prepared. On the basis of these discussions, the data were re-analysed and the results of these analyses were discussed during a second workshop.

In the re-analysis, only studies in which the data were collected symmetrically for cases and controls have been included. Two studies (Finland and Japan) did not fulfil this criterion, in that control subjects were interviewed personally but the patient's history was taken indirectly from an informant.<sup>3,13</sup> A second restriction concerned the control subjects. Only three studies in which the data were collected symmetrically included a group of hospital controls,<sup>5–7</sup> and two of these studies also had a population control group.<sup>5,6</sup> To increase comparability with the other studies, the analysis was restricted to population controls for studies with two control groups. A separate analysis based on hospital controls gave generally similar findings. Since we were interested in aetiological factors, only exposures more than one year before the disease onset were included in the analysis. In control subjects, only exposures before the age of onset of the matched case were considered.

The strength of the association between AD and the putative risk factors was assessed by computing of the odds ratio as an estimate of the relative risk.<sup>14</sup> Relative risks were estimated by maximum likelihood and the 95% confidence intervals were based on the asymptotic standard errors. Since all included studies were matched for age and gender, relative risks were estimated using conditional logistic regression analyses.<sup>14</sup> Thus, possible confounding by age and sex was taken care of by the matched design and the matched analy-

TABLE 3 Risk factors assessed in the 11 case-control studies

Risk Factor (n = number of studies)	Australia	Finland	Italy	Japan	Netherlands	USA Bedford	USA Denver	USA Durham	USA Minneapolis	USA Rochester	USA Seattle	Total
<i>Family history of:</i>												
Dementia												883 cases
n = 9	+	+	+	+	+	+	+	+	-	-	+	1190 controls
Down's syndrome	+	+	+	+	+	-	+	+	-	-	-	678 cases
n = 7	+	+	+	+	+	-	+	+	-	-	-	877 controls
Parkinson's disease	-	-	+	-	+	-	-	-	-	-	-	314 cases
n = 2	-	-	+	-	+	-	-	-	-	-	-	411 controls
Parental age	+	-	+	+	+	-	-	+	+	-	+	653 cases
n = 7	+	-	+	+	+	-	-	+	+	-	+	759 controls
<i>Patient history:</i>												
Head trauma	+	+	+	+	+	+	+	+	+	+	+	1385 cases
n = 11	+	+	+	+	+	+	+	+	+	+	+	1739 controls
Anaesthesia	+	-	+	+	+	-	-	+	+	+	+	1145 cases
n = 8	+	-	+	+	+	-	-	+	+	+	+	1352 controls
Thyroid disease	+	+	+	-	+	+	+	+	+	+	+	1350 cases
n = 10	+	+	+	-	+	+	+	+	+	+	+	1668 controls
Epilepsy	+	+	-	+	+	+	-	+	+	+	-	1145 cases
n = 8	+	+	-	+	+	+	-	+	+	+	-	1401 controls
Viral infections	+	+	+	+	+	-	+	+	+	+	+	1165 cases
n = 10	+	+	+	+	+	-	+	+	+	+	+	1321 controls
Bacterial infections	+	+	-	+	+	-	-	+	+	+	-	975 cases
n = 7	+	+	-	+	+	-	-	+	+	+	-	1123 controls
Atopy	+	-	+	-	+	-	-	-	+	-	+	692 cases
n = 5	+	-	+	-	+	-	-	-	+	-	+	835 controls
Osteoarthritis	+	-	-	-	-	-	-	+	+	-	-	288 cases
n = 3	+	-	-	-	-	-	-	+	+	-	-	374 controls
Blood transfusion	+	-	+	-	+	-	-	+	+	-	-	602 cases
n = 5	+	-	+	-	+	-	-	+	+	-	-	785 controls
Severe headaches	+	-	-	-	+	-	-	+	+	-	-	486 cases
n = 4	+	-	-	-	+	-	-	+	+	-	-	572 controls
Psychiatric disorders	+	+	-	+	+	+	-	+	+	+	-	1145 cases
n = 8	+	+	-	+	+	+	-	+	+	+	-	1401 controls
Alcohol intake	+	+	+	+	+	+	-	+	+	-	+	935 cases
n = 9	+	+	+	+	+	+	-	+	+	-	+	1288 controls
Smoking habits	+	+	+	+	+	+	+	+	+	-	+	991 cases
n = 10	+	+	+	+	+	+	+	+	+	-	+	1300 controls
Occupational exposures	+	-	-	+	-	+	-	+	+	-	-	428 cases
n = 5	+	-	-	+	-	+	-	+	+	-	-	656 controls
Level of education	+	+	+	+	+	+	+	+	+	-	+	996 cases
n = 10	+	+	+	+	+	+	+	+	+	-	+	1349 controls

sis. Potential confounding by family history of dementia and education was controlled by entering these variables into the logistic regression model. For family history of dementia, cases and controls with one or more first degree relatives affected with dementia were considered to have a positive family history. The number of years of education was available in ten studies<sup>3-8,10-13</sup> and was added as a potential confounder to the conditional logistic regression model. Education was also considered as a dichotomous variable (less than 12 years education versus 12 years education or more), to allow for a possible threshold effect. To test whether the relative risks differed significantly across studies, covariables representing the interaction between the studies and the determinant were entered into the model. If the overall test for heterogeneity was significant, the study that differed was excluded and heterogeneity across the other studies was again tested. In case of heterogeneity, pooled relative risks were estimated including and excluding the deviant studies. Stratified analyses were conducted based on gender, onset age and family history of dementia. For onset age and family history of dementia we did not break the matching of the patients and controls.

Two additional analyses were conducted to exclude some possible sources of bias. First, since the studies were partly based on prevalent cases, selection bias may result from differential survival. The observed risk factors may therefore relate to predictors of survival, rather than to the risk of AD. To overcome this problem, subgroup analyses were conducted in incident cases, i.e. in patients who participated in the study within one year after diagnosis. Another subgroup analysis was related to information bias, which may occur in particular when cases and controls are not matched for relationship to informant. To investigate the effect of this type of possible bias, we conducted analyses including only matched pairs which were concordant for relationship to informant.

A great variety of risk factors has been studied in the 11 case-control studies (Table 3). For this re-analysis, the risk factors were grouped into six categories: (1) family history of dementia and related disorders; (2) parental age; (3) head trauma; (4) medical history; (5) psychiatric history; and (6) environmental factors. For each risk factor, exposure definition and comparability of measurement across studies were evaluated before re-analysing the data. This procedure and the results of the collaborative re-analysis are presented in seven separate papers in this supplement.<sup>21-27</sup>

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APPENDIX: EURODEM RISK FACTORS  
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