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Maternal Age and Alzheimer's Disease: A Collaborative Re-analysis of Case-Control Studies

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To investigate the possible association between Alzheimer's disease and late maternal age at index birth, we conducted a collaborative re-analysis of existing case-control data sets. Of the 11 studies participating in the EURODEM project, four were included in the analyses regarding maternal age. In all four studies, cases were matched to controls by age and gender, and only population controls were considered. Analyses were conducted on the individual data sets, on the pooled sample, and on subgroups defined by gender, age at onset, and familial aggregation of dementia. Maternal age of 40 years and over was found to be suggestively associated with a higher risk of Alzheimer's disease (overall relative risk = 1.7; 95% confidence intervals: 1.0–2.9). In subgroup analyses, the association was statistically significant for women and for sporadic cases. Adjustments for education or analyses restricted to case-control pairs matched by type of respondent did not modify these results noticeably. The association was confirmed by a test of consistency with the Down's syndrome risk model; results of this test were again more definite for sporadic Alzheimer's disease. In addition, three of the four studies also suggested an increased risk for maternal age at index birth between 15 and 19 years (overall relative risk = 1.5; 95% confidence intervals: 0.8–3.0). Although consistency across studies was not always complete, only some of the increased relative risks reached statistical significance, and information regarding maternal age obtained through a next-of-kin interview may have limitations, our study suggests that both early and late maternal age should be further investigated as possible risk factors for Alzheimer's disease.

INTRODUCTION

A link between Down's syndrome and Alzheimer's disease (AD) was suggested by the observation that patients with Down's syndrome often develop dementia if they survive beyond age 40; in addition, the pathological and neurochemical changes found in the brains of Down's syndrome patients are similar to those found in AD.[1] Epidemiological data suggest some degree of familial aggregation between Down's syndrome and AD, raising the possibility of a common genetic predisposition.[2,3] In summary, a link between AD and Down's syndrome exists on clinical, pathological, neurochemical, and epidemiological grounds; however, the biological explanation of this link is still not apparent.[3]

Because of the analogy with Down's syndrome, in which the risk rises with increasing maternal age, several researchers investigated late maternal age at the subject's birth as a possible risk factor for AD. We were able to trace 12 studies reporting on this specific putative risk factor;[4–15] one additional study looked at the dementia syndrome.[16] Surprisingly, maternal age was one of the most widely investigated risk factors for AD. In some studies, maternal age was included in a broader list of suspected factors; however, several other investigations were specifically designed to test this hypothesis. The results, as reported in the literature, are summarized in Table 1.

Cohen *et al* and Whalley *et al* found the mean age of the mother at the subject's birth to be significantly higher in cases than in controls.[4,5] However, the difference in mean age was not significant in later studies by

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TABLE 1 *Association between Alzheimer's disease and late maternal age at index birth (as reported in the literature)*

Author	Alzheimer's disease No. of cases	Controls Type & No. *(a)*	Measure of Association *(b)*	Significance *(c)*	Comments
Cohen *et al* 1982[4]	80	(P) 590	Difference in mean age = 8.5 years	S	Mean maternal age at patient's birth vs mean age at control's birth
Whalley *et al* 1982[5]	69	(P) 207	Difference in mean age = 2.0 years	S	(As above). Significant difference also for age of father
Knesevich *et al* 1982[6]	42	(H) 42	Difference in mean age = −2.7 years	NS	(As above). Non-significant negative difference
Corkin *et al* 1983[7]	37	(P) 34	Difference in mean age = 0.3 years	NS	(As above). No significant difference for age of father
Heyman *et al* 1983[8]	36	(P) 36	Difference in mean age = 0.2 years	NS	(As above). No significant difference for age of father
English & Cohen 1985[9]	69	(P+H) 94	RR = 0.4 RR = 1.0 RR = 0.7 RR = 1.4	NS NS NS NS	Mother's age 25–29 vs <25 Mother's age 30–34 vs <25 Mother's age 35–39 vs <25 Mother's age ⩾40 vs <25
Amaducci *et al* 1986[10]	116	(H) 116 (P) 97	(H) RR = 2.5 (P) RR = 4.7	NS S	Mother's age >40 vs ⩽40. Inconsistent findings for paternal age in the 2 control groups
White *et al* 1986[11]	112	(Sibs) 92 *(d)*	Difference in mean age = 1.6 years	NS *(e)*	Mean maternal age at birth of patient vs. mean age at birth of non-affected siblings
Urakami *et al* 1988[12]	77	(H) 52 *(f)*	Difference in mean age = 2.5 years	S	Mean maternal age at patient's birth vs. mean age at control's birth. Significant difference also for age of father.
De Braekeleer *et al* 1988[13]	120	(sibs) (*g*)	Difference in mean age = −2.1 years	[S] *(h)*	Mean maternal age at birth was lower for Alzheimer's disease cases than for normal siblings. Significant negative difference also for paternal age.
Schoenberg *et al* 1988[14] *(i)*	87 (sporadic cases only)	(H) 87 (P) 71	(H) RR = 5.0 (P) RR = 3.7	S S	Mother's age >40 vs ⩽40
Hofman *et al* 1990[15]	184	(P) 184	RR = 1.1 *(j)*	NS	Mother's age ⩾40 vs < 40 No significant difference also for age of father
	94 (sporadic cases only)	(P) 94	RR = 0.9 *(k)*	NS	(As above).

a (H) = Hospital controls; (P) = Population controls.
b RR = Relative Risk, this is the ratio of the risk of disease in those with the factor to the risk of disease in those without the factor. The relative risk was estimated through the odds ratio.
c S = p< = 0.05; NS = p>0.05.
d Also 200 randomly selected births were used as controls (population controls) in the study.
e p = 0.07; the p value was nearly significant.
f Controls were patients affected by multi-infarct dementia. Both cases and control were population-based.
g Unspecified number of Alzheimer's disease patients' siblings. Also spouses and six population control groups were used.
h Significant opposite findings: maternal age at birth was significantly lower for cases than for normal siblings.
i Re-analyses of the Italian case-control study.[10]
j The difference in mean maternal age was also reported = 0.7 years (NS).
k The difference in mean maternal age was also reported = 0.3 years (NS).

Knesevich *et al*, Corkin *et al*, and Heyman *et al*.[6–8] English and Cohen computed a series of relative risks for different ages of the mother; the study failed to show a trend of increasing risk of AD in the offspring with increasing age of the mother.[9] The Italian case-control study showed a significant association when comparing cases to population controls; the association was suggestive but did not reach statistical significance in the comparison with hospital controls.[10] White *et al*, found the mean age of the mother at the subject's

birth to be higher for cases than for unaffected siblings ($p = 0.07$); however, the difference did not reach conventional statistical significance. The authors suggested that late maternal age might be an important risk factor only for a subgroup of AD cases.[11]

Among more recent studies, one conducted in Japan, showed a significant case-control difference for both maternal and paternal age;[12] however, another investigation from Canada showed a significant difference for both maternal and paternal age in the opposite direction: maternal and paternal ages were more advanced at unaffected siblings' than at AD patients' birth. In addition, no association with late maternal age was found using spouses or six population control groups for comparison; such consistent findings strengthen the negative result.[13] Also the study by Hofman *et al*, conducted in the Netherlands, failed to show a significant association.[15]

Despite these inconsistent findings, two facts are in support of a possible association. First, Table 1 shows that in all studies to date, except two, the mean maternal age for cases was consistently greater than for controls; the difference reached statistical significance in some studies. Second, recent subgroup analyses of the Italian case-control study suggested that late maternal age is a specific risk factor for sporadic AD but not for familial AD.[14] Therefore, some of the current negative epidemiological data might simply be due to an intermixture of familial and sporadic cases of AD in the study sample.[3,14]

To further test the possible association between AD and late maternal age, we conducted a collaborative re-analysis of existing case-control data sets as part of the European Community Concerted Action 'Epidemiology and Prevention of Dementia' (EURODEM).

METHODS

Details regarding the overall methodology of the EURODEM collaborative re-analysis of case-control studies are reported elsewhere.[17] Of the 11 case-control studies contributed to the project, only seven investigated late maternal age and employed a symmetrical method of data collection. Of those seven studies, three were excluded because the response rate regarding maternal age was under 60% for either cases or controls (USA, Denver; USA, Durham; and USA, Minneapolis).[17] In summary, only four case-control studies were included in the present re-analyses; their geographical location and sample size are reported in Table 2.

In all four studies, cases were matched to controls by age and gender, and only population controls were considered. Consistent with the matched design, only matched-pair analyses were conducted. The relative risk was estimated through the calculation of the odds ratio. Statistical testing was done at the conventional two-tailed level of 0.05.

In a first statistical approach, the relationship between AD and maternal age was investigated categorizing maternal age in six classes: 15–19; 20–24; 25–29; 30–34; 35–39; and 40 years and over. The age class 25–29 years, which was the most frequent, served as reference. Relative risks and 95% confidence intervals for each age category compared to the reference one were obtained through the conditional logistic regression for matched sets.[18,19] Analyses were conducted on the individual data sets, on the pooled sample, and on subgroups of the pooled sample defined by gender, age at onset, and familial aggregation of AD cases. A case of AD was defined as 'early onset' when the symptoms of the disease started before age 70 years, as 'late onset' otherwise. A case of AD was defined as 'sporadic' when the patient had no known first degree relative affected by dementia, otherwise as 'familial'. To investigate the independent effect of maternal age after adjustment for education, education was included in the conditional logistic regression model in pooled analyses.[17] Finally, some analyses were repeated on the restricted sample of pairs matched by type of respondent.[17]

In a second statistical approach, we tested the hypothesis that the relationship between maternal age and AD follows the same risk curve as in Down's syndrome. In most current studies, the incidence of Down's syndrome was found to increase slowly until age 30–35 years, and rapidly thereafter.[20,21] To test whether this risk curve is a model also for AD, age of the mother was transformed as follows: (1) for maternal ages equal to 30 years or less, the new variable value was zero; (2) for maternal ages over 30, the new variable value was the actual maternal age minus 30 years. The distributions of this transformed variable among cases and matched controls were compared using the paired t-test. Analyses were conducted on individual studies, on the pooled sample, and on sporadic AD cases in individual studies.

RESULTS

Table 2 shows the relationship between Alzheimer's disease and maternal age at index birth in individual studies and in the pooled sample. The relative risks were approximately one in all studies between ages 20–24 and 35–39 years. The relative risk for maternal age between 15 and 19 years was increased in three of the four studies, and reached statistical significance in

TABLE 2 *Association between Alzheimer's disease and maternal age at index birth*

Case-control study	Sample (informative pairs)	Relative risk and 95% confidence intervals of index age category vs reference*					
		15–19	20–24	25–29 (Reference)	30–34	35–39	40+
Australia[24]	112	2.4 (0.4–13.7)	0.6 (0.3–1.4)	1.0	1.1 (0.5–2.2)	1.6 (0.6–4.6)	1.4 (0.5–3.7)
Exposure frequency, cases		4/112	18/112	35/112	28/112	15/112	12/112
Exposure frequency, controls		2/112	27/112	36/112	27/112	11/112	9/112
Italy[10]	67	1.8 (0.3–10.0)	0.9 (0.3–2.8)	1.0	0.7 (0.2–1.9)	1.8 (0.4–8.0)	4.8 (1.2–19.2) [0.03]
Exposure frequency, cases		4/67	11/67	17/67	13/67	7/67	15/67
Exposure frequency, controls		2/67	14/67	21/67	22/67	5/67	3/67
The Netherlands[15]	173	6.5 (1.4–30.3) [0.02]	0.9 (0.5–1.6)	1.0	1.0 (0.6–1.8)	0.6 (0.3–1.2)	1.4 (0.6–3.4)
Exposure frequency, cases		13/173	34/173	51/173	44/173	17/173	14/173
Exposure frequency, controls		2/173	40/173	51/173	42/173	27/173	11/173
USA, Seattle[22]	94	0.3 (0.1–1.3)	1.5 (0.6–3.5)	1.0	0.8 (0.4–1.9)	1.0 (0.3–3.0)	1.2 (0.3–4.5)
Exposure frequency, cases		4/94	24/94	27/94	19/94	14/94	6/94
Exposure frequency, controls		11/94	16/94	27/94	23/94	12/94	5/94
Total sample	446	1.5 (0.8–3.0)	0.9 (0.6–1.4)	1.0	0.9 (0.6–1.3)	1.0 (0.6–1.6)	1.7 (1.0–2.9) [0.04]
Exposure frequency, cases		25/446	87/446	130/446	104/446	53/446	47/446
Exposure frequency, controls		17/446	97/446	135/446	114/446	55/446	28/446

*P values smaller or equal to 0.05 are reported in square brackets under the relative risk. Results did not change noticeably after adjustment for education, (dichotomized: less than 9 years; 9 years or more) or restricting the sample to case-control pairs matched by type of respondent.

one. The relative risk for maternal age of 40 years and over was consistently greater than one in all four studies; the association was significant in one study and in the pooled sample.

Table 3 shows the relationship between AD and maternal age in subgroups of cases and their corresponding matched controls. While there was no trend for male AD patients, female AD patients showed increased relative risks for both early and late maternal age. The increased relative risk for age 40 years and over was statistically significant. For both early onset and late onset cases, the relative risks for age 40 and over were suggestively increased; however, they did not reach statistical significance. The relative risk for maternal age between 15 and 19 years was significantly increased among early onset AD cases, but not among late onset cases. The relative risk was significantly increased for maternal age of 40 years and over among sporadic cases but not among familial cases. Results reported in Tables 2 and 3 did not change noticeably after adjustment for education, or restricting the sample to case-control pairs matched by type of respondent.

Tests of consistency with the Down's syndrome risk curve showed statistically significant findings in one study and in the pooled sample (Table 4). In two other studies, the difference between cases and controls for the modified maternal age variable was consistent with the hypothesis, but did not reach statistical significance. In one study the difference was very small (Table 4). Table 5 shows the same test of consistency with the Down's syndrome model conducted on sporadic AD cases and their matched controls. In all four studies, the difference of the modified maternal age variable between cases and controls was consistent with the hypothesis. In two studies and in the pooled sample the difference reached statistical significance.

DISCUSSION

The present study was a collaborative re-analysis of existing data sets investigating the association between late maternal age and AD. Unfortunately, not all existing studies as listed in Table 1 could be included. Since the investigation of maternal age was part of the EURODEM project, regarding all major risk factors for AD,[17] only studies which investigated several risk factors participated in this activity. The selection of only some of the data sets regarding this association might have influenced our results. In addition, we excluded three of the seven case-control studies which investigated maternal age and were included in the project because the question regarding maternal age had a low response rate. On the other hand, both the reasons for inclusion in the project and the exclusion

TABLE 3 *Association between Alzheimer's disease and maternal age at index birth in subgroups*

Case-control study	Sample (informative pairs)	Relative risk and 95% confidence intervals of index age category vs reference*					
		15–19	20–24	*25–29* (Reference)	30–34	35–39	40+
Total sample	446	1.5 (0.8–3.0)	0.9 (0.6–1.4)	1.0	0.9 (0.6–1.3)	1.0 (0.6–1.6)	1.7 (1.0–2.9) [0.04]
Gender							
Men	178	0.7 (0.2–2.0)	0.6 (0.3–1.1)	1.0	0.5 (0.3–1.0) [0.03]	0.7 (0.3–1.4)	0.8 (0.3–1.9)
Exposure frequency, cases		10/178	32/178	47/178	48/178	25/178	16/178
Exposure frequency, controls		9/178	39/178	31/178	61/178	25/178	13/178
Women	268	2.2 (0.9–5.4)	1.2 (0.7–1.9)	1.0	1.3 (0.8–2.0)	1.2 (0.6–2.2)	2.4 (1.2–4.8) [0.009]
Exposure frequency, cases		15/268	55/268	83/268	56/268	28/268	31/268
Exposure frequency, controls		8/268	58/268	104/268	53/268	30/268	15/268
Age at onset†							
Age <70 years	265	4.2 (1.4–13.0) [0.01]	0.8 (0.5–1.3)	1.0	1.0 (0.6–1.6)	0.8 (0.4–1.4)	1.8 (0.9–3.7)
Exposure frequency, cases		17/265	47/265	78/265	67/265	28/265	28/265
Exposure frequency, controls		4/265	62/265	80/265	68/265	35/265	16/265
Age ≥70 years	156	0.5 (0.2–1.6)	1.3 (0.7–2.6)	1.0	0.9 (0.5–1.6)	1.2 (0.5–2.9)	2.0 (0.8–4.7)
Exposure frequency, cases		6/156	36/156	47/156	30/156	19/156	18/156
Exposure frequency, controls		12/156	30/156	51/156	38/156	16/156	9/156
Familial aggregation‡							
Sporadic AD	241	1.3 (0.5–3.7)	1.0 (0.6–1.7)	1.0	0.7 (0.4–1.2)	1.2 (0.6–2.4)	2.7 (1.2–5.9) [0.01]
Exposure frequency, cases		11/241	52/241	68/241	53/241	29/241	28/241
Exposure frequency, controls		8/241	53/241	72/241	70/241	27/241	11/241
Familial AD	185	1.6 (0.6–4.0)	0.9 (0.5–1.6)	1.0	1.2 (0.7–2.1)	0.9 (0.4–1.7)	1.3 (0.6–2.9)
Exposure frequency, cases		14/185	31/185	55/185	45/185	22/185	18/185
Exposure frequency, controls		9/185	37/185	58/185	39/185	27/185	15/185

*P values smaller or equal to 0.05 are reported in square brackets under the relative risk. Results did not change noticeably after adjustment for education, (dichotomized: less than 9 years; 9 years or more) or restricting the sample to case-control pairs matched by type of respondent.
†Information about age at onset of Alzheimer's disease was missing in 25 cases.
‡Sporadic AD = No first degree relatives affected by dementia; Familial AD = At least one first degree relative affected by dementia. Information regarding familial aggregation of dementia was missing in 20 cases.

criteria used were independent from the results of the studies, and no major selection bais should have occurred.

Of the four case-control studies included, two had been previously published;[10,15] therefore, they were also listed in Table 1. Results from one study were in press at the time.[22] Results from the fourth study are reported here for the first time.[24] For the published data, we reported here new analyses not available in the original publications.

Our analyses suggest that late maternal age could be a risk factor for AD. We found a consistently increased risk for maternal age of 40 years and over as compared to maternal age of 25–29 years. This increase reached statistical significance in one study and in the pooled sample. An increased risk of AD with late maternal age was suggested also by the analyses based on the Down's syndrome risk curve. Our data were consistent with this model in three of the four studies, and reached statistical significance in one. Three of the four studies also suggested a possible increased risk for births occurring at very young maternal age; the difference was significant in one study. In summary, our analyses suggest that there could be an association between both early and late maternal ages and the risk of AD.

Important results came from subgroup analyses. We identified two subgroups of AD patients with a more definite maternal age effect: women and sporadic cases. In particular, sporadic AD showed consistency with the Down's syndrome risk model in all four studies. The case-control difference for the transformed maternal age variable reached statistical significance in two studies and in the pooled sample. Our analyses

TABLE 4 *Association between Alzheimer's disease and maternal age at index birth: Test of consistency with the Down's syndrome risk curve*

Case-control study	Mean in cases* (a)	Mean in controls* (b)	Mean difference (a–b)	Standard error of the mean difference	Matched-pair t-test p value†
Australia	2.57	2.01	0.56	0.501	0.26
Italy	4.17	1.67	2.50	0.857	0.005
The Netherlands	2.08	2.13	−0.05‡	0.402	0.90‡
USA, Seattle	2.22	1.73	0.49	0.507	0.34
Total sample	2.55	1.95	0.60	0.263	0.02

*Maternal age was transformed as follows: If maternal age < = 30, then new variable = 0; if maternal age >30, then new variable = (maternal age −30).

†P values smaller or equal to 0.05 are underlined.

‡The negative sign indicates that the mean difference of the modified maternal age variable between cases and matched controls was in the opposite direction.

confirm the previously suggested association between sporadic AD and late maternal age.[14] The identification of women and sporadic cases as the AD subgroups more specifically associated may be important in suggesting aetiological mechanisms or alternative explanations of the observed link.

In interpreting our results, the major caveat pertains to the quality of information regarding exposure. In three of the four studies the age of the mother at birth of a given case or control was obtained through a face-to-face interview with a next-of-kin; in one study, the interview was by telephone. This indirect data collection may interfere with the quality of information. In addition, in three studies, cases and controls were not matched by type of respondent: for example, a spouse could be interviewed for a case and a sibling for the matched control. Failure to match by type of informant may have created differences in the quality of response between cases and controls. A sibling (sharing parents with the study subject) may tend to recall the age of the mother at index birth more precisely than a spouse (coming from a different family) or an offspring (part of a different generation). On the other hand, in one of the four studies, cases and controls were matched by type of respondent (USA, Seattle),[22] and our analyses restricted to pairs matched by type of respondent did not modify the results noticeably.

In a study of the reliability of the next-of-kin interview, the authors found a non-response rate regarding maternal age of 10% at direct interview and of 27% at next-of-kin interview.[23] This suggests that in all studies based on this approach there is an important loss of information due to non-response. The percentages of non-response regarding maternal age in the four studies considered here were as follows: 28% in cases and 9% in controls for the Australian study; 18% in both cases and controls for the Italian study; 7% in cases and 6% in controls for the Dutch study; and 16% in cases and 15% in controls for the American study. The loss of information may be increased by the matched-pair study design in which analyses are restricted to pairs with complete information. This fact may reduce the power of the statistical test used for analysis.

On the other hand, the reliability study mentioned above showed that among those who responded, the agreement regarding maternal age between next-of-kin and direct interview was good (88%).[23] Therefore, despite the quantitative loss of information, the quality of the information appears to be acceptable. In addition, we have no reason to believe that the next-of-kin of cases would be motivated to report more extreme maternal ages than the next-of-kin of controls.

TABLE 5 *Association between sporadic Alzheimer's disease and maternal age at index birth: Test of consistency with the Down's syndrome risk curve*

Case-control study	Mean in cases* (a)	Mean in controls* (b)	Mean difference (a–b)	Standard error of the mean difference	Matched-pair t-test p value†
Australia	2.43	1.27	1.16	0.549	0.04
Italy	4.65	1.61	3.04	0.947	0.002
The Netherlands	2.32	2.02	0.30	0.544	0.58
USA, Seattle	1.98	1.68	0.30	0.625	0.64
Total sample	2.77	1.70	1.07	0.339	0.002

*Maternal age was transformed as follows: If maternal age < = 30, then new variable = 0; if maternal age >30, then new variable = (maternal age–30).

†P values smaller or equal to 0.05 are underlined.

It is premature to discuss the possible interpretation of the suggested association between late maternal age and AD. Further data are needed to test this hypothesis. Since analogy with Down's syndrome and possible chromosomal mechanisms have been widely debated,[3] this remains the major working hypothesis. However, other indirect and non-genetic mechanisms might explain the association. This line of interpretation is suggested by the fact that both extremes of maternal age seem to be associated with an increased risk. Early and late maternal age at birth of a subject may, for example, influence the psychological and cognitive development of the child so as to make her or him predisposed to AD in later life.

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