

Parental Age and the Risk for Alzheimer's Disease in Offspring: Systematic Review and Meta-Analysis

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Keywords

Alzheimer's disease · Meta-analysis · Parental age · Systematic review

Abstract

Background: Alzheimer's disease (AD) is the most common cause of dementia worldwide, accounting for 50–75% of all cases. While older maternal and paternal age at childbirth are established risk factors for Down syndrome which is associated with later AD, it is still not entirely clear whether parental age is a risk factor for AD. Previous studies have suggested contradictory findings. **Objectives:** We conducted a systematic review and meta-analysis to examine whether parental (maternal and paternal) age at birth was associated with AD and whether individuals born to younger or older parents were at an increased risk for AD. **Methods:** Two reviewers searched the electronic database of PubMed for relevant studies. Eligibility for the meta-analysis was based on the following criteria: (1) studies involving patients with AD and an adequate control group, (2) case control or cohort studies, (3) studies investigating parental age. All statistical analyses were completed in STATA/IC version 16. **Results:**

Eleven studies involving 4,371 participants were included in the systematic review and meta-analysis. Meta-analysis demonstrated no significant association between maternal (weighted mean difference [WMD] 0.49, 95% CI –0.52 to 1.49, $p = 0.34$) and paternal age and AD (WMD 1.00, 95% CI –0.55 to 2.56, $p = 0.21$). Similarly, individuals born to younger (<25 years) or older parents (>35 years) did not demonstrate a differential risk for AD. **Conclusions:** Overall, this meta-analysis did not demonstrate an association between parental age and the risk of AD in offspring. These findings should be interpreted with caution given the limited power of the overall meta-analysis and the methodological limitations of the underlying studies as in many cases no adjustment for potential confounders was included.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide, accounting for 50–75% of all cases [1]. It is also well known that AD is highly heritable

with several genes responsible for susceptibility including such as mutations in *APP*, *PSEN1*, *PSEN2*, *APOE* and *ADAM10* [2, 3], but the strongest genetic predictor of AD remains the high-risk variant *APOE ε4*. Also several environmental factors, such as head injury, age, diabetes mellitus, conjugated equine estrogen use with medroxyprogesterone acetate, current smoking, and lower social engagement have been reported to increase the risk for AD [4]. Moreover, it is well known that almost all patients with Down syndrome develop neuropathological changes typical for AD by the age of 40 [5], and the incidence of AD in those patients is as high as 55–100% depending on the age group (up to 100% in patients aged 70 years or older) [6–9]. While older maternal [10, 11] and paternal ages [12] at childbirth are established risk factors for Down syndrome, it is still not clearly known what is the influence of parental age on the risk for AD.

The majority of studies investigating the relationship between parental age and AD were published in the 1980 and 1990s. Several of these studies have reported a significant association between older or younger parental age and risk of AD [13–17] while many others have not [18–24]. Researchers who found an influence between parental age and the risk of AD postulated a number of mechanisms involved in this process. Particularly, Whalley et al. [13] pointed out that the parents of AD patients may have reduced fertility, leading to delayed reproduction and reduced family size. Urakami et al. [15] suggested that advanced age may become a cause of chromosome abnormality, and advanced parental age at the subject's birth may be a possible risk factor of AD. Finally, Farrer et al. [16] pointed out that several other maternal-fetal environmental factors, for example, toxic or infectious exposure and maternal immune response as well as cytoplasmic or mitochondrial inheritance could also be involved. Bertram et al. [17] concluded that increased paternal age is a risk factor for AD in the absence of a major gene, whereas increased maternal age and AD are associated only weakly and independently of genetic disposition.

The aim of our study was to conduct a systematic review of the existing literature about the effect of parental age on AD and to perform a meta-analysis. Although this topic has been investigated in many studies, their results have been conflicting. To our knowledge, there have been no systematic reviews and meta-analyses examining these data. Our meta-analysis will also examine the association between maternal and paternal age separately and risk for AD.

Methods

Two reviewers (N.S., V.J.A.-Q.) searched the electronic database of PubMed and CENTRAL on July 18, 2019, for relevant studies using the search: (((“parents”[MeSH Terms] OR “parents”[All Fields] OR (“parental”[All Fields] AND “age”[All Fields]) OR “parental age”[All Fields]) AND (“maternal age”[MeSH Terms] OR (“maternal”[All Fields] AND “age”[All Fields]) OR “maternal age”[All Fields])) AND (“paternal age”[MeSH Terms] OR (“paternal”[All Fields] AND “age”[All Fields]) OR “paternal age”[All Fields])) AND (“nervous system diseases”[MeSH Terms] OR (“nervous”[All Fields] AND “system”[All Fields] AND “diseases”[All Fields]) OR “nervous system diseases”[All Fields] OR (“neurological”[All Fields] AND “disorders”[All Fields]) OR “neurological disorders”[All Fields])). Reviews and meta-analyses in the area were further searched for relevant citations.

The titles and abstracts of the studies obtained through the search were examined by 2 reviewers (N.S., V.J.A.-Q.) in order to determine article inclusion. Each article was also checked for further potential references. Discrepancies were addressed by the reviewers through discussion and eventually conversation with the senior reviewer (M.H.B.). Eligibility for the meta-analysis was based on the following criteria: (1) studies involving patients with AD and an adequate control group, (2) case control or cohort studies, (3) studies investigating parental age. Articles were excluded based on the following criteria: (1) meta-analyses or review papers, (2) not investigating AD, (3) not investigating parental age, (4) no control group available. Several studies that met inclusion criteria did not report data about mean parental age or age category. Data collected on each article included year, study design, number of subjects in disease and control groups, parental gender, adjustment for confounders, mean age at childbirth for mothers and fathers and age groups at childbirth for mothers and fathers.

All statistical analyses were completed in STATA/IC version 16 (StataCorp LLC) [25]. Our primary outcome of interest was the mean age of parents at childbirth as well as the number of parents belonging to each age category at childbirth. For mean parental age as an outcome, weighted mean differences (WMDs) were utilized as the primary outcome measures. When examining risk of AD by parental age categories the odds ratio (OR) was used in the AD group as compared to the control group. A random-effects model was used as the primary model for meta-analysis. To examine heterogeneity between studies, we utilized the I^2 statistic. Publication bias was assessed by visually examining funnel plots and utilizing Egger's test [26].

Results

Selection of the Studies

Figure 1 is a PRISMA diagram that depicts our procedure for the selection of studies. Our search yielded 357 potential citations that were possibly eligible for inclusion. Further examination of the full texts of these papers identified 36 studies that were eligible for inclusion in our meta-analysis, but 2 studies were excluded as they did not provide sufficient statistical data, while 23 examined the

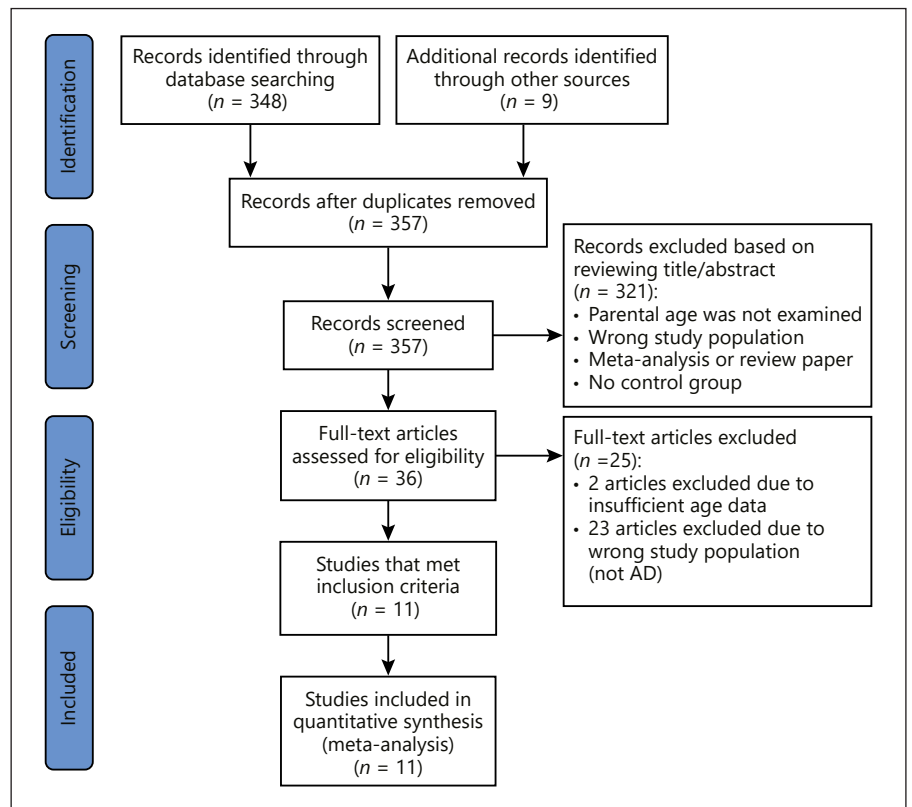


Fig. 1. PRISMA flow diagram (from Moher, 2009 [34]).

Table 1. Characteristics of studies included in the analysis

Author	Year	Site	Number	Data type	Age grouping, years			Parental gender	Adjustment for potential confounders
					younger	ref.	older		
Whalley et al. [13]	1982	UK	276	Continuous	-	-	-	Both	No statistical adjustments
Knesevich et al. [18]	1982	USA	84	Continuous, categorical	12-19	20-29	>40	Maternal	No statistical adjustments
English and Cohen [20]	1985	USA	163	Categorical	<25	30-34	>40	Maternal	Adjusted for mother's year of birth
Urakami et al. [15]	1989	Japan	112	Continuous	-	-	-	Both	No statistical adjustments
Hofman et al. [21]	1990	The Netherlands	396	Categorical	<20	25-29	>40	Both	Age, sex, and area of residence
Farrer et al. [16]	1991	USA	1,422	Continuous	-	-	-	Both	No statistical adjustments
Rocca et al. [27]	1991	The Netherlands	892	Categorical	15-19	25-29	>40	Maternal	Adjusted for education
Clarnette et al. [22]	1992	Canada	318	Continuous, categorical	≥15	26-30	>41	Both	No statistical adjustments
Fratiglioni et al. [23]	1993	Sweden	364	Categorical	<25	25-34	>35	Both	Adjusted for age, sex, education, and type of relatives
Bertram et al. [17]	1998	Germany	154	Continuous	-	-	-	Both	No statistical adjustments
Ptok et al. [24]	2000	Germany	190	Continuous	-	-	-	Both	No statistical adjustments

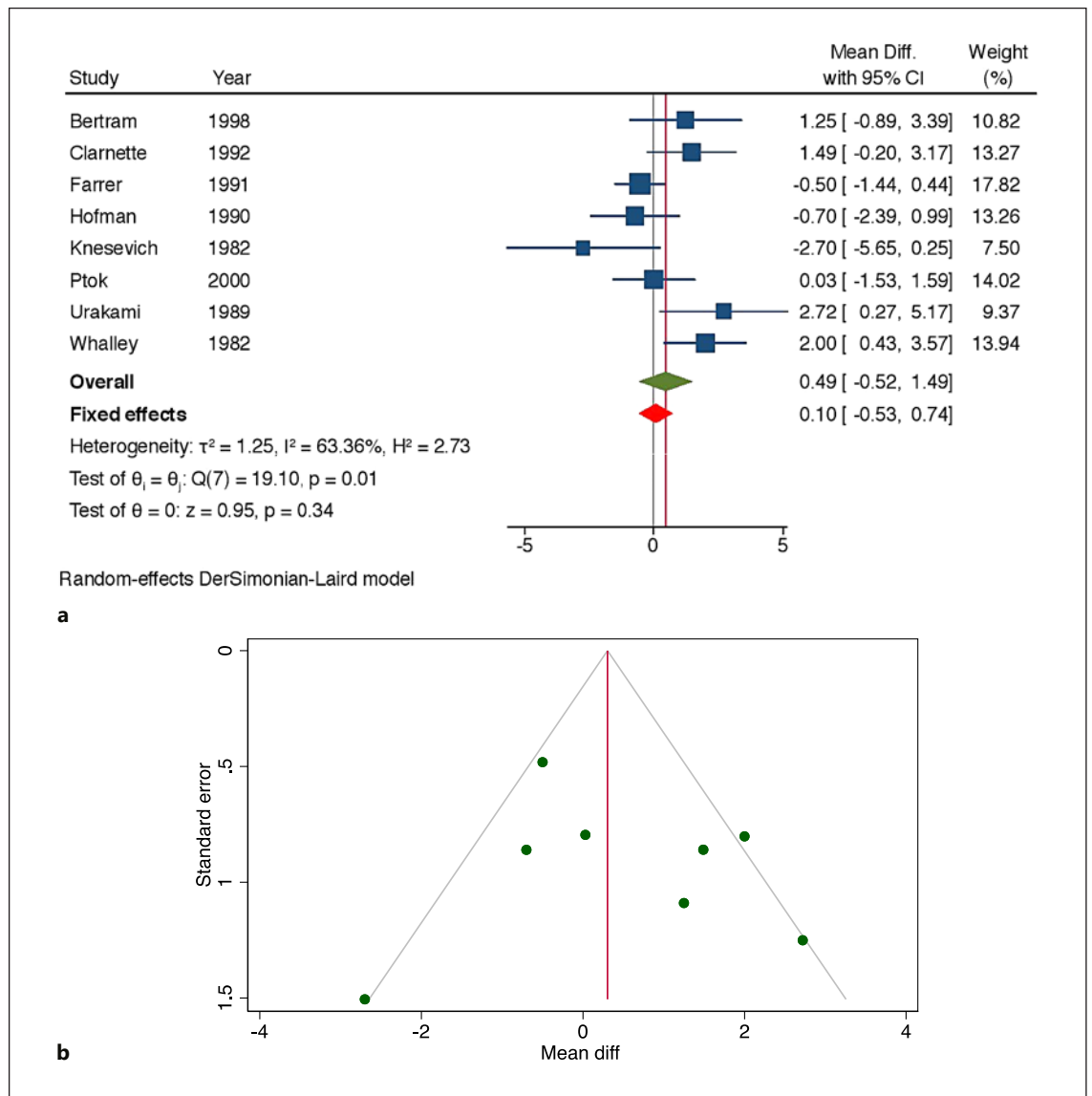


Fig. 2. a Weighted mean difference for mother's age at childbirth in AD versus controls. **b** Mean differences for mother's age at childbirth in AD versus controls.

wrong study population, so that we included 11 studies in the final analysis. Table 1 depicts the characteristics of included studies that are described in greater detail. This systematic review and meta-analysis included data from 11 studies with 4,371 participants. In 7 studies, both maternal and paternal ages were examined, and in 4 studies only maternal age was reported. Few studies (4 of 11) provided statistical adjustment for possible confounding variables in the analysis.

Maternal Age and Risk of AD

Although 11 studies aimed to investigate either the influence of both paternal and maternal age or maternal age on the occurrence of AD, we included 8 studies in this analysis, as 3 studies [20, 23, 27] did not provide sufficient information to conduct the analysis. Meta-analysis of 8 studies involving 1,126 cases of AD and 2,082 healthy controls demonstrated no significant difference in maternal age between AD and controls (WMD 0.49, 95% CI -0.52 to 1.49, $p = 0.34$). Figure 2a depicts a forest plot

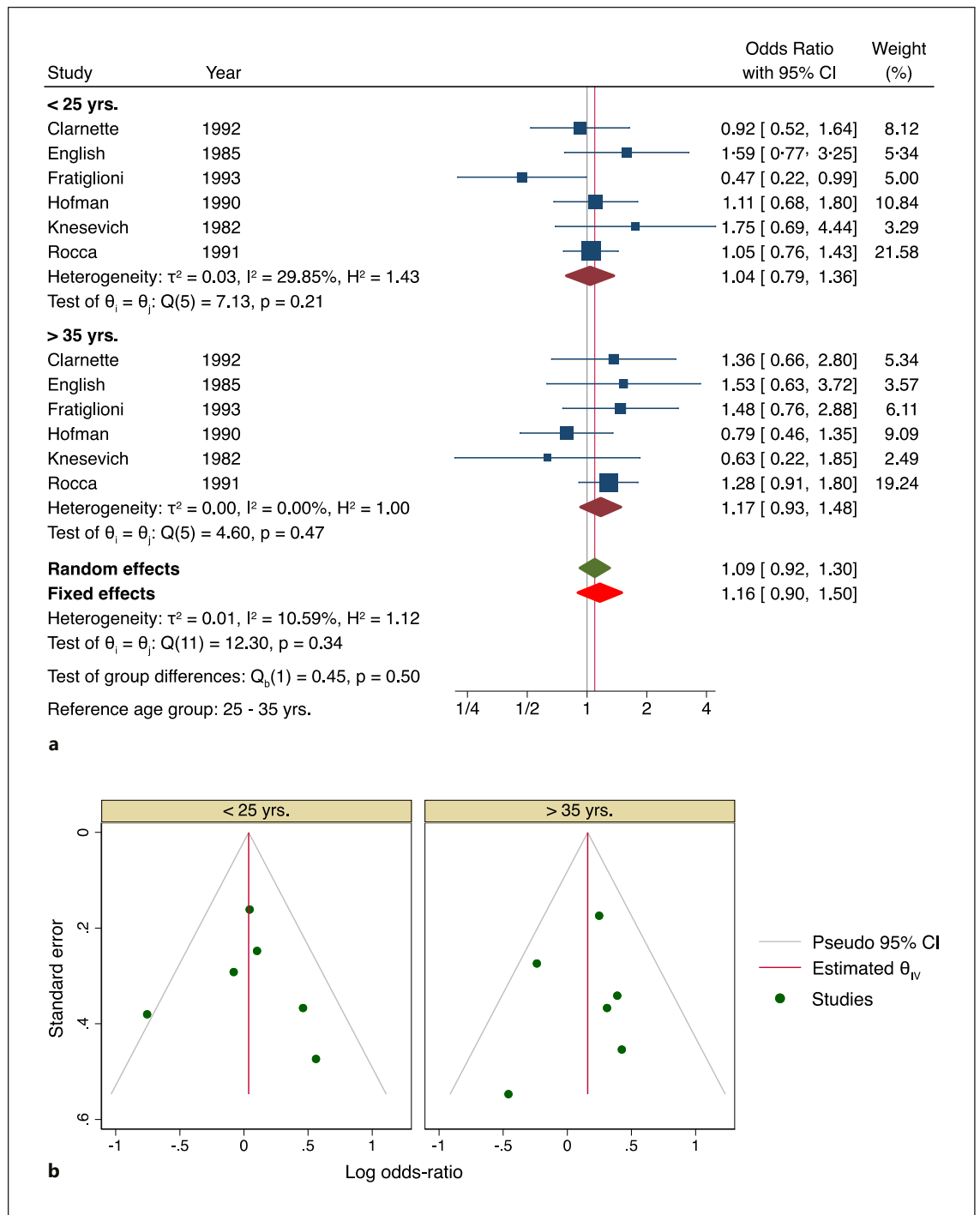


Fig. 3. a Risk of AD in offspring by mother's age groups at childbirth. **b** Funnel plots examining publication bias for maternal ages <25 and >35 years old.

describing the WMD for mother's age at childbirth in AD versus controls. There was significant heterogeneity in estimates of the mean difference in maternal age be-

tween studies ($Q = 19.1$, $df = 7$, $p = 0.007$, $I^2 = 63.7\%$) but there was no evidence of publication bias ($p = 0.98$, Fig. 2b).

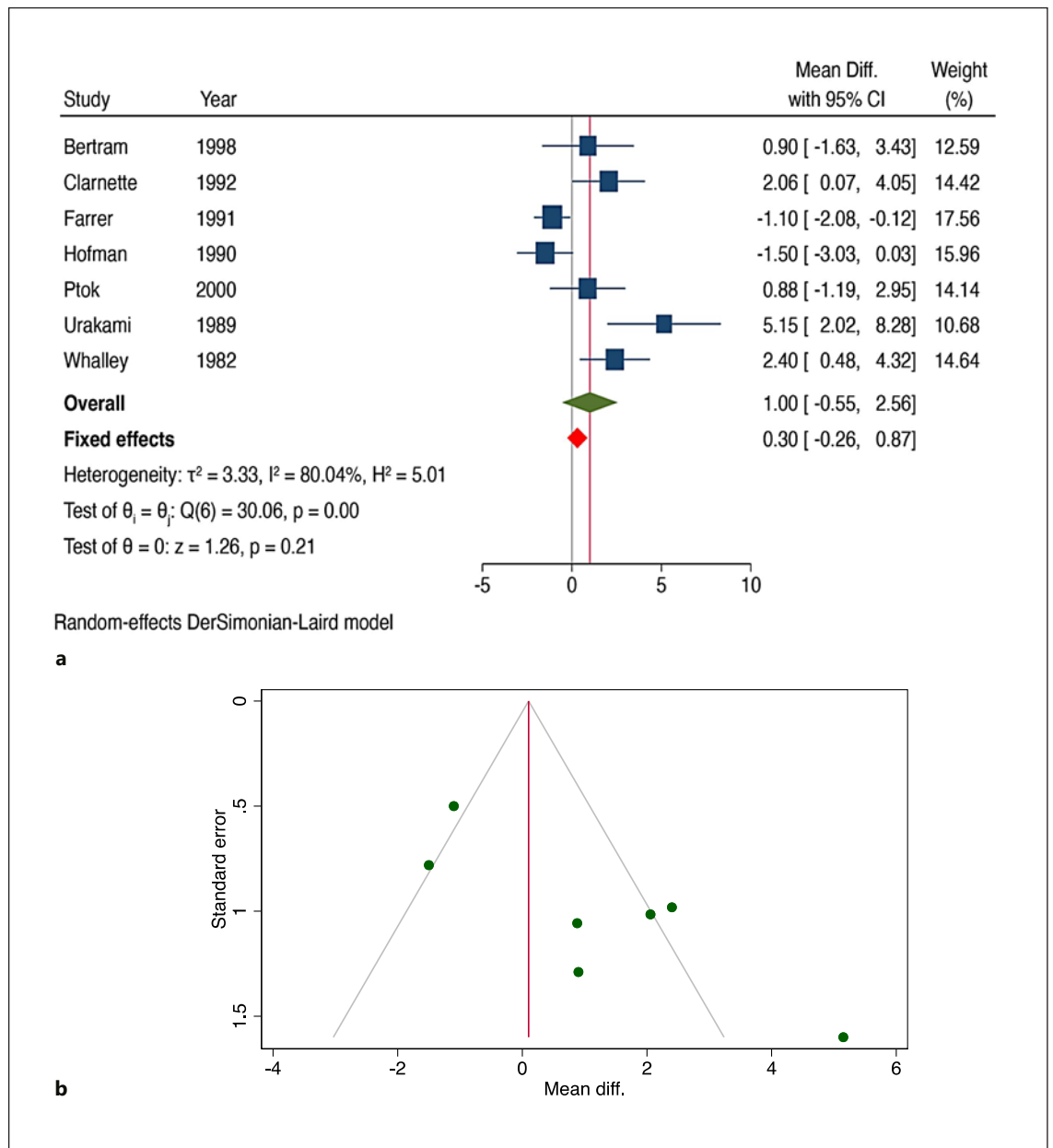


Fig. 4. a Weighted mean differences for father's age at childbirth in AD versus controls. **b** Mean differences for father's age at childbirth in AD versus controls.

For categorical age group analysis, we established 3 age groups of maternal age: <25 (with 327 cases and 394 controls), 25–34 (with 664 cases and 823 controls) and >35 (with 331 cases and 342 controls). Figure 3a depicts a forest plot describing the relative risk ratio of AD in offspring by mother's age groups at childbirth (with age 25–34 years as reference) among individual studies. Neither younger maternal age (OR 1.04, 95% CI 0.79–1.36, $p =$

0.21; heterogeneity $Q = 7.1$, $df = 5$, $p = 0.21$, $I^2 = 29.9\%$) nor older maternal age (OR = 1.17, 95% CI 0.93–1.48, $p = 0.47$; heterogeneity $Q = 4.6$, $df = 5$, $p = 0.47$, $I^2 = 0\%$) were associated with risk of AD in offspring. There was no evidence of publication bias in the meta-analysis ($p = 0.84$ for younger maternal age and $p = 0.71$ for older maternal age, Fig. 3b).

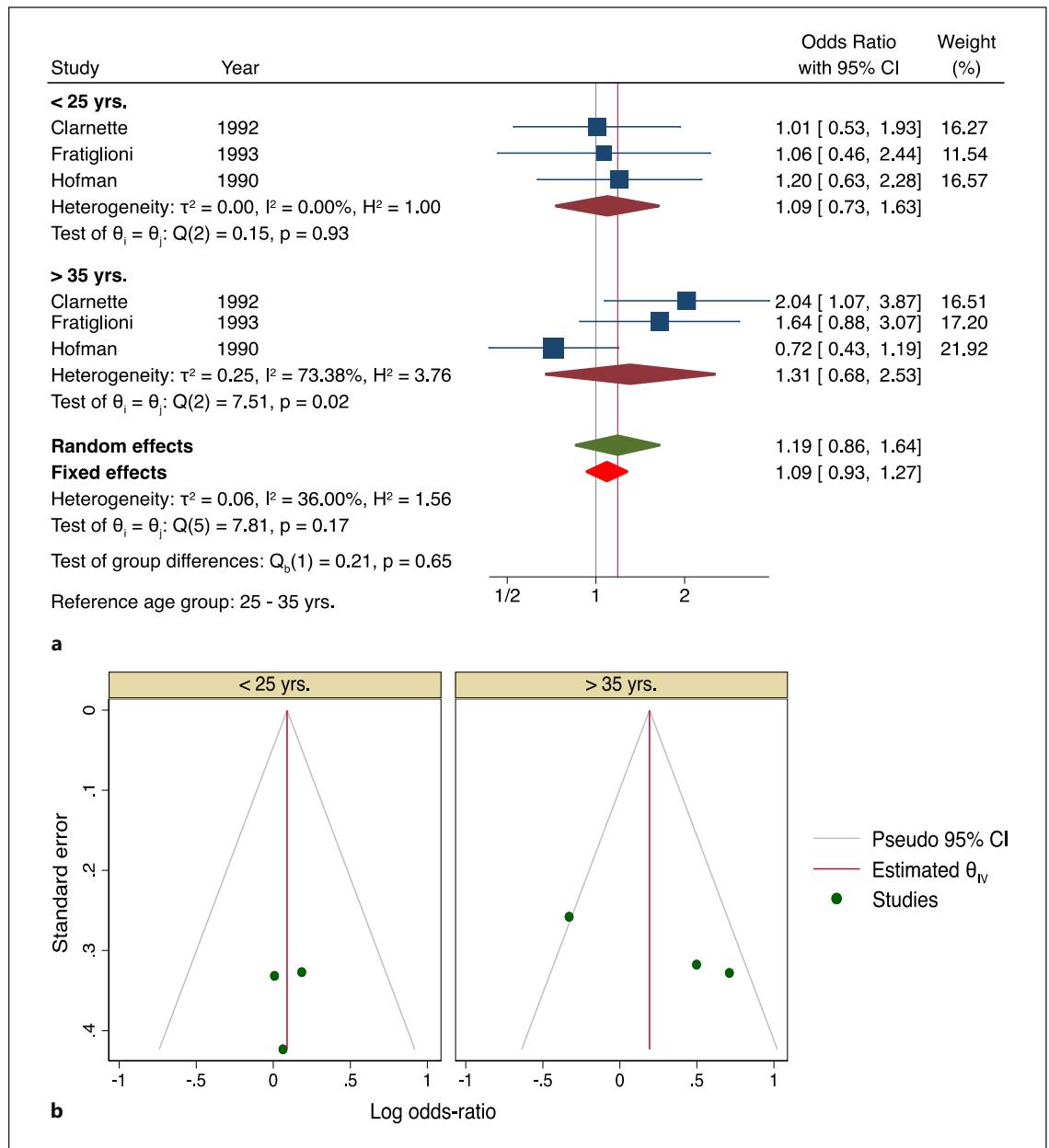


Fig. 5. a Risk of AD in offspring by parental age group at childbirth. **b** Funnel plots examining publication bias for paternal ages <25 and >35 years old.

Paternal Age and Risk of AD

Meta-analysis of 8 studies involving 1,049 cases of AD and 2,172 healthy controls demonstrated no significant difference in paternal age between AD and controls. Figure 4a depicts a forest plot describing the WMD for father's age at childbirth in AD versus controls (WMD 1.00, 95% CI -0.55 to 2.56, $p = 0.21$). There was significant heterogeneity in estimates of the mean difference in paternal

age between studies ($p < 0.001$, $I^2 = 79.5\%$). Egger's test demonstrated significant evidence of publication bias ($p = 0.0012$, Fig. 4b).

For categorical age group analysis, we used the same categories as for maternal age analysis. Figure 5a depicts a forest plot describing the relative risk ratio of AD in offspring by father's age groups at childbirth (with age 25–34 years as reference). There were no significant differences

Table 2. Diagnostic criteria used to establish diagnosis of AD in the studies included in the meta-analysis: only studies reporting about AD criteria are included

Study	Inclusion criteria	Exclusion criteria
Whalley et al. [13]	(a) Admission to mental hospital before age 65 (b) History of gradually failing memory (c) Neuropathological evidence of cortical atrophy (d) Absence of cerebral infarcts or other major cerebrovascular pathology and, on silver impregnation of representative slices of cerebral cortex, neuronal loss, senile plaques, and neurofibrillary tangles	(a) Previous history of mental handicap (b) Functional mental illness (c) Alcoholism (d) Head injury
Knesevich et al. [18]	Sustained deterioration of memory in an alert subject, plus impairment in at least 3 of the following 5 cognitive abilities: – Orientation – Judgment and problem solving – Function in community affairs – Function in home and hobbies – Function in personal care – Gradual onset and progression – Duration: 6 months or longer	(a) Other neurological disorders, including parkinsonism (b) Huntington’s disease, communicating hydrocephalus, progressive supranuclear palsy, infection, brain tumor, subdural hematoma, multiple sclerosis, stroke, multi-infarct dementia, seizure disorder, and brain trauma (c) Psychiatric disorders, including primary affective disorder or major depression, schizophrenia, alcoholism, or other substance abuse (d) Other reversible dementias and other medical disorders that may reduce cognition, including overmedication; impaired function of lungs, heart, kidneys, or liver; anemia; hypothyroidism; vitamin B ₁₂ or folate deficiency; malignancy; and diabetes mellitus (if insulin-dependent or if more than mild in degree)
English and Cohen [20]	History of progressive dementia with a gradual onset	Other possible causes of dementia
Urakami et al. [15]	History of progressive dementia with a gradual onset	Other possible causes of dementia according to the diagnostic criteria of the DSM-III
Hofman et al. [21]	(a) Slow progressive decline of intellectual function; (b) CDRS >0.5 [31] (c) SPMSQ score of <20 [32]; (d) Hachinski scale score of 7 [33]	(a) No evidence of abnormalities other than cerebral atrophy, on a computerized tomography (b) No evidence for focal dysfunction on an electroencephalograph
Clarnette et al. [22]	A standardized history from the patient, relatives and caregivers and the following scales: (a) MMSE [31] (b) Lawton [32] (c) ADL (d) IADL (e) Behaviour Problem Checklist The clinical diagnosis of possible or probable AD was made on the basis of the NINCDS-ADRDA criteria	History of significant head trauma Heavy alcohol use within 10 years of the onset of the cognitive impairment
Fratiglioni et al. [23]	(a) MMSE <23 (b) Criteria of DSM-III (c) CDRS was used to stage the severity of dementia	MMSE >24
Bertram et al. [17]	(a) Criteria for dementia according to the ICD (b) Criteria for probable AD as proposed by the NINCDS-ADRDA	NA
Ptok et al. [24]	Probable AD according to the diagnostic criteria of the NINCDS-ADRDA	Age <60

DSM-III, Diagnostic and Statistical Manual of Mental Disorders; CDRS, Clinical Dementia Rating Scale; AD, Alzheimer’s disease; NINCDS-ADRDA, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association; ICD, International Classification of Diseases; SPMSQ, Short Portable Mental Status Questionnaire; MMSE, Mini Mental State Examination; ADL, activities of daily living; IADL, instrumental activities of daily living; NA, not available.

in the mean paternal age between AD and controls. There was no significant heterogeneity in estimates of the mean paternal age between studies ($p = 0.167$, $I^2 = 36.0\%$). A regression-based Egger test did not show publication bias for studies with paternal age <25 years ($p = 0.9272$, Fig. 5b) but detected publication bias in case of paternal age >35 years ($p = 0.0062$, Fig. 5b).

Discussion

Our meta-analysis demonstrated no evidence of an association between parental age and the risk of AD in offspring. Neither maternal nor paternal age, whether examined as a continuous variable or examining categorical age, suggested an association.

The results we demonstrate have to be interpreted with caution, mainly because of the methodological limitations of the studies included in the meta-analysis and the small sample sizes of each individual study. The main methodological discrepancies were related to diverse methodology used for selection of cases and controls and publication bias, in case of studies investigating the impact of paternal age on risk of AD.

Importantly, the method of investigation of parental age at birth differed between different studies. Some studies examined only the birth certificates, while the others relied on several written sources of information and therefore could be considered as more reliable. Moreover, different studies applied different criteria to diagnose AD (detailed criteria are listed in Table 2); this is provoked by the fact that the studies included in our meta-analysis come from different time frames, between 1982 and 2000. It is therefore possible that not only patients with AD, but also vascular dementia, mixed dementia or even Lewy body dementia were included. Therefore, these findings are subjected to significant confounding by comorbidities influencing the occurrence of dementia or genetically determined dementia other than AD.

Moreover, some studies included an autopsy confirmation, while the others were only based on clinical judgment and various criteria depending on the period of time in which a particular study took place. Another issue is the representation of parental age which in some cases only included the mean, without dividing into further subcategories. An additional limitation is the limited overall power of the meta-analysis which cannot rule out the possibility of a small but significant association between parental age and AD risk in offspring. Furthermore, few studies included in this meta-analysis adjusted

for potentially important confounding variables in their analysis.

Our findings do not provide evidence of an association between AD incidence and parental age at birth. Previous individual-level studies claimed that a potential influence of increased parental age could be related to chromatin instability or a genetic imprinting mechanism and DNA methylation. Today we know that while the lifetime risk of developing AD is as high as 10–12% [28], it doubles with the presence of a first-degree relative with the disorder, but this is not related to the imprinting mechanism, but is the consequence of the complex genetic architecture of this disorder that could be described according to the common disease-common variant (CD-CV) hypothesis. The CD-CV [29] hypothesis describes the nature of susceptibility to relatively common and complex diseases and argues that genetic variations with appreciable frequency in the population at large, but relatively low “penetrance” (or the probability that a carrier of the relevant variants will express the disease), are the major contributors to genetic susceptibility to common diseases. While in AD, several genes mainly related to apolipoprotein E have been described for early-onset cases, it seems that for the wide majority of cases the CD-CV hypothesis is true. A recently published genome-wide association study [30] with 71,880 cases and 383,378 controls aimed to show susceptibility loci for AD identified 29 disease-associated genomic loci implicating 215 potential causative genes. Associated genes were strongly expressed in immune-related tissues and cell types (spleen, liver and microglia). Gene-set analyses indicate biological mechanisms involved in lipid-related processes and degradation of amyloid precursor proteins. These results indicate the genetic complexity of AD.

Further studies are needed to definitively conclude that there is no association between parental age and risk of AD. Our meta-analysis does not provide evidence of an association and suggests if present that this association is at most small. The lack of a demonstrated association between parental age and AD risk in offspring suggests that mechanisms such as genetic imprinting or chromatin instability are probably not responsible for the occurrence of AD.

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Statement of Ethics

The subjects included in the original studies have given their written informed consent, and the study protocols were approved by the institute's committee on human research.

Conflict of Interest Statement

Michael Howard Bloch receives research support from Biohaven Pharmaceuticals, Neurocrine Biosciences, Janssen Pharmaceuticals, Emalex Pharmaceuticals and Therapix Biosciences, he also receives research support from the Lesbian Health Fund, the National Institutes of Health, the Tourette Association of America, the Brain & Behavior Research Foundation (formerly NARSAD) and the Patterson Foundation. Natalia Szejko, Pedro Macul Ferreira de Barros and Victor J. Avila-Quintero have no conflicts of interest to disclose.

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Author Contributions

N.S. and M.H.B. conceived and designed the study, N.S. and V.J.A.-Q. acquired data. N.S. set up the electronic database. N.S., M.H.B., V.J.A.-Q., P.M.F.B. and A.L. interpreted the data and reviewed and edited the paper. N.S. wrote the original draft of the paper.

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