Advancing Maternal Age Is Associated With Increasing Risk for Autism: A Review and Meta-Analysis

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Objective: We conducted a meta-analysis of epidemiological studies investigating the association between maternal age and autism. **Method:** Using recommended guidelines for performing meta-analyses, we systematically selected, and extracted results from, epidemiological scientific studies reported before January 2012. We calculated pooled risk estimates comparing categories of advancing maternal age with and without adjusting for possible confounding factors. We investigated the influence of gender ratio among cases, ratio of infantile autism to autism spectrum disorder (ASD), and median year of diagnosis as effect moderators in mixed-effect meta-regression. **Results:** We found 16 epidemiological papers fulfilling the a priori search criteria. The meta-analysis included 25,687 ASD cases and 8,655,576 control subjects. Comparing mothers ≥35 years with mothers 25 to 29 years old, the crude relative risk (RR) for autism in the offspring was 1.52 (95% confidence interval [CI] = 1.12–1.92). Comparing mothers ≥35 with mothers 25 to 29, the adjusted relative risk (RR) for autism in the offspring was 1.52 (95% CI = 1.12–1.92). For mothers <20 compared with mothers 25 to 29 years old, there was a statistically significant decrease in risk (RR = 0.76; 95% confidence interval = 0.60–0.97). Almost all studies showed a dose-response effect of maternal age on risk of autism. The meta-regression suggested a stronger maternal age effect in the studies with more male offspring and for children diagnosed in later years. **Conclusions:** The results of this meta-analysis support an association between advancing maternal age and risk of autism. The RR increased monotonically with increasing maternal age. The association persisted after the effects of paternal age and other potential confounders had been considered, supporting an independent relation between higher maternal age and autism. J. Am. Acad. Child Adolesc. Psychiatry, 2012;51(5):477–486. **Key Words:** autism, epidemiology, maternal age, meta-analysis, perinatal

Most plausible neurodevelopmental theories of autism focus on genetic factors.[1] However, there is evidence that nonheritable, pre-, or perinatal events, and/or environmental exposures are likely to also have a significant etiological role.[2]

Advanced maternal age is one of the most frequently studied risk factors for autism.[3-20] However, the results from the individual studies are mixed, and the presence of the associations is still disputed.[21]

It is important to examine the relationship between advanced maternal age and autism for two main reasons. First, an association between maternal age and autism may provide clues to the biological pathways leading to autism. Older maternal age has been associated with increased rates of chromosomal abnormalities.[22] Older mothers also have increased risk of obstetric complications, possibly because of uterine muscle dysfunction and diminished blood supply with age.[23,24] Cumulative exposure to environmental toxins may also be important for the association between advanced

This article is discussed in an editorial by Dr. James C. Harris on page 461.

Supplemental material cited in this article is available online.

maternal age and neurological and psychiatric disorders.[12]

Second, age of parenting has been increasing in the United States and Europe in recent decades,[25,26] and an association between maternal age and autism may help to explain the increase in prevalence estimates of autism during the past two decades.

To elucidate the association between advanced maternal age and autism, we conducted a systematic review and meta-analysis of all population-based epidemiological studies published until June 2011 that investigated the association between advancing maternal age and autism. We also explored possible sources of heterogeneity across studies.

METHOD

The meta-analysis was based on recommended guidelines.[27-29]

Data Sources

We identified published peer-reviewed studies through search of PUBMED using the keywords "autism" together with "maternal" or "paternal" or "parental" or "obstetric" or "perinatal" together with the words "risk" or "association" or "associated." We included only those papers published in English between January 1, 1990 and December 31, 2011. We screened the resulting abstracts and obtained full-text versions of potentially relevant studies. We then hand searched the reference lists of original articles to identify any missing papers.

Study Selection

We used the following inclusion criteria: a population based sample of cases using one of two of the major clinical diagnosis systems, *DSM,* or ICD (Table 1)[3-8,11,12,30,31]; comparison subjects drawn from the general population with information on parental age obtained from the same source; use of a format for presentation of data allowing for comparisons between studies and calculation of relative risk measures; presentation of results for maternal age; and adjustment for paternal age. The standard of reporting associations for maternal age in the autism literature is using age-band categories.

Data Extraction

The following information was extracted from each study: estimates of relative risk (odds ratios from case-control or cohort studies, or incidence rate ratios or hazard ratios from cohort studies) separate from crude and multivariable-adjusted models, study design, number of ASD cases and non-ASD controls, confounding covariates used in adjusted model(s), year of diagnosis, birth cohort, diagnostic method, ratio of autistic disorder and autism spectrum disorder cases, male to female ratio among the autism cases, and how maternal and paternal age was modeled (e.g., categorically). These data are summarized in Table 1.

Additional Data

When necessary, authors were contacted and additional information was requested.

Statistical Methods

We calculated weighted relative risk (RR) estimates and associated two-sided 95% confidence intervals (CIs). Computations used the published RR and CI values assuming approximately normal distribution. Extensive research has demonstrated that age 35 is the age at which risk for a range of adverse developmental outcomes (e.g., Down syndrome) increases, and therefore younger ages are typically used as a reference points. Because it was best supported by the available studies, the primary comparison contrasted maternal age group 25 to 29 years with maternal age group ≥35 or >40 years.

To examine whether there is an increasing risk with increasing maternal age and the potential risk associated with younger maternal age, we also contrasted maternal age group 25 to 29 years with mothers <20 years and with mothers 30 to 34 years.

When modeling the log(RR), we allowed for both a within-study variance of the log relative risk and for a between-study variance term assuming the data to follow a normal distribution. With y_i indicating the log(RR) extracted from the publications, the random-effects models can be defined as $y_i = \mu + u_i + e_i$, where $u_i \sim N(0,\tau^2)$ denotes the normal distributed between-study variation and $e_i \sim N(0,\sigma^2)$ denotes the normal distributed within-study variation. The statistical model accommodates the inclusion of both crude and adjusted RR estimates. From the published papers we extracted both crude models, including a categorical covariate for maternal age only, and adjusted models, including and adjusting for possible confounding effects as well. Models were fitted separately for the crude and multivariable-adjusted estimates and separately for the different category comparisons (e.g., ages 25 to 29 versus ≥35 years). Robustness of results was evaluated by (a) excluding the study with the largest effect size, and (b) excluding the study with the largest sample.

Potential publication bias was examined using funnel plots[32] and by calculating Egger's test.[33] The funnel plot shows the effect size of the different studies on the x-axis and an estimate of the sample size on the y-axis. Small studies should have higher variability in esti-

TABLE 1 List of Studies and Study Characteristics Identified for Meta-Analysis

First Author, Country, Publication Year	Diagnostic Method	Birth Years	Median Year of Diagnosis	% AD	M/F Sex Ratio	Design	Cases	Non-Cases	Type of Adjustment for Confounding					
									Birth Order	Birth Year	SES	Pre-natal	Psych History	Ethni-city
Durkin[3], US (10 states), 2008	*DSM-IV*	1994	1998	80.7	4.5	Case-cohort	1,251	253,347	X	X	X	X		
Larsson[4], DenmarK, 2004	ICD 8/10	1973–1999	1986	NK	3.2	NCC	698	17,450	X	X	X	X	X	
Glasson[5], Australia, 2010	*DSM-III/IV*	1980–1995	1989.5	68	5.3	CC	465	1,313	X	X		X		
Maimburg[6], Denmark, 2006	ICD 8/10	1990–1999	1994.5	100	4.1	NCC	473	4,730		X		X		X
Croen[7], US (California), 2007	ICD 9	1995–1999	1999.5	47	5.4	Cohort	593	132,251	X	X	X			X
Reichenberg[8], Israel, 2006[a]	ICD 10	1980–1985	1983	>90	5.5	Cohort	110	132,161		X	X			
Hultman[30], Sweden, 2010	ICD 9/10	1983–1992	1994.5	100	3.2	Cohort	860	1,034,627	X	X	X	X	X	X
Sasanfar[31], Iran, 2010	*DSM-IV*	1994–2001	2005	68	3.8	Case-cohort	179	549,354	X	X	X			
Grether[11], US (California), 2009[c]	*DSM III/IV*	1989–2002	1997.5	NK	4.9	Cohort	20,701	6,506,555	X	X	X	X		X
Lundstrom[12], Sweden, 2010[b]	*DSM-IV*	1992–1998	1995	NK	NK	Cohorts of twins	164	10,884	X	X	X			
Lundstrom[12], UK, 2010[b]	*DSM-IV*	1994–1996	2005	57	5.4	Cohort of twins	193	12,904				X		

Note: All studies adjusted for paternal age and sex. The five right-most columns for confounding represent model covariates for birth order, socio- economic status (paternal and/or maternal education, source of payment delivery), prenatal (gestational age, weight for gestational age, birth weight, fetal distress, Apgar score, congenital malformations, fetal position), psychiatric history (maternal and/or paternal psychiatric history), ethnicity (maternal/paternal race or country of origin). AD = infantile autism; CC = case-control; NCC = nested case-control; NK = not known; SES = socio-economic status.

[a]*Additionally adjusted for smoking during pregnancy.*

[b]*Included two parts, one from Sweden and one from the United Kingdom (UK). For the UK part, we received additional data from the authors.*

[c]*Use of the California Department of Development Services did not allow us to distinguish between autistic disorder and autism spectrum disorders because a service registry was used.*

mates of relative risk compared with larger studies, and divergence from this pattern may indicate the presence of publication bias.

Potential sources for study heterogeneity were examined using meta-regression analysis. Using the above model, this was done by replacing the term u_i with $\beta_0 + \beta_1 x_{i2} + \beta_2 x_{i2}$, where the parameters β_1 and β_2 measure the size of the association of the moderators in a mixed-effects model. The mixed-effects models were fitted by a maximum likelihood technique that allows for model comparisons using the Akaike Information Criteria (AIC)[34] for which a lower AIC value indicates better model fit. The proportion of males among cases and the proportion of autistic disorder among the cases were examined. Also, because the rate of autism has been increasing, we included a covariate allowing for a fixed change of exposure effect across calendar time in a supplementary model to reduce the between-study heterogeneity. For descriptive purposes, RR estimates calculated by levels of the moderating variables on RR estimates of maternal age are presented by median levels of the moderating variables.

Data were analyzed using R statistical software version 2.12.1 with the Metafor package version 1.4.0[35,36] and SAS version 9.22 procedure GLIMMIX. Statistical significance level was set at the two-sided 5% level corresponding to two-sided 95% confidence intervals of the pooled relative risk estimates.

RESULT

Overview of Study Characteristics

Our search criteria resulted in 631 published papers. 598 studies were excluded after an initial review of the titles and abstracts carried by two of the authors (S.S. and A.R.). The remaining 33 studies were carefully reviewed, and 17 were further excluded (Figure S1, available online).

Eleven studies, from the United States,[3,7,11] Denmark,[4,6] Australia,[5] Israel,[8] Sweden,[12,30] Iran,[31] and the United Kingdom[12] fulfilled all five inclusion criteria and were included in the meta-analysis (Table 1). The two Danish studies[4,6] used nested case-control designs drawn from the national total populations. The study from Western Australia[5] was a population based case-control design with the entire population of Western Australia as reference population. The study from Iran[31] was a case-cohort design drawn from a cohort of pre-school children aged 4 to 11 years. The three studies from the United States, the Israeli study,[8] and the most recent Swedish study[30] all used population-based cohort designs, whereas studies[12] were cohort studies on Swedish and UK twins.

Six other studies were excluded from the meta-analysis mainly because of overlap. Two studies from Sweden were excluded[37,38] because they overlapped with a later study[30] and because of concern for under-ascertainment of autism cases because of changes in autism services in Sweden in one of the studies.[37] Two studies from the United States[10,19] were not included because of substantial overlap with another study[11] that examined a considerably larger cohort. Another US study[39] was also excluded due to overlap with the two earlier studies and did not meet the initial requirement of clear presentations of the results for the risk associated with maternal age, with only crude estimates available and a different categorization of maternal age (<20, 20–34, >34). One study[20] was excluded because of substantial overlap with another study,[5] use of case prevalence instead of case incidence, and subdividing the cases into children with and without intellectual disability. Two Danish studies[13,40] were not included in the formal pooling because of overlap with the other two Danish studies and lack of adjustment for paternal age, as only crude estimates were available.

Covariates used for adjustment for possible confounding in each study are specified in Table 1. All studies included in the meta-analysis adjusted for paternal age, birth year, and sex. All but two studies[5,6] were adjusted for socioeconomic status (SES), all but three studies[7,8,31] for obstetric condition (e.g., Apgar score, small size for gestational age, birth weight), and all but five[4,5,8,12,31] for parental ethnicity. Only two studies[4,30] adjusted for parental psychiatric history.

Meta-Analyses

The primary meta-analysis was conducted on the association between maternal age and ASD. The 10 studies included in the analysis had a total of 25,687 ASD cases and 8,655,576 subjects without an ASD diagnosis.

The crude results showed statistically significant support for an increased risk of autism in the offspring of mothers aged 35 or older compared with mothers aged 25 to 29 in eight of the 10 studies (Table 2). The random-effect pooled estimate of the crude RR of autism in mothers aged 35 or older compared with mothers aged 25 to 29 years was 1.52 (95% CI = 1.21-1.92), $p < .001$.

The crude associations were reduced in all studies after adjustment for potentially confounding covariates (Table 2). Associations nev-

TABLE 2 Relative Risk (RR) Point Estimates and Two-Sided 95% Confidence Intervals Comparing Mothers 25–29 Years Old With Mothers ≥35 or ≥40 Years Old, Adjusting for Potentially Confounding Covariates

Study	Crude RR	Crude 95% Confidence Interval	Adjusted RR	Adjusted 95% Confidence Interval	Weights	Weights[a]
Durkin[3]	1.38	1.17–1.64	1.30	1.06–1.60	16	30
Larsson[4, b]	2.19	1.36–3.52	1.55	0.88–2.74	3	4
Glasson[5]	NA	NA	1.54	1.03–2.30	5	8
Maimburg[6]	1.60	1.28–2.00	1.30	0.99–1.70	11	18
Croen[7, b]	1.53	1.05–2.24	1.27	0.83–1.95	5	7
Reichenberg[8]	9.68	3.51–26.7	2.68	0.80–8.96	1	1
Hultman[30, b]	1.53	1.26–1.86	1.15	0.91–1.47	12	22
Sasanfar[31]	1.17	0.69–1.99	0.85	0.42–1.69	2	3
Grether[11, b]	1.84	1.72–1.97	1.43	1.32–1.55	41	0
Lundstrom[12], Sweden	1.01	0.67–1.52	0.78	0.43–1.40	3	4
Lundstrom[12], UK	0.78	0.51–1.20	0.91	0.50–1.65	3	4
Pooled I	1.52	1.21–1.92	1.31	1.19–1.45		
Pooled II[a]	1.59	1.25–2.03	1.24	1.11–1.39		

Note: Relative study weights were used in the pooling procedure.
[a]Excluding the study by Grether et al.[11]
[b]25–29 Years old vs. ≥ 40 (all others 25–29 vs. ≥35 years old).

ertheless remained statistically significant in three of the studies.[3-5] After adjustment for potential confounding covariates, the random-effect pooled estimate of risk of autism in mothers aged 35 or older compared with mothers aged 25 to 29 years was 1.31 (95% CI = 1.19-1.45; $p < .001$) (Figure 1).

There was no evidence to support publication bias (Figure S2, available online), and the test of heterogeneity between studies was not statistically significant. Because the study from California,[11] which showed a statistically significant association between advancing maternal age and ASD contributed as much as 20,701 of the ASD cases to the meta-analysis, this study was excluded in a sensitivity analysis. The pooled results were similar even after this study was excluded.

When the association between maternal age and autism was examined across the range of categories of maternal age, there was evidence for a monotonic increase in risk of autism with increasing maternal age categories. Of the nine studies that included more than one age group comparison, all but two studies[4,12] reported findings that were consistent with a monotonic maternal age effect. Figure 1 shows the associations between increasing categories of maternal age and risk of ASD in the offspring. The effect was only minimally attenuated after excluding the study from California.[11]

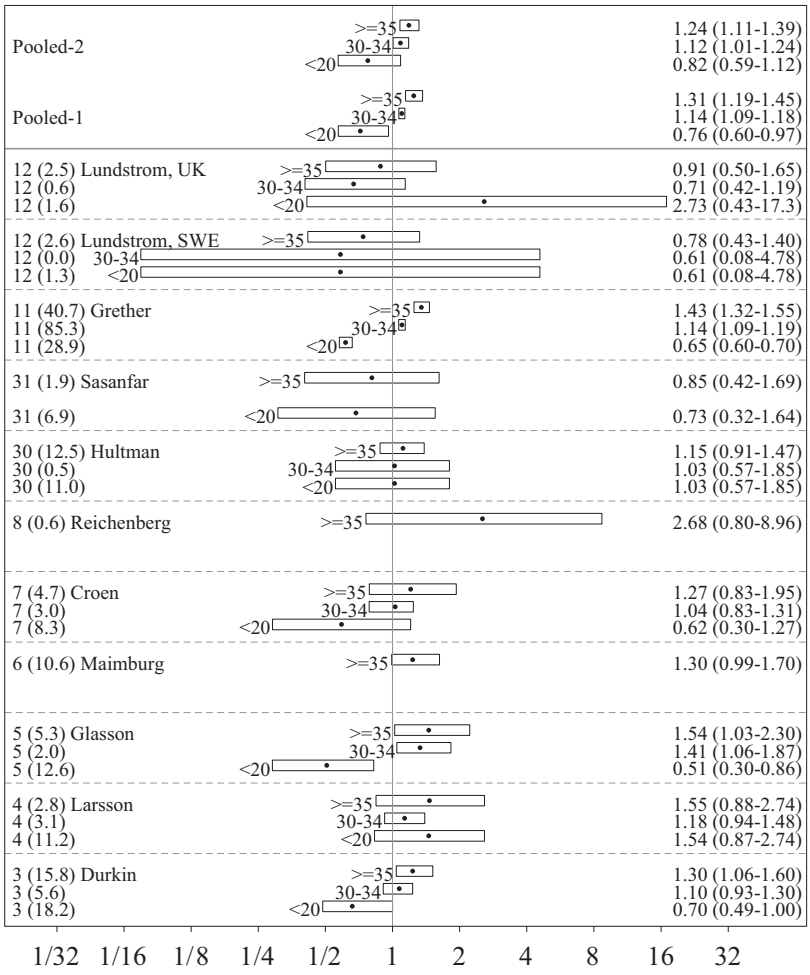
In a complementary analysis, we also examined the studies reporting RR for maternal ≥40 years old[4,7,11,30] and the studies reporting only on maternal age ≥35 years[3,5,6,8,12,30,31] separately, and compared the RR for the highest age category. The RR for maternal age ≥40 compared with maternal age 25 to 29 years was 1.37 (95% CI = 1.19-1.58), and the RR for maternal age ≥35 compared with maternal age 25 to 29 years was 1.23 (95% CI = 1.09–1.39; $p < .001$).

Combining studies[3-5,7,11,30,31] to evaluate the risk associated with younger maternal age (<20) with mothers 25 to 29 years old showed a statistically significant decrease in risk (RR = 0.76; 95% CI = 0.60–0.97, $p = .028$). Excluding a highly influential study,[11] the RR point estimate was slightly higher but now the confidence interval included 1.0 (RR = 0.82; 95% CI = 0.59–1.12).

Moderator Analysis and Meta-Regression

Meta-regression was used to assess whether the effect of maternal age on the risk of autism was modified by other study-specific covariates. Three variables were considered as potential moderators in the meta-regression analyses: Percent male offspring in the study, study year of

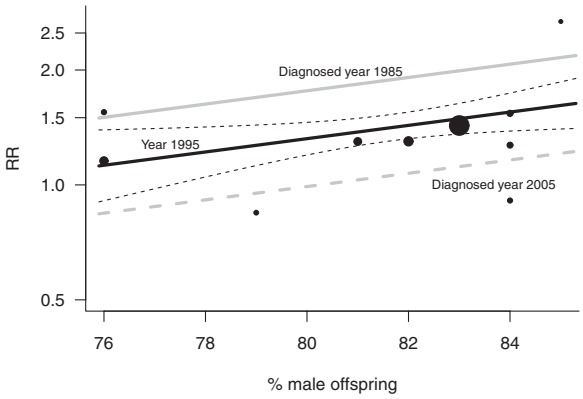
FIGURE 1 Association between increasing categories of maternal age and risk for autism spectrum disorder (ASD). Presented are the adjusted relative risk (RR) comparing 25- to 29-year-old mothers with younger (<20) and older (30–34 or ≥35 years) mothers. Note: RR on the x-axis. Black dots and horizontal bars outline relative risk point estimates and associated two-sided 95% confidence intervals for the relative risk of autism spectrum disorder in offspring comparing mothers <20, 30 to 34, and ≥35 years (bottom to top within each study) years with mothers 25 to 29 years. Study number to the far left. Pooled results on the upper part of the figure where pooled-2 do not include one study (reference 11) in the calculations. Exact numbers for RR and the confidence intervals to the right. In parentheses to the right of the study number the study weight (value 0–100) in the pooling procedure is shown.



autism diagnosis (median of first and last diagnoses), and percentage of ASD cases diagnosed as autistic disorder. Information about study year of autism diagnosis was available in all 11 studies.[3-8,11,12,31,41] Information on percentage of male offspring was available in 10 studies, and information on percentage with autistic disorder was available in 8 studies.

For mothers ≥35 years, the covariates percentage of male offspring and year of autism diagnosis were both statistically significant when controlling for each other jointly. Year of diagnosis was statistically significant among mothers 30 to 34 years old when simultaneously adjusting for percentage of male offspring or percentage with autistic disorder. For maternal age <20 years, the percentage of male offspring was statistically significant when entered as a single variable and also when adjusting for year of diagnosis. To summarize: For all three categories of maternal age, a higher number of male offspring strengthened the effect of maternal age (positive for maternal ages 30 to 34 and ≥35 years and negative for maternal age <20), whereas the maternal age effect diminished with later year of diagnosis. The moderating effects of the percentage of

FIGURE 2 Predicted relative risk of autism (RR) for maternal age ≥35 vs. maternal age 25 to 29 years as a function of percent male offspring and year of diagnosis. Note: Each dot indicates the RR for each study. Solid line and 95% confidence limits predicting association for diagnosis in 1995. Gray solid and dashed lines for predictions 1985 and 2005, respectively.



male offspring and year of diagnosis among mothers ≥35 are summarized in Figure 2.

For ease of interpretation and to quantify the impact of the three potential moderators, RR estimates were calculated in subgroups of these variables (Table 3). The increasing effect with increasing maternal age remain in all subgroups.

Additional Analyses

Advancing maternal age has been associated with increased risk for obstetric complications,[42] and several obstetric conditions have been associated with increased risk for autism.[24] Six studies in the meta-analysis also controlled for the effects of obstetric conditions (Table 1). After adjustment for obstetric conditions, the association between advancing maternal age and autism remained statistically significant in three[3,4,11] of the six studies,[3-6,11,41] with RR for maternal age ≥35 years compared with maternal age 25 to 29 years estimated at 1.41 (CI = 1.31-1.52) and 1.37 (CI = 1.27-1.49), respectively ($p < .001$) (Table 2). Two of the studies not included in the meta-analysis also reported a statistically significant association between autism and older age of mothers after adjustment for obstetric complications.[17,18] The RR of autism associated with a 10-year continuous linear increase in maternal age was available in six studies[3,7,8,11,12,30] with a pooled estimate RR of 1.23 (95% CI = 1.19–1.27) and when excluding one study[11] (RR = 1.07, 95% CI = 0.99–1.15).

DISCUSSION

The role of advancing maternal age in the aetiology of autism has been debated.[43,44] This meta-analysis supports the assertion that advancing maternal age at the time of birth is associated

TABLE 3 Relative Risk (RR) and Associated Two-Sided 95% Confidence Intervals Comparing Maternal Age 25–29 Years With Maternal Ages <20, 30–34, and ≥35 Years in Subgroups of the Moderator Variables

	<20 Years			30–34 Years			≥35 Years		
	n	RR	95% Confidence Interval	n	RR	95% Confidence Interval	n	RR	95% Confidence Interval
Subgroups by % male offspring[a]									
≤82%	4	0.93	0.64–1.37	3	1.12	0.98–1.28	5	1.25	1.10–1.42
>82%	4	0.65	0.60–0.70	4	1.14	1.09–1.19	5	1.42	1.32–1.53
Subgroups by year of diagnosis[a]									
≤1995	4	0.90	0.50–1.61	4	1.24	1.05–1.46	6	1.26	1.08–1.46
>1995	5	0.65	0.61–0.70	4	1.13	1.09–1.18	5	1.34[b]	1.19–1.51
Subgroups by % infantile autism[a]									
<74%	4	0.62	0.43–0.89	3	1.07	0.76–1.50	4	1.22	0.94–1.58
≥74%	2	0.79	0.56–1.12	2	1.09	0.93–1.29	4	1.26	1.10–1.45

Note: n = Number of studies in each subgroup.

[a]*Median across studies (Percent male offspring = 82.5%, year of diagnosis = 1995 and percent male offspring = 74%).*

[b]*In the subgroups of year of diagnosis for mothers ≥35 years old, one study[11] had a substantial impact on the >1995 subgroup potentially accounting for the high RR in this group.*

with an increasing risk for autism spectrum disorders. The association between advancing maternal age and risk of autism in the offspring was robust to adjustment for confounding including paternal age, obstetric complications, birth year, birth order, and markers for socio-economic status, with offspring of mothers older than 35 years having 30% increased risk for developing autism.

There was some support for the association between maternal age and autism varying as a function of the proportion of male cases and year of diagnosis. A stronger association between maternal age and risk of autism was observed in studies with a higher proportion of male offspring cases. These results are not conclusive but are intriguing nonetheless. Two previous studies[7,8] observed that the effects of paternal and maternal age on risk of autism varied as a function of the offspring sex. The association between advancing paternal age and autism was stronger in female offspring, whereas the association between advancing maternal age and autism was stronger in male offspring. The moderator analysis supports this hypothesis, which may point to a possible sex-specific etiology in autism.

Year of diagnosis was another potentially moderating variable, suggesting that the effect of advancing maternal age may have been decreasing over time. Year of diagnosis was also noted as diluting the effect of maternal age in an earlier study.[11] A possible explanation includes age-dependent changes in ascertainment of autism and autism spectrum disorders, or changes related to changes in the risk or ascertainment of phenotypic subtypes.[11]

Although previously reported[7] and speculated as a cause for the moderating effect of year of diagnosis,[11] the association between maternal age and autism did not vary between different autism subtypes in the meta-regression.

These results, like those of any meta-analysis, should be viewed with caution. Meta-regression is a form of observational association and therefore cannot be used to make causal inferences about the data.[45] There may be confounding factors that underlie the relationships reported here. In addition, given the differences between studies in covariates selected and availability, the meta-regression analysis captured only some of the studies included in the meta-analysis. Despite these potential shortcomings, our results suggest that research on maternal age and autism should consider the effects of potential moderating factors. Another potential issue for this article is the largest study included in the meta-analysis,[11] contributing 80% of the number of cases. Inclusion of this study could be considered problematic also because autism cases were ascertained only if the patients had both a diagnosis of autism and a substantial functional impairment.[11] However, our sensitivity analysis demonstrated that inclusion of this study did not bias the results of the meta-analysis or the moderator analysis. Removing this study from the analysis did not substantially change the magnitude of the association of the meta-analysis, and the effect of year of diagnosis and proportion of males remained statistically significant. A potential limitation of the study is that access to the data was restricted to categories of maternal age. This did not allow exploration of the full underlying maternal age continuum. Finally, in our focus on published epidemiological studies, we do recognize there may also be other important aspects that would have required inclusion of more clinically oriented papers but, in the context of the meta-analysis, may be less reliable.

Potential Etiological Mechanisms of Maternal Age

One possible explanation for the maternal age effect is an increased occurrence of genomic alterations. Numerous neurological and psychiatric disorders have been related to genomic alterations.[46] Maternal age is an important factor in the etiology of chromosome anomalies[47,48] and genomic modifications.[49,50] Interestingly, a number of studies have uncovered an increased prevalence of de novo copy-number variants and other forms of genomic alterations in autistic children,[51-53] supporting the notion that novel mutational events may be important in the pathogenesis of autism. Whether these events are also related to advancing maternal age remains to be determined.

An alternative explanation is that epigenetic dysfunction underlies some parental age effects. "Epigenetics" refers to the heritable, but reversible, regulation of gene expression.[54] Epigenetic dysfunction has been associated with several neuropsychiatric disorders,[55] and is also implicated in single-gene disorders, including Rett and Fragile X syndromes, characterized by autistic-like features in some patients.[46]

It is also possible that the accumulated exposure to various environmental toxins over the life course could result in genomic and/or epigenetic alterations in the germ cells of older parents. Toxins have been shown to induce DNA damage, germline mutations, and global hypermethylation[56] in germ cells, and have long term developmental consequences in offspring.[57] In addition, increasing maternal age may be

related to endocrine and hormonal factors, not only by ageing alone but also through maternal stress, increasing infertility, and use of assisted reproductive treatment.[58]

In conclusion, this meta-analysis supports an association between advancing maternal age and risk of autism. The relative risk increased monotonically with increasing maternal age. The association persisted after the effects of paternal age and other potential confounders have been considered, supporting an independent relation between higher maternal age and autism. &

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FIGURE S1 Flow chart with numbers showing published papers selected and excluded from the initial search in PubMed to the publications included in the final pooling and meta-analysis. Note: Overlap indicates a published paper in which the study population overlap with another study already included in the meta-analysis.

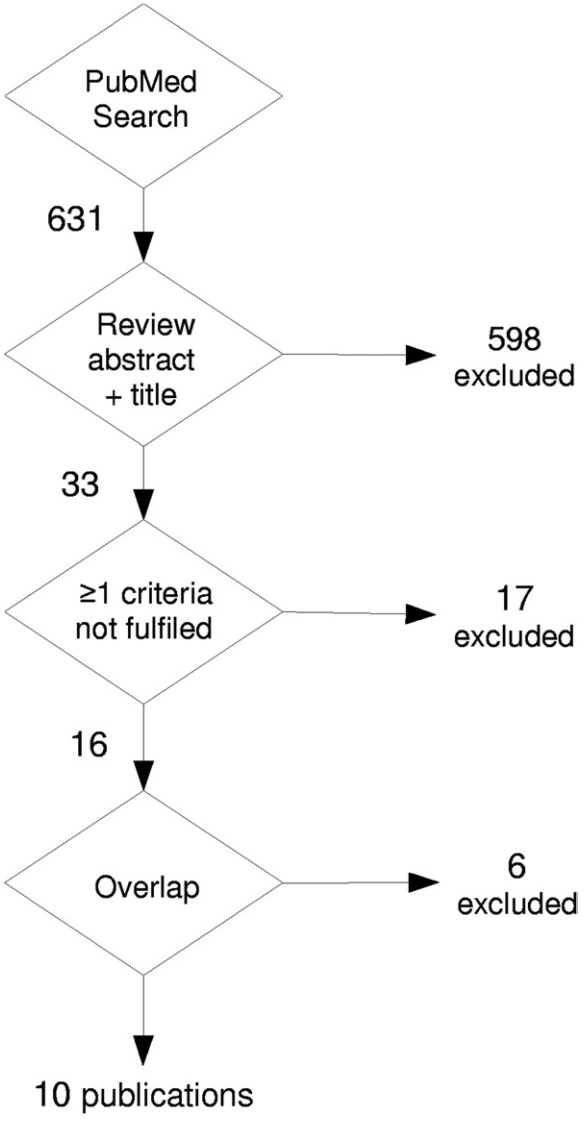

FIGURE S2 Funnel plots. Note: Standard error vs. log(relative risk (RR)) corresponding to RR estimates in Table 2. *P* values corresponding to Egger's test of publication bias.