Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2017: 135: 29–41

DOI: 10.1111/acps.12666

Meta-analysis

Advanced parental age and autism risk in children: a systematic review and meta-analysis

Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Advanced parental age and autism risk in children: a systematic review and meta-analysis.

Objective: Advanced parental age has raised additional concern as a risk factor of autism. We conducted a meta-analysis of observational studies investigating the association between advanced parental age and risk of autism.
Method: PubMed, EMBASE, and Web of Science were searched for reports published up to November 11, 2015. Risk estimates from individual studies were pooled using random-effects models.
Results: Twenty-seven studies were included in the meta-analysis. Compared with the reference points, the lowest parental age category was associated with a reduced risk of autism in the offspring, with adjusted odds ratios (ORs) 0.89 (95% confidence intervals [CIs] 0.75–1.06) and 0.81 (95% CI 0.73–0.89) for mother and father, respectively, and the highest parental age category was associated with an increased risk of autism in the offspring, with adjusted ORs 1.41 (95% CI 1.29–1.55) and 1.55 (95% CI 1.39–1.73) for mother and father respectively. Dose–response meta-analysis indicated that an increase of 10 years in maternal and paternal age was associated with an 18% and 21% higher risk of autism.
Conclusion: Advanced parental age was associated with an increased risk of autism in the offspring. More mechanistic studies are needed to further explain this positive association.

S. Wu[1,†], F. Wu[2,†], Y. Ding[3,†], J. Hou[1], J. Bi[1], Z. Zhang[1]

[1]Research Center for Clinical and Translational Medicine, Beijing 302 Hospital, Beijing, [2]Department of General Surgery, The 309th Hospital of PLA, Beijing and [3]Department of Medical Microbiology and Parasitology, Second Military Medical University, Shanghai, China

Key words: autism spectrum disorders; maternal age; paternal age; child

Dr Jingfeng Bi and Dr Zheng Zhang, Research Center for Clinical and Translational Medicine, Beijing 302 Hospital, Beijing 100039, China. E-mails: 123bjf@163.com and zhangzheng1975@aliyun.com

[†]These authors contributed equally to this article.

Accepted for publication October 18, 2016

Summations

- Lower maternal age was associated with over 10% reduced risk of autism in children, and lower paternal age was associated with nearly 20% reduced risk.
- Higher maternal age was associated with 41% increased risk of autism, and higher paternal age was associated with 55% increased risk.
- An increase of 10 years in maternal and paternal age was associated with an 18% and 21% higher risk of autism.

Considerations

- So far, the risk of autism according to the highest vs. the lowest parental age category is unknown.
- Several important confounders were not reported in some of the included studies.
- Further studies are needed to elucidate the cause–effect relationship between advanced parental age and increased risk of autism.

Introduction

Autism is a chronic disorder with onset in early infancy. The clinical presentation is characterized by behavioural disturbances such as social abnormalities, communication impairments, and repetitive and stereotyped patterns of behaviour (1). During the last two decades, the reported prevalence of autism in children has increased dramatically (2). The cause of autism is uncertain; however, evidence from twin studies suggests a strong genetic contribution (3) and environmental factors (3–5).

Symptoms of autism can be identified as early as in the first 2 years of life. Identification of pre- and perinatal risk factors of autism may help better understanding the causal mechanisms for autism. As the mean age at maternity and paternity has increased in many countries during latter decades (6), advanced parental age has attracted considerable attention as a potential risk factor for autism in the offspring. Older maternal age is related to both genetic and environmental risk factors. Increased risk of chromosomal abnormalities such as Down syndrome has been associated with advanced maternal age (7). Additionally, pregnancies to older mothers are subject to the effect of exposure to toxins for a longer time (8). Advanced paternal age has also been associated with adverse reproductive outcomes, including miscarriage (9, 10), fetal death (11), autoimmune disorders (12), childhood cancers (13), schizophrenia (14, 15), and other neuropsychiatric diseases (16). However, the associations between parental age and autism risk have varied in population-based studies. Results include reports that the age of both parents is associated (17), that only maternal age is associated (18), that only paternal age is associated (19, 20), and that there is no association of autism with parental age (21). Methodologic limitations, including small sample size, different methodologies, different study population, and lack of statistical control for potential confounding factors, have made these findings difficult to interpret.

Confirmation of the association between parental age and autism risk could have important public health implications, because both maternal and paternal age has shown increasing trend in recent decades. Furthermore, it is likely to be helpful in the search for etiologic factors, because age-related reproductive mechanisms are different between women and men. Sandin et al. (22) have conducted a meta-analysis on this subject, and their results supported an association between advanced maternal age and risk of autism. However, data on paternal age and risk of autism were not reported in their study and relevant studies included in their meta-analysis were all published before the year of 2011. We therefore conducted a systematic review and meta-analysis of updated evidence for the relation between advanced parental age and risk of autism in children.

Material and methods

Search strategy and eligibility criteria

We followed guidelines made by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (23) group and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (24) groups. Two investigators (SW and YD) performed a systematic search of literature in PubMed, EMBASE, and Web of Science for relevant articles published between 1965 to November 11, 2015. Synonymous terms were selected and used to develop the search strategy (Panel S1). The search was restricted to studies published in English language and in human beings. The reference lists of identified studies were also checked for other potentially relevant reports. The authors of the included studies were contacted for (J.K. Gretherand and X. Sun) unpublished data and additional information.

The eligible studies should meet the following inclusion criteria: (i) The study population consisted of children with childhood autism or autism spectrum disorder (ASD); (ii) examination of maternal and/or paternal age as the variable of interest; (iii) the association between advanced parental age and risk of autism/ASD was assessed; and (iv) reporting the relative risks (RRs) or odds ratios (ORs) of autism or ASD calculated according to the lowest and/or highest maternal/paternal age category with a referenced age group, with their 95% confidence intervals (CIs). Studies about mechanistic research, review research, and letters were excluded.

Data extraction and study quality evaluation

Two reviewers (SW and FW) independently extracted the study characteristics and crude and adjusted effect sizes with 95% CI and recorded the data in a standard form. The quality of included studies was assessed by two researchers (JB and JH), using the Newcastle-Ottawa Scale (NOS) recommended by Wells and colleagues (25). The quality of each included study ranges from one to nine stars.

Statistical analysis

In the most studies we reviewed, parental age was classified into several categories, and the authors used a midpoint parental age category as the referenced group to calculate the relative risks of autism according to the lower age categories vs. the midpoint and the higher age categories vs. the midpoint. Other studies only reported the risks of autism according to either higher age categories vs. the lowest age category or lower age categories vs. the highest age category. The detailed categories of parental age and relative risks of autism according to the referenced point in each included study are shown in Table S1. As the reference groups are quite different in different studies, it is impossible for us to define a specific age range as the reference group. Therefore, we can only perform meta-analyses of risk estimates comparing the lowest category of parental age with the referenced age group and the highest category of parental age with the referenced age group respectively. Risks associated with maternal age and paternal age were pooled separately. We did separate analyses for crude and adjusted ORs. We also did dose–response meta-analyses of parental age and risk of autism using previous reported methods (26, 27), which facilitated the calculation of a pooled OR across studies with a common unit of comparison with studies, assuming a linear dose–response relation. In this study, we estimated the OR per unit 10 years decrease and increase of parental age for each study and then pooled them together. We converted the parental age categories based on the calculated midpoint of age if the study did not report the median of exposure category.

Random-effects model was used in this meta-analysis to take into account the heterogeneity between studies, because the study design and measuring time varied across studies (28). We used *I*-squared (I^2) statistic and *Q*-statistic to explore the heterogeneity between studies. Large I^2 (>50%) or $P < 0.1$ for *Q*-statistic indicates potential heterogeneity between studies. We did several subgroup analysis: study design (cohort or case–control), geographical area (North America, Europe or Asia and Oceania), diagnostic method, and outcome (ASD or childhood autism). Sensitivity analyses were performed by removing each individual study from the pooled analyses (29). Publication bias was examined by funnel plots and was further assessed by Egger's regression test and Begg–Mazumdar test. All the analyses were conducted with STATA version 12.0 software (Stata Corp, College Station, TX, USA).

Results

Search results

Our initial search yielded 998 records, of which 950 remained after removal of duplications (Fig. S1). Overall, 27 studies met the inclusion criteria and were included in the meta-analysis, including six cohort studies (19, 20, 30–33) and 21 case–control studies (1, 17, 18, 21, 34–50), with a total of 17 658 960 participants and 66 948 autism events. Characteristics of these included studies are provided in Table 1. We recorded relative risks of autism according to both the lowest parental age category vs. reference point and highest parental age category vs. reference point. Overall, the quality of the included studies was relatively good, with median (range) NOS score 7 (6–9) stars. The study quality assessments of the included studies were presented in Tables S2 and S3 in detail.

Risk of autism according to the lowest parental age category vs. reference points

The crude results showed that compared with the reference point, the lowest category for parental age was associated with a reduced risk of autism in the offspring, although it did not quite reach statistical significance for paternal age (OR = 0.76 with 95% CI 0.61–0.94 and OR = 0.83 with 95% CI 0.68–1.01 for maternal age and paternal age respectively) (Fig. S2). The results varied in some subgroup analyses (Table 2). Sensitivity analysis indicated that the difference in the risk of autism was not materially changed in most leave-one-out analyses by omitting one study in turn (Fig. S4a, b).

Comparing the lowest parental age category to the reference points, the adjusted ORs of autism in the offspring were 0.89 (95% CI 0.75–1.06) and 0.81 (95% CI 0.73–0.89) for maternal age and paternal age respectively (Fig. S3). The results also varied in some subgroups (Table 2). Sensitivity analysis indicated that the difference in the risk of autism was not materially changed in the leave-one-out analyses by omitting one study in turn (Fig, S4c,d).

Risk of autism according to the highest parental age category vs. reference points

For the crude results, the highest category for parental age significantly increased the risk of autism in the offspring, compared with the reference points (OR = 1.66 with 95% CI 1.52–1.82 and OR = 1.64 with 95% CI 1.44–1.86 for maternal

Table 1. Characteristics of included studies

Study	Study site	Study design	*n*	Number with autism in study	Outcome	Diagnostic method	Factors adjusted for
Bilder et al. (2009) (34)	The United States	Case–control	13 332	120	ASD	DSM-IV-TR	None
Buizer-Voskamp et al. (2011) (35)	The Netherlands	Case–control	11 310	2262	ASD	DSM-IV-TR	Average income of the neighborhood, and difference in age between the father and the mother and the ethnic background
Burstyn et al. (2010) (30)	Canada	Cohort	218 890	1138	ASD	ICD 9	Maternal weight, maternal height, prepregnancy diabetes, gestational diabetes, bleeding <20 weeks, bleeding ≥20 weeks, cigarette smoking, poor weight gain, parity, and socioeconomic status of mother
Croen et al. (2007) (31)	The United States	Cohort	132 884	593	ASD	ICD 9	Other parent's age, birth order, date of birth, sex of the child, maternal and paternal educational level, and maternal and paternal race/ethnicity
D'Onofrio et al. (2014) (32)	Sweden	Cohort	900 337	2424	ASD	ICD 9/10	Sex, birth parity, year of birth, parental education, lifetime history of psychiatric hospitalization, lifetime history of any criminal conviction, maternal age, and paternal income
Durkin et al. (2008) (17)	The United States	Case–control	253 347	1251	ASD	DSM-IV-TR	Other parent's age, birth order, gender, maternal education, child's race/ethnicity, multiple birth, gestational age, and birthweight for gestational age
Frans et al. (2013) (36)	Sweden	Case–control	36 859	5936	Childhood autism	ICD 9/10	Birth year, sex, age of spouse, family history, highest educational level, and county
Glasson et al. (2004) (18)	Australia	Case–control	2259	465	ASD	DSM-IV	Year of birth, birth order, maternal age, threatened abortion, fetal distress, and elective cesarean section
Golding et al. (2010) (37)	United Kingdom	Case–control	13 971	86	ASD	Health service records and the education system	Gender
Grether et al. (2009) (38)	The United States	Case–control	6 527 256	20701	Childhood autism	DSM-IV	Child's sex and birthweight, maternal age, paternal age, maternal race/ethnicity, paternal race/ethnicity, maternal education, paternal education, parity, gestational age, delivery method of payment, and birth year
Hultman et al. (2011) (39)	Sweden	Case–control	1 075 588	883	Childhood autism	ICD 9/10	Paternal age, paternal education level, maternal country of birth, paternal country of birth, maternal psychiatric hospitalization, paternal psychiatric hospitalization, birthweight, birthweight for gestational age, fetal distress, and parity
Idring et al. (2014) (40)	Sweden	Case–control	417 303	4746	ASD	ICD 9/10	Maternal and paternal age main effects penalized cubic regression spline smooths, tensor product smooth interaction of maternal and paternal age, birth year, offspring sex, parity, maternal and paternal psychiatric history, occupational class, family income, maternal region of birth and random effects for birth mother
Lampi et al. (2013) (41)	Finland	Case–control	5647	1132	Childhood autism	ICD 9/10	The other parent's age, number of previous births, weight for gestational age, intellectual disability, maternal socioeconomic status, and maternal and paternal psychiatric history
Larsson et al. (2005) (21)	Denmark	Case–control	18 148	698	Childhood autism	ICD 8/10	Fetal presentation, Apgar score at 5 min, gestational age at birth, birthweight for gestational age, no. of antenatal visits, no. of previous pregnancies, the other parent's age, parental psychiatric history, maternal education, and parental wealth
Lauritsen et al. (2005) (20)	Denmark	Cohort	943 664	818	Childhood autism	ICD 10	Age and its interaction with gender, calendar year of diagnosis, the other parent's age, maternal history of psychiatric disorder, paternal identity, paternal history of psychiatric disorder, history of psychiatric disorder in siblings, degree of urbanization of place of birth, maternal country of birth, and parental countries of births
Lundstrom et al. (2010) (42)	Sweden and The United Kingdom	Case–control	24 646	230	ASD	DSM-IV	Maternal age, zygosity and socioeconomic status
Maimburg et al. (2006) (43)	Denmark	Case–control	5203	473	Childhood autism	ICD 8/10	Mother and father's age, mothers citizenship, birthweight and gestational age, Apgar, birth defect, and irregular fetal position
Mamidala et al. (2013) (44)	India	Case–control	942	471	ASD	DSM-IV	Maternal age at delivery, gender and birth year
Parner et al. (2012) (33)	Denmark	Cohort	1 311 736	9556	ASD and Childhood autism	ICD 8/10	None

Table 1. (Continued)

Study	Study site	Study design	*n*	Number with autism in study	Outcome	Diagnostic method	Factors adjusted for
Pinborough-Zimmerman et al. (2011) (45)	The United States	Case–control	26 108	99	ASD	DSM-IV	Gender, maternal ethnicity, the other parent's age, maternal education, paternal education, adjusted gross income, federal taxes paid, and number of tax exemptions
Reichenberg et al. (2006) (19)	Israel	Cohort	132 271	110	ASD	ICD 10	Year of birth, socioeconomic status, and maternal age
Sasanfar et al. (2010) (46)	Iran	Case–control	549 553	179	ASD	DSM-IV-TR	Paternal education, maternal education, birth order, sex, consanguinity, and urban/rural
Shelton et al. (2010) (47)	The United States	Case–control	4 947 935	12159	Childhood autism	ICD code	Other parent's age, both parents race/ethnicity, parity, year of birth, insurance type, and sum of parental education
Sun et al. (2014) (48)	United Kingdom	Case–control	3329	46	ASD	ICD 10	None
van Balkom et al. (2012) (49)	Aruba	Case–control	442	95	ASD	DSM-IV	Paternal age, maternal age, and preterm birth
Williams et al. (2008) (50)	Australia	Case–control	85 810	182	ASD	DSM-IV	Gender, gestational age, multiple birth, Apgar 1 min, mother's country of birth, birthweight, Apgar 5 min, fetal growth not including gender, birth order, and fetal growth including gender
Zhang et al. (2010) (1)	China	Case–control	190	95	Childhood autism	ICD 10	Paternal age at delivery, gender and birth year

ASD, autism spectrum disorder; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria; ICD, International Classification of Diseases.

age and paternal age respectively) (Fig. 1). The results were quite consistent in most subgroup analyses (Table 2). Sensitivity analysis indicated that the significantly increased risk of autism was not materially changed in the leave-one-out analyses by omitting one study in turn (Fig. S4e,f).

Similarly, the adjusted results showed advanced parental age was significantly associated with an increased risk of autism in the offspring, comparing the highest category for parental age to the reference points (OR = 1.41 with 95% CI 1.29–1.55 and OR = 1.55 with 95% CI 1.39–1.73 for maternal age and paternal age respectively) (Fig. 2). The results were quite consistent in most subgroup analyses (Table 2). Additionally, sensitivity analysis indicated that the significant difference in the risk of autism was not materially changed in the leave-one-out analyses by omitting one study in turn (Fig. S4 g,h).

Dose–response meta-analysis

As dose–response meta-analysis requires data for the distribution of cases and person-time across at least three categories of exposure (51), thus, only studies that provided at least three categories of maternal age or paternal age were included in the dose–response meta-analysis.

In the dose–response meta-analysis, a decrease of 10 years in maternal age was not significantly associated with reduced risk of autism (OR = 0.93 with 95% CI 0.69–1.24) (Fig. S5a). However, a decrease of 10 years in paternal age was associated with a 26% reduced risk of autism (OR = 0.74 with 95% CI 0.64–0.86) (Fig. S5b). Furthermore, an increase of 10 years in maternal age was associated with an 18% higher risk of autism (OR = 1.18 with 95% CI 1.10–1.26) and an increase of 10 years in paternal age was associated with a 21% higher risk of autism (OR = 1.21 with 95% CI 1.18–1.24) (Fig. 3).

Publication bias

There was no potential publication bias in most of our meta-analyses as assessed by funnel plots, Egger's regression test, and Begg–Mazumdar test (Fig. S6). Egger's regression test (P = 0.010) and Begg–Mazumdar test (P = 0.023) indicated there was potential publication bias when assessing the risk of autism comparing the highest paternal age category to the reference points in the adjusted result (Fig. S6h). After using the trim and fill approach, seven studies were filled and the pooled result did not reverse (OR = 1.40 with 95% CI 1.24–1.59) (Fig. S6i).

Table 2. Subgroup analyses for studies included in the analysis

Subgroup analysis	Number of estimates in included studies (n), pooled OR (95% CI), I^2 statistics (%), and P-value for the heterogeneity Q-test			
	n	Maternal	n	Paternal
Lowest vs. referred (crude)				
Design				
Cohort	1	0.37 (0.21, 0.66)	1	0.29 (0.11, 0.77)
Case–control	10	0.80 (0.64, 1.00); $I^2 = 94.7$, $P < 0.001$	13	0.89 (0.70, 1.05); $I^2 = 83.5$, $P < 0.001$
Geographical area				
North America	6	0.58 (0.47, 0.72); $I^2 = 92.8$, $P < 0.001$	6	0.64 (0.52, 0.79); $I^2 = 80.8$, $P < 0.001$
Europe	4	1.20 (0.95, 1.52); $I^2 = 50.0$, $P = 0.111$	7	1.12 (0.79, 1.58); $I^2 = 68.5$, $P = 0.004$
Asia and Oceania	1	0.59 (0.27, 1.30)	1	0.68 (0.34, 1.34)
Diagnostic method				
DSM-IV	5	0.56 (0.47, 0.68); $I^2 = 45.1$, $P = 0.121$	8	0.88 (0.58, 1.32); $I^2 = 84.0$, $P < 0.001$
ICD	6	0.88 (0.60, 1.27); $I^2 = 93.7$, $P < 0.001$	6	0.83 (0.63, 1.10); $I^2 = 77.0$, $P = 0.001$
Outcome				
ASD	5	0.60 (0.48, 0.75); $I^2 = 12.7$, $P = 0.333$	8	0.87 (0.55, 1.38); $I^2 = 74.9$, $P < 0.001$
Childhood autism	6	0.89 (0.66, 1.15); $I^2 = 97.1$, $P < 0.001$	6	0.78 (0.63, 0.98); $I^2 = 87.8$, $P < 0.001$
Lowest vs. referred (adjusted)				
Design				
Cohort	2	1.06 (0.40, 2.82); $I^2 = 81.1$, $P = 0.022$	2	0.78 (0.58, 1.04); $I^2 = 0.0$, $P = 0.320$
Case–control	11	0.87 (0.73, 1.03); $I^2 = 87.1$, $P < 0.001$	13	0.81 (0.73, 0.90); $I^2 = 53.4$, $P = 0.012$
Geographical area				
North America	5	0.70 (0.57, 0.87); $I^2 = 85.7$, $P < 0.001$	6	0.79 (0.67, 0.93); $I^2 = 58.5$, $P = 0.034$
Europe	6	1.19 (0.98, 1.43); $I^2 = 59.6$, $P = 0.030$	8	0.83 (0.70, 0.97); $I^2 = 34.5$, $P = 0.153$
Asia and Oceania	2	0.57 (0.36, 0.89); $I^2 = 0.0$, $P = 0.475$	1	0.91 (0.45, 1.84)
Diagnostic method				
DSM-IV	5	0.65 (0.60, 0.70); $I^2 = 0.0$, $P = 0.655$	7	0.98 (0.68, 1.41); $I^2 = 66.0$, $P = 0.007$
ICD	8	1.07 (0.91, 1.26); $I^2 = 75.2$, $P < 0.001$	8	0.80 (0.74, 0.86); $I^2 = 23.4$, $P = 0.243$
Outcome				
ASD	6	0.69 (0.51, 0.94); $I^2 = 65.1$, $P = 0.014$	8	0.94 (0.68, 1.31); $I^2 = 59.4$, $P = 0.016$
Childhood autism	7	1.04 (0.82, 1.32); $I^2 = 91.2$, $P < 0.001$	7	0.76 (0.72, 0.81); $I^2 = 0.0$, $P = 0.591$
Highest vs. referred (crude)				
Design				
Cohort	4	1.83 (1.26, 2.66); $I^2 = 81.6$, $P = 0.001$	4	1.53 (1.29, 1.82); $I^2 = 72.0$, $P = 0.013$
Case–control	15	1.79 (1.70, 1.88); $I^2 = 0.0$, $P = 0.616$	17	1.67 (1.41, 1.98); $I^2 = 78.8$, $P < 0.001$
Geographical area				
North America	6	1.84 (1.73, 1.94); $I^2 = 0.0$, $P = 0.629$	6	1.73 (1.45, 2.06); $I^2 = 63.2$, $P = 0.018$
Europe	8	1.52 (1.38, 1.66); $I^2 = 0.0$, $P = 0.483$	11	1.61 (1.37, 1.90); $I^2 = 74.3$, $P < 0.001$
Asia and Oceania	5	1.96 (1.29, 2.98); $I^2 = 69.5$, $P = 0.011$	4	1.74 (0.95, 3.19); $I^2 = 76.5$, $P = 0.005$
Diagnostic method				
DSM-IV	7	1.80 (1.68, 1.93); $I^2 = 0.0$, $P = 0.581$	9	1.42 (1.12, 1.82); $I^2 = 69.6$, $P = 0.001$
ICD	12	1.66 (1.45, 1.90); $I^2 = 62.0$, $P = 0.002$	12	1.78 (1.52, 2.08); $I^2 = 85.8$, $P < 0.001$
Outcome				
ASD	10	1.59 (1.32, 1.92); $I^2 = 50.8$, $P = 0.032$	12	1.35 (1.18, 1.55); $I^2 = 51.9$, $P = 0.019$
Childhood autism	9	1.81 (1.72, 1.91); $I^2 = 0.0$, $P = 0.550$	9	1.94 (1.66, 2.26); $I^2 = 70.6$, $P = 0.001$
Highest vs. referred (adjusted)				
Design				
Cohort	4	1.47 (1.22, 1.77); $I^2 = 0.0$, $P = 0.479$	4	1.84 (1.23, 2.75); $I^2 = 75.8$, $P = 0.006$
Case–control	15	1.41 (1.27, 1.56); $I^2 = 65.8$, $P < 0.001$	16	1.49 (1.33, 1.67); $I^2 = 56.8$, $P = 0.003$
Geographical area				
North America	5	1.44 (1.36, 1.53); $I^2 = 0.0$, $P = 0.608$	5	1.44 (1.28, 1.62); $I^2 = 19.5$, $P = 0.291$
Europe	8	1.34 (1.11, 1.61); $I^2 = 73.9$, $P < 0.001$	10	1.54 (1.31, 1.81); $I^2 = 63.8$, $P = 0.003$
Asia and Oceania	5	1.35 (0.92, 1.98); $I^2 = 47.9$, $P = 0.104$	4	2.26 (1.10, 4.65); $I^2 = 84.8$, $P < 0.001$
Diagnostic method				
DSM-IV	7	1.43 (1.33, 1.53); $I^2 = 1.1$, $P = 0.416$	8	1.46 (1.18, 1.80); $I^2 = 43.9$, $P = 0.086$
ICD	12	1.38 (1.21, 1.57); $I^2 = 66.7$, $P = 0.001$	12	1.61 (1.40, 1.86); $I^2 = 71.3$, $P < 0.001$
Outcome				
ASD	10	1.54 (1.36, 1.75); $I^2 = 42.6$, $P = 0.074$	11	1.51 (1.29, 1.77); $I^2 = 60.3$, $P = 0.005$
Childhood autism	9	1.34 (1.22, 1.48); $I^2 = 37.8$, $P = 0.117$	9	1.68 (1.36, 2.09); $I^2 = 69.1$, $P = 0.001$

OR, odds ratio; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICD, International Classification of Diseases; ASD, autism spectrum disorder.

Discussion

The main results of the current meta-analysis are the following: (i) Lower parental age was associated with a reduced risk of autism in the offspring; (ii) advanced parental age was associated with an increased risk of autism in the offspring; (iii) a decrease of 10 years in paternal age was

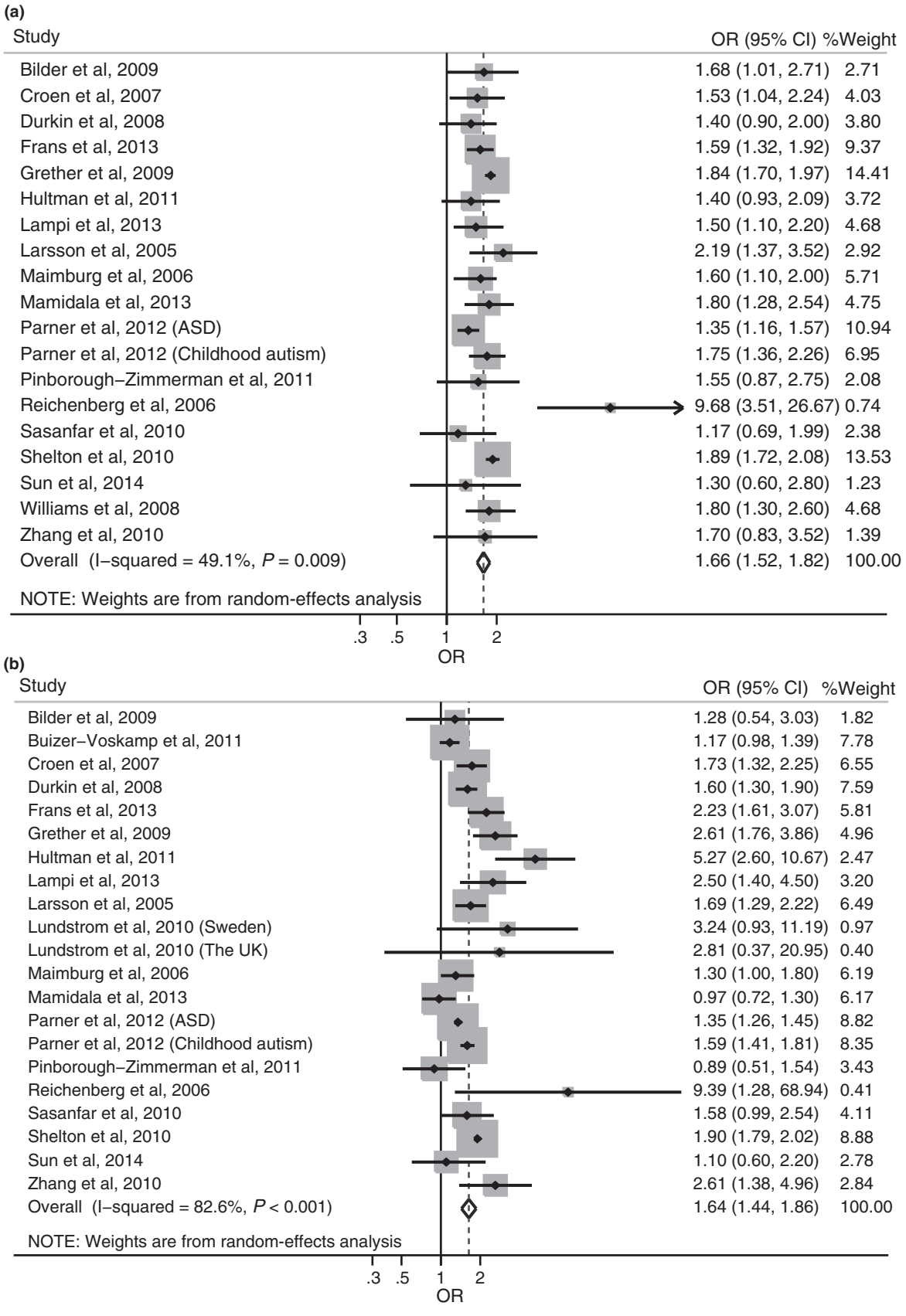

Fig. 1. Risk of autism according to the highest parental age category vs. reference points. Pooled effects for maternal age (a) and paternal age (b) from random-effects meta-analyses for unadjusted results are shown.

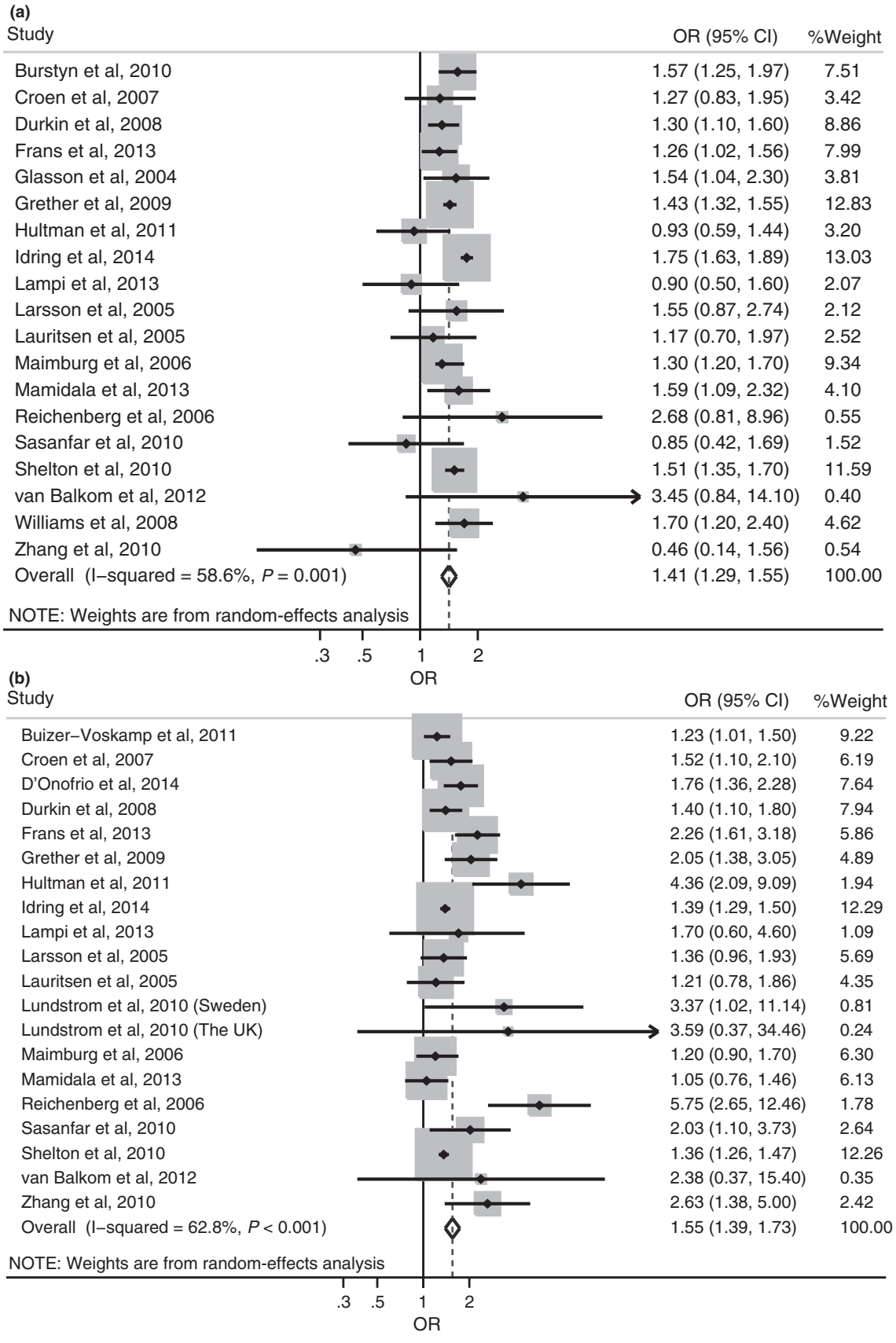

Fig. 2. Risk of autism according to the highest parental age category vs. reference points. Pooled effects for maternal age (a) and paternal age (b) from random-effects meta-analyses for adjusted results are shown.

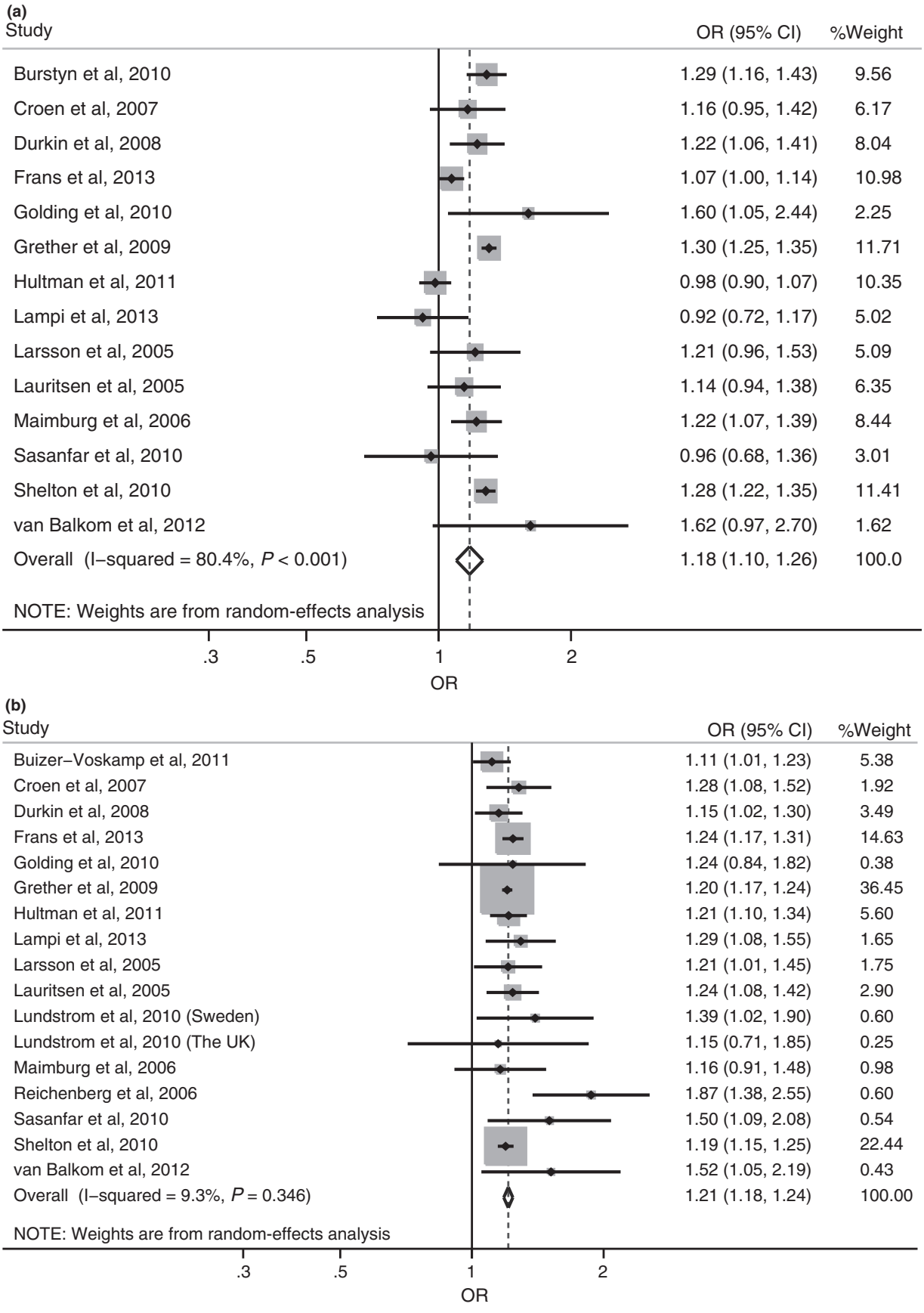

Fig. 3. Relative risks of autism for an increase of 10 years in maternal (a) and paternal (b) age.

associated with a 26% reduced risk of autism, while an increase of 10 years in maternal and paternal age was associated with an 18% and 21% higher risk of autism. All these results suggest that both increasing maternal age and increasing paternal age were associated with increased risk of autism in the offspring. These findings are important because the identified risk factors may help better understanding the causal mechanisms for autism in children because the potential trigger and mechanism for the underlying pathology in this disease are still unclear.

Combining estimates from all available published studies allowed us to examine the status of advanced parental age as a risk factor for autism with a more comprehensive evidence base and greater precision than has previously been possible. Our findings are consistent with a previous meta-analysis (22) of advanced maternal age and increasing risk of autism reviewing data from 8 655 576 participants and 25 687 ASD cases—a substantially smaller evidence base than that in the current meta-analysis. In our meta-analysis, we expand those findings by including paternal age in addition to maternal age and including many newly published articles (after the year of 2010). Our results support the hypothesis that advanced parental age contributes to an increased risk of psychiatric and mental disorders (15, 52). Additionally, our results are consistent with the previous findings that prenatal factors, genetic factors, and environmental factors are associated with autism (53–55). The association between parental age and risk of autism in the offspring is various and mixed as reported in the previous studies, which is reflected by the included studies in our meta-analysis. Most studies focused on the influence of maternal age or paternal age on autism. This is the first meta-analysis to make a comprehensive evaluation on the association of both the maternal age and the paternal age and risk of autism in the offspring. As our analysis represents a comparison of the lowest or the highest parental age category with the referenced points, the difference in the odds of autism in the offspring would probably be even greater if the studies were expanded to compare the highest parental age category with the lowest parental age category. In addition, two included studies indicated that advanced grandparental age was also associated with increased risk of autism, suggesting that risk of autism could develop over generations (36, 37).

There are several plausible mechanisms by which advanced parental age might affect autism in the offspring; however, mechanisms underlying maternal and paternal age effects are likely different. Increased rates of *de novo* mutations (56–58) and epigenetic alternations (59) with increasing age are the most frequently proposed mechanisms underlie paternal age effects. Of possible relevance to autism, an independent association of schizophrenia (14) and bipolar disorder (60) in the offspring with advanced paternal, but not maternal, age has been identified. The association for schizophrenia is consistent with the hypothesis of accumulating *de novo* mutations in the germ cells of fathers with advanced age (61). For the mechanisms underlie maternal age effects, in addition to the increased rates of genomic alternations (62, 63), advanced maternal age is associated with a much higher rate of perinatal and obstetric complications (64), which have been shown to increase risk of autism (65, 66). Moreover, older mothers have more opportunities for exposure to environmental factors such as medications (67) or air pollutions (68), reported to increase risk of autism. Advanced maternal age has also shown to associate with other risk factors for autism such as nutritional deficiencies (69), metabolic conditions (70), or autoimmunity (53).

Our study has several limitations. First, observational studies cannot provide causal evidence of an effect of advanced parental age on the development of autism outcomes; they can describe only associations. Further studies are needed to explain the association between advanced parental age and autism in the offspring and elucidate the cause–effect relationship. Second, there was potential heterogeneity in most of the analyses. Although random-effects and subgroup analyses were performed, we are unlikely to have fully accounted for heterogeneity. Thus, the results should be interpreted with caution. Although the included studies were heterogeneous, the associations we observed were largely consistent. Third, it is noteworthy that the potential causes of advanced reproductive age at birth of the first child may also influence the risk of autism (71); however, we are unable to consider it as a confounder in the current meta-analysis. Fourth, in most of our included studies, the authors used a midpoint of parental age categories as the reference group, and we can only assess the risk of autism according to the lowest or highest parental age category vs. reference points. The risk of autism based on the highest vs. lowest parental age was unable to assess according to current literatures. Finally, the maternal age may be correlative with the paternal age, and vice versa. However, other parent's age, as an important confounder, was not adjusted in some of the included studies.

Our study has important strengths. First, to our knowledge, this is the largest study focusing on both maternal and paternal age and autism

outcomes. The pooled analysis has greater power than any of the included individual studies to detect differences. This is evident in the adjusted analysis comparing the lowest paternal age category to the reference points, in which 10 of the included 15 studies did not detect a difference. In addition, our meta-analysis produced much more narrow 95% CIs compared with each individual study, making the results more precise. Second, the pooled ratios of relative risk for autism were broadly consistent in several different sensitivity analyses. Third, there was no publication bias in most analyses. Although there was potential publication bias when assessing the risk of autism comparing the highest paternal age category to the reference points in the adjusted result, the analysis by the trim and fill approach did not reverse the result. Thus, the likelihood that our findings are largely a result of selective publication seems to be minimal.

In conclusion, there is evidence that advanced parental age is associated with an increased risk of autism in the offspring. Recognition of this risk is of great importance in both clinical psychiatric practice and as a public health issue. Avoidance of delayed reproductive age needs to be emphasized, and more attention should be paid to the children with advanced parental age. Further studies are needed to elucidate the cause–effect relationship and mechanism between advanced parental age and increased risk of autism in the offspring.

Acknowledgements

The authors sincerely thank Yan Hu, Guoming Xie, and Rong Gao for their generous assistance with this study. This work was supported in part by grants from the National Key Basic Research Program of China (2012CB519005).

Declaration of interest

The authors declare no financial or other conflicts of interest.

References

1. Zhang X, Lv CC, Tian J et al. Prenatal and perinatal risk factors for autism in China. J Autism Dev Disord 2010;**40**:1311–1321.
2. Skalny AV, Skalnaya MG, Bjorklund G, Nikonorov AA, Tinkov AA. Mercury as a possible link between maternal obesity and autism spectrum disorder. Med Hypotheses 2016;**91**:90–94.
3. Bailey A, le Couteur A, Gottesman I et al. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 1995;**25**:63–77.
4. Stilp RL, Gernsbacher MA, Schweigert EK, Arneson CL, Goldsmith HH. Genetic variance for autism screening items in an unselected sample of toddler-age twins. J Am Acad Child Adolesc Psychiatry 2010;**49**:267–276.
5. Abrahams BS, Geschwind DH. Advances in autism genetics: on the threshold of a new neurobiology. Nat Rev Genet 2008;**9**:341–355.
6. Bray I, Gunnell D, Davey Smith G. Advanced paternal age: how old is too old? J Epidemiol Community Health 2006;**60**:851–853.
7. Salem Yaniv S, Levy A, Wiznitzer A, Holcberg G, Mazor M, Sheiner E. A significant linear association exists between advanced maternal age and adverse perinatal outcome. Arch Gynecol Obstet 2011;**283**:755–759.
8. Maramara LA, He W, Ming X. Pre- and perinatal risk factors for autism spectrum disorder in a New Jersey cohort. J Child Neurol 2014;**29**:1645–1651.
9. de la Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. Hum Reprod 2002;**17**:1649–1656.
10. Slama R, Werwatz A, Boutou O, Ducot B, Spira A, Hardle W. Does male age affect the risk of spontaneous abortion? An approach using semiparametric regression. Am J Epidemiol 2003;**157**:815–824.
11. Nybo Andersen AM, Hansen KD, Andersen PK, Davey Smith G. Advanced paternal age and risk of fetal death: a cohort study. Am J Epidemiol 2004;**160**:1214–1222.
12. Montgomery SM, Lambe M, Olsson T, Ekbom A. Parental age, family size, and risk of multiple sclerosis. Epidemiology 2004;**15**:717–723.
13. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 2001;**30**:1428–1437.
14. Malaspina D, Harlap S, Fennig S et al. Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry 2001;**58**:361–367.
15. Byrne M, Agerbo E, Ewald H, Eaton WW, Mortensen PB. Parental age and risk of schizophrenia: a case-control study. Arch Gen Psychiatry 2003;**60**:673–678.
16. El-Saadi O, Pedersen CB, McNeil TF et al. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. Schizophr Res 2004;**67**:227–236.
17. Durkin MS, Maenner MJ, Newschaffer CJ et al. Advanced parental age and the risk of autism spectrum disorder. Am J Epidemiol 2008;**168**:1268–1276.
18. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry 2004;**61**:618–627.
19. Reichenberg A, Gross R, Weiser M et al. Advancing paternal age and autism. Arch Gen Psychiatry 2006;**63**:1026–1032.
20. Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. J Child Psychol Psychiatry 2005;**46**:963–971.
21. Larsson HJ, Eaton WW, Madsen KM et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol 2005;**161**:916–925.
22. Sandin S, Hultman CM, Kolevzon A, Gross R, Maccabe JH, Reichenberg A. Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2012;**51**:477–486 e471.
23. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for

reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;**283**:2008–2012.
24. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;**6**:e1000097.
25. Wells G, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: University of Ottawa, 2011.
26. Larsson SC, Orsini N. Fish consumption and the risk of stroke: a dose-response meta-analysis. Stroke 2011;**42**:3621–3623.
27. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;**135**:1301–1309.
28. Li JW, He SY, Liu P, Luo L, Zhao L, Xiao YB. Association of gestational diabetes mellitus (GDM) with subclinical atherosclerosis: a systemic review and meta-analysis. BMC Cardiovasc Disord 2014;**14**:132.
29. Tobias A. Assessing the influence of a single study in meta-analysis. Stata Tech Bull 1999;**47**:15–17.
30. Burstyn I, Sithole F, Zwaigenbaum L. Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. Chronic Dis Can 2010;**30**:125–134.
31. Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. Arch Pediatr Adolesc Med 2007;**161**:334–340.
32. D'Onofrio BM, Rickert ME, Frans E et al. Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry 2014;**71**:432–438.
33. Parner ET, Baron-Cohen S, Lauritsen MB et al. Parental age and autism spectrum disorders. Ann Epidemiol 2012;**22**:143–150.
34. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics 2009;**123**:1293–1300.
35. Buizer-Voskamp JE, Laan W, Staal WG et al. Paternal age and psychiatric disorders: findings from a Dutch population registry. Schizophr Res 2011;**129**:128–132.
36. Frans EM, Sandin S, Reichenberg A et al. Autism risk across generations: a population-based study of advancing grandpaternal and paternal age. JAMA Psychiatry 2013;**70**:516–521.
37. Golding J, Steer C, Pembrey M. Parental and grandparental ages in the autistic spectrum disorders: a birth cohort study. PLoS ONE 2010;**5**:e9939.
38. Grether JK, Anderson MC, Croen LA, Smith D, Windham GC. Risk of autism and increasing maternal and paternal age in a large North American population. Am J Epidemiol 2009;**170**:1118–1126.
39. Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. Mol Psychiatry 2011;**16**:1203–1212.
40. Idring S, Magnusson C, Lundberg M et al. Parental age and the risk of autism spectrum disorders: findings from a Swedish population-based cohort. Int J Epidemiol 2014;**43**:107–115.
41. Lampi KM, Hinkka-Yli-salomaki S, Lehti V et al. Parental age and risk of autism spectrum disorders in a Finnish national birth cohort. J Autism Dev Disord 2013;**43**:2526–2535.
42. Lundstrom S, Haworth CM, Carlstrom E et al. Trajectories leading to autism spectrum disorders are affected by paternal age: findings from two nationally representative twin studies. J Child Psychol Psychiatry 2010;**51**:850–856.
43. Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. Acta Psychiatr Scand 2006;**114**:257–264.
44. Mamidala MP, Polinedi A, Praveen Kumar PTV et al. Prenatal, perinatal and neonatal risk factors of Autism Spectrum Disorder: a comprehensive epidemiological assessment from India. Res Dev Disabil 2013;**34**:3004–3013.
45. Pinborough-Zimmerman J, Bilder D, Bakian A et al. Sociodemographic risk factors associated with autism spectrum disorders and intellectual disability. Autism Res 2011;**4**:438–448.
46. Sasanfar R, Haddad SA, Tolouei A, Ghadami M, Yu D, Santangelo SL. Paternal age increases the risk for autism in an Iranian population sample. Mol Autism 2010;**1**:2.
47. Shelton JF, Tancredi DJ, Hertz-Picciotto I. Independent and dependent contributions of advanced maternal and paternal ages to autism risk. Autism Res 2010;**3**:30–39.
48. Sun X, Allison C, Auyeung B, Baron-Cohen S, Brayne C. Parental concerns, socioeconomic status, and the risk of autism spectrum conditions in a population-based study. Res Dev Disabil 2014;**35**:3678–3688.
49. van Balkom ID, Bresnahan M, Vuijk PJ, Hubert J, Susser E, Hoek HW. Paternal age and risk of autism in an ethnically diverse, non-industrialized setting: Aruba. PLoS ONE 2012;**7**:e45090.
50. Williams K, Helmer M, Duncan GW, Peat JK, Mellis CM. Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. Child Care Health Dev 2008;**34**:249–256.
51. Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. Am J Clin Nutr 2009;**89**:1402–1409.
52. McGrath JJ, Petersen L, Agerbo E, Mors O, Mortensen PB, Pedersen CB. A comprehensive assessment of parental age and psychiatric disorders. JAMA Psychiatry 2014;**71**:301–309.
53. Wu S, Ding Y, Wu F et al. Family history of autoimmune diseases is associated with an increased risk of autism in children: a systematic review and meta-analysis. Neurosci Biobehav Rev 2015;**55**:322–332.
54. Hallmayer J, Cleveland S, Torres A et al. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 2011;**68**:1095–1102.
55. Hertz-Picciotto I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. Environ Health Perspect 2006;**114**:1119–1125.
56. Neale BM, Kou Y, Liu L et al. Patterns and rates of exonic *de novo* mutations in autism spectrum disorders. Nature 2012;**485**:242–245.
57. O'Roak BJ, Vives L, Girirajan S et al. Sporadic autism exomes reveal a highly interconnected protein network of *de novo* mutations. Nature 2012;**485**:246–250.
58. Sanders SJ, Murtha MT, Gupta AR et al. *De novo* mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 2012;**485**:237–241.
59. Flanagan JM, Popendikyte V, Pozdniakovaite N et al. Intra- and interindividual epigenetic variation in human germ cells. Am J Hum Genet 2006;**79**:67–84.

60. Frans EM, Sandin S, Reichenberg A, Lichtenstein P, Langstrom N, Hultman CM. Advancing paternal age and bipolar disorder. Arch Gen Psychiatry 2008;**65**:1034–1040.
61. Sipos A, Rasmussen F, Harrison G et al. Paternal age and schizophrenia: a population based cohort study. BMJ 2004;**329**:1070.
62. Ginsburg C, Fokstuen S, Schinzel A. The contribution of uniparental disomy to congenital development defects in children born to mothers at advanced childbearing age. Am J Med Genet 2000;**95**:454–460.
63. Kaytor MD, Burright EN, Duvick LA, Zoghbi HY, Orr HT. Increased trinucleotide repeat instability with advanced maternal age. Hum Mol Genet 1997;**6**:2135–2139.
64. Cnattingius S, Forman MR, Berendes HW, Isotalo L. Delayed childbearing and risk of adverse perinatal outcome. A population-based study. JAMA 1992;**268**:886–890.
65. Abel KM, Dalman C, Svensson AC et al. Deviance in fetal growth and risk of autism spectrum disorder. Am J Psychiatry 2013;**170**:391–398.
66. Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparen P, Cnattingius S. Can association between preterm birth and autism be explained by maternal or neonatal morbidity? Pediatrics 2009;**124**:e817–e825.
67. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. BMJ 2013;**346**:f2059.
68. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry 2013;**70**:71–77.
69. Schmidt RJ, Tancredi DJ, Ozonoff S et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr 2012;**96**:80–89.
70. Krakowiak P, Walker CK, Bremer AA et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 2012;**129**:e1121–e1128.
71. Lee BK, McGrath JJ. Advancing parental age and autism: multifactorial pathways. Trends Mol Med 2015;**21**:118–125.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flowchart for the selection of eligible studies.
Figure S2. Risk of autism according to the lowest parental age category vs. reference points.
Figure S3. Risk of autism according to the lowest parental age category vs. reference points.
Figure S4. Sensitivity analyses.
Figure S5. Relative risks of autism for a decrease of 10 years in maternal (A) and paternal (B) age.
Figure S6. Funnel plots to assess publication bias.
Table S1. Categories of parental age group and relative risks of autism in the included studies.
Table S2. Quality assessment of the included studies (cohort studies).
Table S3. Quality assessment of the included studies (case-control studies).
Panel S1. Search strategy in Medline and Embase.