Human Reproduction Update, Vol.24, No.3 pp. 320–389, 2018
Advanced Access publication on February 15, 2018 doi:10.1093/humupd/dmy005

human reproduction update

The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis

Nan B. Oldereid [1,*], Ulla-Britt Wennerholm[2], Anja Pinborg[3], Anne Loft[4], Hannele Laivuori[5,6,7,8], Max Petzold[9], Liv Bente Romundstad[10,11], Viveca Söderström-Anttila[12], and Christina Bergh[13]

[1]Livio IVF-klinikken Oslo, Sørkedalsveien 10A, 0369 Oslo, Norway [2]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Sahlgrenska University Hospital East, SE 416 85 Gothenburg, Sweden [3]Department of Obstetrics and Gynecology, Hvidovre Hospital, Institute of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark [4]Fertility Clinic, Section 4071, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK–2100 Copenhagen, Denmark [5]Department of Obstetrics and Gynecology, Tampere University Hospital, Teiskontie 35, FI-33521 Tampere, Finland [6]Faculty of Medicine and Life Sciences, University of Tampere, Arvo Ylpön katu 34, FI-33520 Tampere, Finland [7]Medical and Clinical Genetics, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 8, FI-00290 Helsinki, Finland [8]Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, Tukhomankatu 8, FI-00290 Helsinki, Finland [9]Swedish National Data Service and Health Metrics Unit, University of Gothenburg, 405 30 Gothenburg, Sweden [10]Spiren Fertility Clinic, Norwegian University of Science and Technology, Trondheim NO-7010, Norway [11]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway [12]Mehiläinen Felicitas, Mannerheimintie 20A, 00100 Helsinki, Finland [13]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Reproductive Medicine, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden

*Correspondence address. Livio IVF-klinikken Oslo, Sørkedalsveien 10A, 0369 Oslo, Norway.
E-mail: nan.b.oldereid@gmail.com orcid.org/0000-0003-3959-3942

Submitted on November 20, 2017; resubmitted on December 28, 2017; editorial decision on January 19, 2018; accepted on January 21, 2018

TABLE OF CONTENTS

BACKGROUND: Maternal factors, including increasing childbearing age and various life-style factors, are associated with poorer short- and long-term outcomes for children, whereas knowledge of paternal parameters is limited. Recently, increasing paternal age has been associated with adverse obstetric outcomes, birth defects, autism spectrum disorders and schizophrenia in children.

OBJECTIVE AND RATIONALE: The aim of this systematic review is to describe the influence of paternal factors on adverse short- and long-term child outcomes.

SEARCH METHODS: PubMed, Embase and Cochrane databases up to January 2017 were searched. Paternal factors examined included paternal age and life-style factors such as body mass index (BMI), adiposity and cigarette smoking. The outcome variables assessed were short-term outcomes such as preterm birth, low birth weight, small for gestational age (SGA), stillbirth, birth defects and chromosomal anomalies. Long-term outcome variables included mortality, cancers, psychiatric diseases/disorders and metabolic diseases. The systematic review follows PRISMA guidelines. Relevant meta-analyses were performed.

OUTCOMES: The search included 14 371 articles out of which 238 met the inclusion criteria, and 81 were included in quantitative synthesis (meta-analyses). Paternal age and paternal life-style factors have an association with adverse outcome in offspring. This is particularly evident for psychiatric disorders such as autism, autism spectrum disorders and schizophrenia, but an association is also found with stillbirth, any birth defects, orofacial clefts and trisomy 21. Paternal height, but not BMI, is associated with birth weight in offspring while paternal BMI is associated with BMI, weight and/or body fat in childhood. Paternal smoking is found to be associated with an increase in SGA, birth defects such as congenital heart defects, and orofacial clefts, cancers, brain tumours and acute lymphoblastic leukaemia. These associations are significant although moderate in size, with most pooled estimates between 1.05 and 1.5, and none exceeding 2.0.

WIDER IMPLICATIONS: Although the increased risks of adverse outcome in offspring associated with paternal factors and identified in this report represent serious health effects, the magnitude of these effects seems modest.

Key words: paternal age / BMI / smoking / perinatal outcome / birth defects / autism / schizophrenia / cancer / mortality

Introduction

There is evidence that reproductive failures originate during the periconceptional period and that such failures are influenced by the age and the life-style of the partners (Sinclair and Watkins, 2013; Steegers-Theunissen *et al.*, 2013). Maternal factors, such as the woman's childbearing age and various life-style factors, are associated with poorer short- and long-term outcomes in the offspring (Jacobsson *et al.*, 2004; Wennberg *et al.*, 2016) whereas knowledge of the influence of paternal factors is limited (Soubry *et al.*, 2014).

Over the last few decades, the childbearing age of the mother has increased worldwide from the early 20s to the early 30s (National Institute for Health and Welfare. Nordic perinatal statistics, 2014. Helsinki, Finland). This has increased the focus on the influence of maternal age on the short and long-term health of mothers and children (Jacobsson *et al.*, 2004). However, there has been less focus on the age of the male partner, which has been rising in parallel with maternal childbearing age (Khandwala *et al.*, 2017). Recently, paternal age has been associated with a wide range of adverse health effects in offspring, including both autism spectrum disorders (ASDs) and schizophrenia (Reichenberg *et al.*, 2006). The mechanisms explaining these associations remain unclear (Frans *et al.*, 2015). As a man ages, the number of *de novo* mutations in his sperm increases along with the chance that a child might carry a deleterious mutation leading to possible diseases (Kong *et al.*, 2012). Recently, a novel mechanism has been suggested which may contribute to the association with paternal age, the process known as 'selfish spermatogonial selection' (Goriely and Wilkie, 2012) where rare spermatogonial cells bearing mutations are positively selected leading to their progressive clonal expansion. This process seems to affect all men, especially as they age.

Furthermore, advanced paternal age has been linked to aneuploidy in autosomes and sex-chromosomes (Lowe *et al.*, 2001; Zhu *et al.*, 2005b) and epigenetic alterations have been proposed as mechanisms by which modifications in gene expression can be transmitted to the offspring (Perrin *et al.*, 2007). In addition, older fathers may represent a non-typical male population, as both higher and lower socio-economic statuses are overrepresented among older fathers (Nilsen *et al.*, 2013).

Whereas, it is well known that maternal smoking, alcohol consumption and high BMI are associated with poorer short- and long-term outcomes for the children, knowledge of the effects of paternal life-style factors is limited. Malnutrition may impair several metabolic pathways (Steegers-Theunissen *et al.*, 2013), and cigarette smoking can cause DNA or chromosomal damage in human germinal cells, including spermatozoa (Zenzes, 2000). Because ejaculated sperm has minimal, if any, repair capacity it is likely that these changes can be transmitted to the offspring.

The aim of this systematic review was to assess the influence of periconceptional paternal factors on adverse short and long-term child outcomes. These include preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA), birth defects, chromosomal anomalies, psychiatric disorders such as schizophrenia and autism disorders, mortality, impaired neurodevelopment and cognitive functions, and cardio-metabolic functions. We have included the following paternal exposure factors: age, BMI, height, and/or weight and cigarette smoking.

Methods

We searched the PubMed, Cochrane and Embase databases up to January 2017. Exposures were periconceptional paternal age, paternal smoking and paternal BMI, height, and/or weight. Short-term obstetric outcomes we looked for included PTB, birth weight (BW), LBW, SGA, stillbirth and neonatal death (NND). Further significant outcomes were children with birth defects in general, and selected birth defects i.e.

orofacial clefts, gastroschisis, congenital heart defects (CHDs), spina bifida and trisomy 21. Long-term outcomes included childhood mortality and morbidity e.g. leukaemia and other malignancies, childhood body weight and BMI, cardio-metabolic disorders, autism/ASD, schizophrenia, other psychiatric disorders and impaired cognitive function. Several of these outcomes when appropriate were used for meta-analysis.

Systematic search for evidence

The terms used in the searches are listed below:

('Paternal Age'[Mesh]) OR ('Paternal Exposure'[Mesh]) AND ('Congenital Abnormalities')[Mesh] OR congenital malformat*[tiab] OR congenital abnormal*[tiab] OR birth defect*[tiab] OR 'Birth Weight'[Mesh] OR birth weight[tiab] OR birth weight[tiab] OR premature birth[tiab] OR premature delivery[tiab] OR 'Perinatal Mortality'[Mesh] OR 'Perinatal Death'[Mesh] OR perinatal outcome*[tiab] OR 'Stillbirth'[Mesh] OR 'Live Birth'[Mesh] OR stillbirth[tiab] OR live birth*[tiab] OR outcome[tiab] OR outcomes[tiab] OR gestational age[tiab] OR children[tiab] OR child[tiab] OR 'Autism Spectrum Disorder'[Mesh] OR 'Autistic Disorder'[Mesh] OR 'Schizophrenia'[Mesh] OR autism[tiab] OR autistic[tiab] OR schizophrenia[tiab]) NOT (animals [mh] AND humans[mh])) NOT ('News'[Publication Type] OR 'Newspaper Article'[Publication Type]).

We also manually searched reference lists of identified articles for additional references. Guidelines for meta-analysis and systematic reviews of observational studies were followed (Stroup *et al.*, 2000). The literature search was performed by two researchers (C.B. and U.B.W.) and one librarian. Screening of abstracts and of full papers for inclusion was done by pairs of reviewers (C.B. and U.B.W., A.P. and A.L., N.O. and L.B.R., V.S.A. and H.L.). Differences of opinion in the team were solved by discussion until consensus was achieved.

Inclusion and exclusion of studies

Original studies published in English and the Nordic languages were included. In the case of double publication, the latest study was included. Studies with a control group and case series with more than 100 patients were included. Concerning very rare diseases, studies with fewer cases were also included. Studies published only as abstracts and case reports were excluded. Studies dealing with paternal age were excluded if they did not adjust for maternal age. Systematic reviews without meta-analyses were excluded.

Definitions

PTB was defined as gestational age <37 weeks, very PTB (VPTB) as a gestational age <32 weeks. LBW was defined as BW <2500 g and very LBW (VLBW) as a BW <1500 g. SGA/intrauterine growth retardation (IUGR), stillbirth and birth defects were defined by each author.

Appraisal of certainty of evidence

The methodological quality of the studies, in terms of risk of bias, was assessed by pairs of reviewers. We used the tools developed by SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) (www.sbu.se/sv/Evidensbaserad-vard/Utvardering-av-metoder-i-halso-och-sjukvarden–En-handbok/) for assessing original articles, which grade articles as being of low, moderate and high quality. For systematic reviews we used AMSTAR (AMSTAR: Assessing the Methodological Quality of Systematic Reviews Systematic reviews, cohort and case control studies, but not case series, were assessed for methodological quality. For certainty of evidence we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Guyatt *et al.*, 2008).

The GRADE system evaluates the following variables for all studies, both combined and per outcome: Design, study limitations, consistency, directness, precision, publication bias, magnitude of effect, relative effect and absolute effect. Certainty levels are divided into high, moderate, low and very low certainty. Certainty levels are based on our confidence in the effect estimate, which in turn is based on the number of studies, design of studies, consistency of associations between studies, study limitations, directness, precision, publication bias, effect size, and relative and absolute effect.

The certainty levels are; very confident = high certainty, moderately confident = moderate certainty, limited confidence = low certainty and very little confidence = very low certainty. If conclusions are based on RCTs, GRADE starts at high certainty level (level 4) but can be downgraded, while if conclusions are based on observational studies GRADE starts at low certainty level (level 2) but might be upgraded (or downgraded). If conclusions were based on case series, no assessment of GRADE was performed.

Statistics

Outcomes are given in odds ratio (OR), adjusted odds ratio (AOR), adjusted prevalence odds ratio (APOR), hazard ratio (HR), adjusted hazard ratio (AHR), RR (relative risk), adjusted relative risk, adjusted prevalence ratio (APR), adjusted incidence rate ratio (AIRR) or adjusted mortality rate ratio (AMRR) with 95% CI. A few studies used mean standardized BW and standardized regression coefficient (Beta).

Meta-analyses were performed despite significant heterogeneity in reference groups for paternal age and despite the fact that outcomes were given in AOR, AHR or APR. A random effects meta-analysis using the DerSimonian and Laird method, with the estimate of heterogeneity being taken from the Mantel-Haenszel model, was used in the analysis (command metan in Stata 15: StataCorp LLC, TX, USA).

Results

The search strategy identified a total of 14 371 articles, of which 238 were selected for inclusion in the systematic review and 81 for inclusion in quantitative synthesis (meta-analysis) (Fig. 1, PRISMA Flow chart)

Among the studies included were 10 meta-analyses, 127 cohort studies, 96 case control studies and 5 case series (Supplementary Tables SI–III). Excluded studies, with reasons for exclusion, are presented in Supplementary Table SIV.

A quality assessment of the cohort and case control studies included is presented in Supplementary Tables SV–VII and for systematic reviews in Supplementary Table SVIII. Of the selected cohort and case control studies, 35 articles were of high quality, 103 were of moderate quality and 85 of low quality. Of the systematic reviews included, nine were of medium quality and one was of low quality.

Paternal age at childbirth and short-term outcomes for offspring

Obstetric outcomes

PTB and very PTB. Nine cohort studies, comprising more than 10 million births in total, reported on PTB or VPTB or both (Supplementary Table SI, Table I). Six cohort studies were of high quality and three of medium quality. Three studies (Abel *et al.*, 2002; Zhu *et al.*, 2005a; Astolfi *et al.*, 2006) found a small but significantly increased risk of PTB

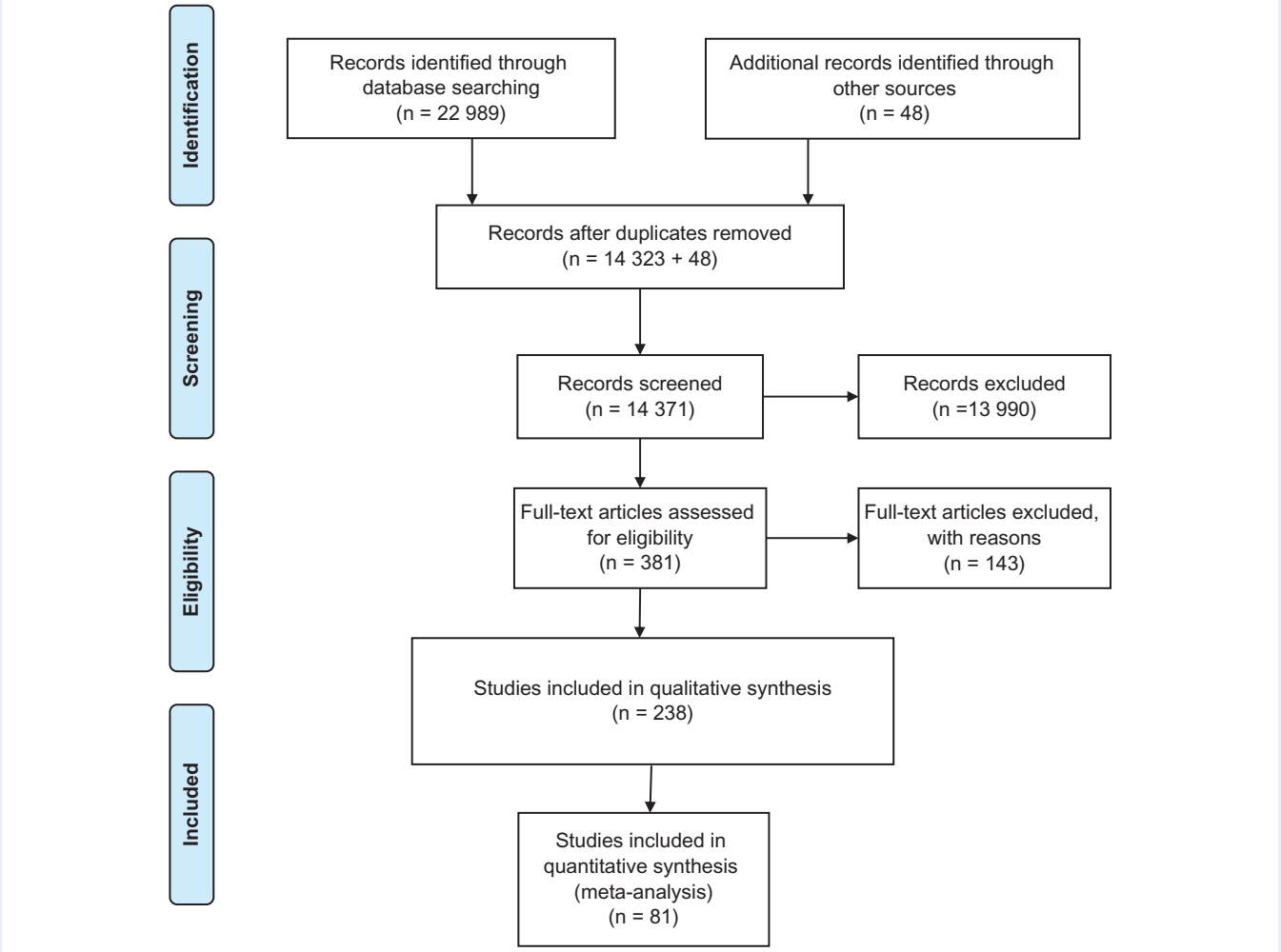

Figure 1 PRISMA flow diagram for a systematic review and meta-analysis on the effect of paternal factors on perinatal and paediatric outcomes.

associated with advanced paternal age. Low paternal age (<20 or <25 years) was associated with a higher risk of PTB in four studies (Abel *et al.*, 2002; Chen *et al.*, 2008; Alio *et al.*, 2012; Astolfi *et al.*, 2006). Our meta-analysis including eight of the studies showed a pooled AOR estimate of 1.02 (95% CI 1.00–1.05) of PTB in older versus younger (reference groups varied between 20 and 34 years) fathers (the forest plot is shown in Fig. 2). In the Danish study by Zhu *et al.* (2005a) the risk of VPTB in older fathers was increased, but not in the US study by Basso and Wilcox (2006).

Conclusion: There may be little or no difference in the rate of PTB between older and younger fathers. Low certainty of evidence (GRADE⊕⊕◯◯).

Low BW and very low BW. Nine cohort studies (three high, three medium and three low quality) comprising almost 6 million births assessed LBW, two of them also VLBW (Abel *et al.*, 2002: Chen *et al.*, 2008) (Supplementary Table SI, Table I).

We performed a meta-analysis with LBW as outcome. We included six studies, and found a pooled estimate of 1.00 (95% CI 0.97–1.03) for LBW in older versus younger (reference groups varied between 20 and 34 years) fathers (Fig. 3). Low paternal age (<20 or <25 years) was associated with a higher risk of LBW in three studies (Abel *et al.*, 2002; Chen *et al.*, 2008; Alio *et al.*, 2012).

None of the studies assessing the risk of VLBW in older fathers found an increased risk.

Conclusion: There may be little or no difference in the rate of LBW between older and younger fathers. Low certainty of evidence (GRADE⊕⊕◯◯).

Small for gestational age. Five cohort studies (two high, two medium and one low quality), comprising almost 4 million births, found no association between infants born SGA and increased paternal age (Supplementary Table SI, Table I).

Conclusion: There may be little or no difference in the rate of SGA between older and younger fathers. Low certainty of evidence (GRADE⊕⊕◯◯).

Stillbirth/neonatal mortality. Four cohort studies, comprising between 23 821 and 3 610 647 births, three of high quality and one of medium quality, reported stillbirths (Supplementary Table SI, Table I. In an analysis of more than 3 million births, Astolfi *et al.* (2004) (high quality) found in an Italian cohort study a significantly increased risk of

Table I Studies on human paternal age and obstetric outcomes identified in a systematic review of the literature on the effect of paternal factors on perinatal and paediatric outcomes.

Author, year, country	Study design	Number of pregnancies, births or children	Result		Outcomes Comments Adjustments	Study quality
			Outcomes (risk estimates)	Reference group/ controls		
Original articles *n* = 16						
Abel *et al.* (2002), USA	Cohort study	155 903 births	Paternal age < 20 years: PTB: AOR 1.24 (1.02–1.52) LBW: AOR 1.28 (1.02–1.61)	Paternal age 21–25 years	PTB and LBW: Significantly higher risk for low paternal age. No other significances. Adjusted for maternal age, socio-economic status, infant gender and race	High
Alio *et al.* (2012), USA	Cohort study	755 334 singletons	LBW, PTB (33–37 weeks), VPTB (<33 weeks): Paternal age < 20, 20–24 years: AORs 1.10 to 1.31 (1.07 to 1.41)* >45 years: AORs 1.13 to 1.19 (1.05 to 1.44)* SGA: <20 years: AORs 1.18 (1.13–1.24) 20–24 years: 1.12 (1.10–1.15) Stillbirth (≥20 weeks): 40–45 years: AOR 1.24 (1.04–1.47) >45 years: 1.33 (1.02–1.77) *lowest and highest 95% CI	Paternal age 25–29 years	LBW, PTB, VPTB: U-shaped risk with significantly higher risk for low and high paternal age. SGA: Significantly higher risk for younger fathers. Stillbirth: Significantly higher risk for older fathers. Adjusted for maternal age, race, education, marital status, years of birth, maternal complications, prenatal care, smoking and alcohol	High
Astolfi *et al.* (2004), Italy	Cohort study	3 619 647 births	Stillbirth: Paternal age ≥ 40 years, maternal age <35 years, high education OR 1.12 (1.00–1.25) Paternal age ≥40 years, maternal age <35 years, low education: OR 1.29 (1.17–1.43)	Paternal age <40 years, maternal age <35 years	Stillbirth: Significantly higher risk for high paternal age with low parental education Stratified for maternal age (<35 and ≥35 years) and parental education	High
Astolfi *et al.* (2006), Italy	Cohort study	1 510 893 births	Paternal age <25 years: PTB: OR 1.19 (1.12–1.26) VPTB: 1.36 (1.19–1.56) PTB: 35–39, 40–44, 45–49 years ORs 1.01 to 1.36 (1.08 to 1.56)* VPTB: 35–39, 40–44, 45–49 years ORs 1.16 to 1.72 (1.06 to 2.36)* *lowest and highest 95% CI	Paternal age 25–29 years, maternal age 25–29 years	PTB, VPTB: U-shaped risk with significantly higher risk for low and high paternal age	High

Basso and Wilcox (2006), Denmark	Cohort study	2 499 633 live singletons	VPTB: Paternal age 30–34, 35–39, 40–44, 45–49 years: AORs 0.86 to 1.11 (0.47 to 1.55)* Highest AOR among fathers ≥50 years 1.3 (0.6–2.8) among women 20–24 years *lowest and highest 95% CI	Paternal age 25–29 years, maternal age 25–29 years	No increase in VPTB by paternal age. Stratified for maternal age (20–24, 25–29, 30–34 years), adjusted for mother's education and smoking	High
Chen *et al.* (2008), USA	Cohort study	2 614 966 singletons	Paternal age <20 years: PTB, VPTB, LBW, SGA, NND, low Apgar score: AORs 1.13 to 1.22 (1.01 to 1.49)* *lowest and highest 95% CI	Paternal age 20–29 years	PTB, VPTB, LBW, SGA, NND, low Apgar score: Significantly higher risk for young age. For high age no significantly increased age up to >50 years. Adjusted for paternal race, maternal age, educational level, smoking, alcohol, prenatal care and infant gender	High
Iwayama *et al.* (2011), Japan	Cohort study	55 005/73 993 infants selected at 1 month and 17 263/73 993 at 12 month healthy baby check-up, 3588 underwent both 1 and 12 months check-up	BW increased with paternal age for non-firstborn infants ($P = 0.0004$) and LBW decreased with paternal age for non-firstborn infants ($P = 0.0022$)	Paternal age was categorized: <20, 20–29, 30–39, 40–49 and ≥50 years. The younger category group was the reference group.	Birth weight: Also included in childhood morbidity. Adjusted for maternal age	Low
Nybo Andersen *et al.* (2004), Denmark	Cohort study	23 821 pregnancies	Late foetal death (≥20 weeks): Paternal age ≥ 50 years: AHR 3.9 (1.12–13.8) (3 events), otherwise NS	Paternal age 25–29 years	Stillbirth: Significantly higher high for older fathers. Adjustment for maternal age, reproductive history and maternal life style during pregnancy. Not included in meta-analysis, due to overlap with Urhoj *et al.* (2017a)	Medium
Olshan *et al.* (1995), USA	Cohort study	254 892 singletons	No increase in PTB, LBW and SGA by paternal age	Paternal age 25–29 years	PTB, LBW, SGA: Adjusted for maternal age, race, gravidity, smoking, marital status, education and infant gender	Medium
Reichman and Teitler (2006), USA	Cohort study	4621 singletons	Paternal age >34 years: LBW: AOR 1.7 (1.3–2.2)	Paternal age 20–34 years	LBW: Significantly increased for older fathers. Adjusted for maternal age, gender, mother's birth place, parity, marital status and health insurance status.	Medium/low
Selvin and Garfinkel (1972), USA	Cohort study	1 515 433 singletons	U-shaped relation with slightly higher rates of LBW at young and older paternal ages	No	LBW: Adjusted for maternal age	Low
Stern *et al.* (2014), USA	Cohort study	9092 ART singletons 6238 subfertile singletons 318 816 fertile singletons	Fertile group: Paternal age 35–40, 41–45, ≥46 years: No association with paternal age and PTB, LBW or SGA	Paternal age ≤34 years, maternal age ≤34 years	PTB, LBW, SGA: Adjusted for parental race and ethnicity, parental education, diabetes, chronic hypertension. Stratified for maternal age, ≤34 and 35–40 years.	Medium

Continued

Table I *Continued*

Author, year, country	Study design	Number of pregnancies, births or children	Result		Outcomes Comments Adjustments	Study quality
			Outcomes (risk estimates)	Reference group/ controls		
Tough *et al.* (2003), Canada	Cohort study	283 956 births	Paternal age 20–24, 25–29, 30–34. 35–39, 40–44 years: Significantly decreased risk of LBW: AORs 0.76 to 0.84 (0.67 to 0.95)* PTB: AORs 0.75 to 0.87 (0.66 to 0.97)* * lowest and highest 95% CI	Paternal age ≤19 years	LBW, PTB: Reference group inadequate. Adjusted for maternal age.	Medium
Urhoj *et al.* (2017a), Denmark	Cohort study	944 031 pregnancies with gestational age ≥22 weeks, 4946 stillbirths	Paternal age 35–39, 40–44 and ≥50 years: Stillbirth: AHRs 1.16 to 1.58 (1.07 to 2.11)* * lowest and highest 95% CI	Paternal age 30–34 years	Stillbirth: Paternal age associated with the risk of stillbirth in a J-shaped manner with the highest adjusted HRs among fathers >50 years. Adjusted for maternal age in 1 year categories, year of birth: 1994–1999, 2000–2005, 2006–2010, parental education, in sensitivity analysis also for ethnicity, maternal reproductive history	High
Zakar *et al.* (2015), Pakistan	Cohort study	5724 births	Paternal age (15–24 years or ≥40 years) was not associated with 'small size at birth' (SSB) or NND	Paternal age 25–39 years	LBW: LBW was a composite of several variables and defined as 'small size at birth (SSB)' (no standard definitions). Controlled for maternal and pregnancy related factors.	Low
Zhu *et al.* (2005a), Denmark	Cohort study	70 347 singletons	PTB: 35–39 years: AOR 1.1 (1.0–1.3) 40–44 years: AOR 1.2 (1.0–1.4) VPTB: 35–39 years: AOR 1.4 (1.0–2.0) 40–44 years: AOR 1.7 (1.1–2.6)	Paternal age 20–24 years	PTB, VPTB: Risk of PTB, mainly VPTB increased with paternal age Adjusted maternal age, parity, paternal education and income, calendar year and infant gender	High

AOR, adjusted odds ratio; AHR, adjusted hazard ratio; LBW, low birth weight (<2500 g); NND, neonatal death; OR, odds ratio; PTB, preterm birth (<37 weeks); SGA, small for gestational age; SSB, small size at birth; VPTB, very PTB (<32 weeks)

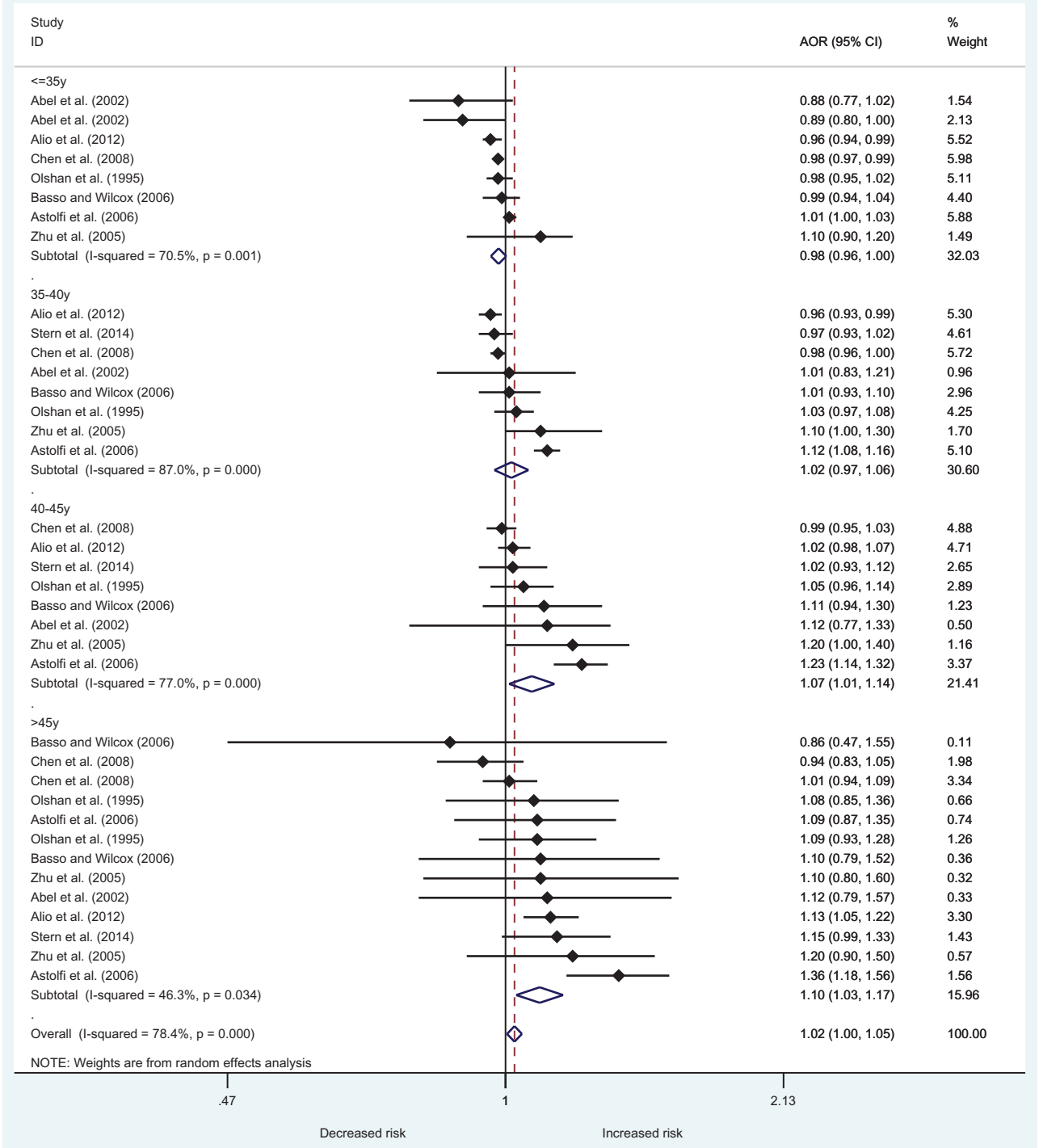

Figure 2 Forest plot describing the association between paternal age and risk for PTB. AOR, adjusted odds ratios.

stillbirth when fathers were 40 or more, compared with fathers below 40 years of age. Alio *et al.* (2012) also found a significantly increased risk of stillbirth (more than 700,000 US births) for fathers more than 40 years old, when compared to fathers between 25 and 29 years after adjustment for multiple confounders. Two Danish studies with partial overlap (Nybo Andersen *et al.*, 2004 ~24 000 births and Urhoj *et al.*, 2017a almost 1 million births) found significantly increased risks for the offspring of fathers of 50 years or more (Nybo Andersen HR 3.9, reference group 25–29 years and Urhoj HR 1.58, reference group 30–34 years) (Nybo Andersen *et al.*, 2004;

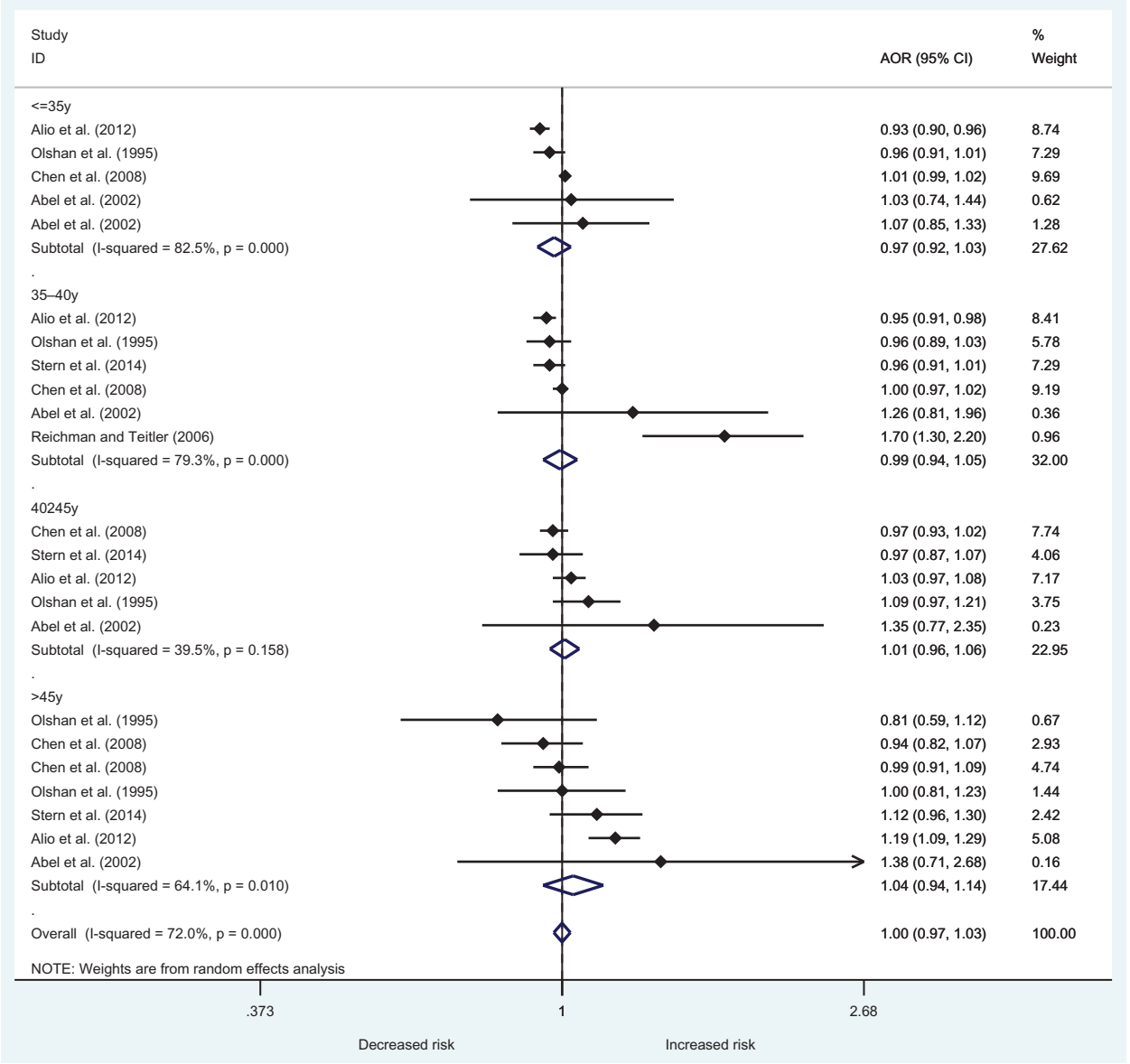

Figure 3 Forest plot describing the association between paternal age and risk for LBW in offspring.

Urhoj *et al.*, 2017a). Our meta-analysis, including three studies, showed a higher risk of stillbirth for the children of older than younger fathers (reference groups varied between 20 and 40 years) with a pooled estimate of 1.19 (95% CI 1.10–1.30) (Fig. 4). Two cohort studies reported on NND; one of high quality (Chen *et al.*, 2008) and one of low quality (Zakar *et al.*, 2015). No increased risk of NND was found.

Conclusion: The risk of stillbirth may be slightly increased for older fathers. Low certainty of evidence (GRADE⊕⊕◯◯). It is uncertain whether there is an association between paternal age and NND. Very low certainty of evidence (GRADE⊕◯◯◯).

Birth defects and chromosomal anomalies

Children with birth defects. Five studies assessed children with birth defects, three of high quality, one of medium and one of low quality (Supplementary Table SI, Table II). In a meta-analysis, four of these studies could be included. A small, but significantly higher risk of birth defects was associated with increasing paternal age (pooled estimate 1.05, 95% CI 1.02–1.07) (Fig. 5). The increase was found already at age 35 years and above.

Conclusion: Higher paternal age is probably associated with a small increase in birth defects. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

Congenital heart defects. Seven studies investigated the association between paternal age and CHDs (Supplementary Table SI, Table II). Five of these studies were high quality, one medium and one of low quality. All studies could be included in the meta-analysis. No significant association was identified between paternal age and CHD (pooled estimate 1.03, 95% CI 0.99–1.06) (Fig. 6).

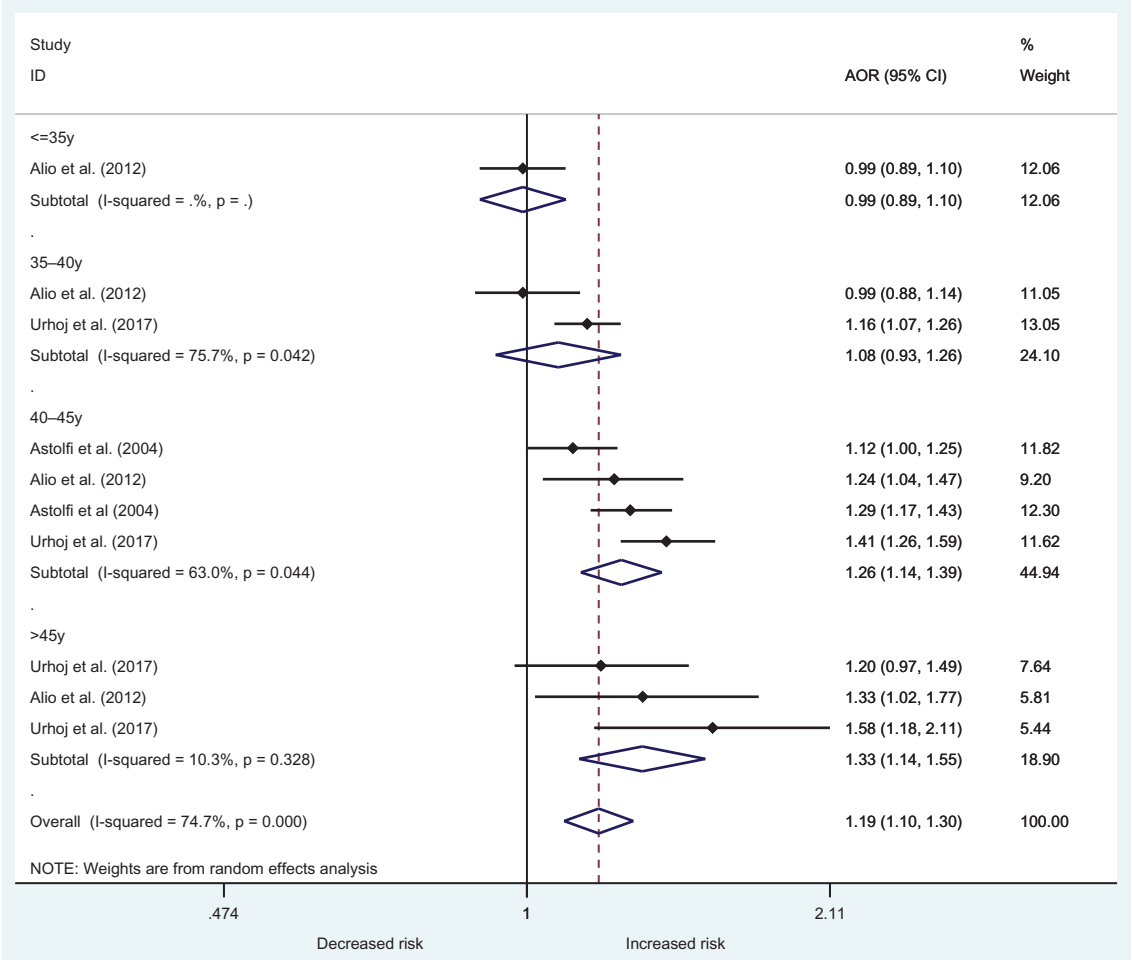

Figure 4 Forest plot describing the association between paternal age and risk for stillbirth in offspring.

Conclusion: Higher paternal age is probably associated with little or no difference in the risk of CHD. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

Orofacial clefts. We identified 13 studies, eight of high quality, three of medium quality and two of low quality, for an assessment of orofacial clefts (Supplementary Table SI, Table II). In addition, a systematic review/meta-analysis has analysed the influence of parental age on oral clefts (Herkrath *et al.*, 2012). For paternal age, only two studies could be included in their meta-analysis. A paternal age of 40 years and above was associated with an increased risk of cleft palate (OR 1.58, 95% CI 1.15–2.17). We performed a meta-analysis including five studies (Fig. 7). No overall effect of increased paternal age on the incidence of orofacial clefts was found (pooled estimate 0.99, 95% CI 0.95–1.04) while an age of above 45 years was associated with a small but significant increase in orofacial clefts (pooled estimate 1.14, 95% CI 1.02–1.29 (Fig. 7).

Conclusion: Paternal age above 45 years may be associated with a small increase in orofacial clefts. Low certainty of evidence (GRADE ⊕⊕◯◯).

Gastroschisis. Five studies assessed the risk of gastroschisis in association with paternal age, four of high and one of medium quality (Supplementary Table SI, Table II). All these five studies are included in the meta-analysis (Fig. 8). Overall, higher paternal age was not associated with the risk of gastroschisis (pooled estimate 0.88 95% CI 0.78–1.00) (Fig. 8). A significantly lower rate was observed in children whose fathers' paternal ages were between 35 and 40 years, compared to a reference age of between 25 and 29 years (*U*-shaped association).

Conclusion: Children of fathers aged 35 to 40 years probably have a lower risk of gastroschisis than children of younger fathers. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

Spina bifida. Five studies assessed the risk of spina bifida in association with paternal age, three of high and two of medium quality (Supplementary Table SI, Table II). All these five studies could be included in a meta-analysis. No overall higher risk of spina bifida was associated with increasing age (pooled estimate 0.97, 95% CI 0.90–1.04) (Fig. 9).

Conclusion: Higher paternal age is probably associated with little or no difference in the risk of spina bifida. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

Chromosomal anomalies. Twenty-three studies of chromosomal anomalies were identified, most of them assessing trisomy 21

Table II Studies on the association of paternal age with birth defects and chromosomal anomalies in offspring.

Author, year, country	Study design	Number of deliveries or children	Result		Outcomes Comments Adjustments	Study quality
			Outcomes (risk estimates)	Reference group/ controls		
Systematic review						
Herkrath *et al.* (2012), Brazil	Systematic review and meta-analysis	80 articles included in SR, 13 articles in meta-analysis, 2 articles about increased paternal age	Paternal age >40 years: Cleft palate: OR 1.58 (1.15–2.17)	Paternal age 20–39 years	Non-syndromic oral cleft lip with or without cleft palate and cleft palate. Meta-analysis included Harville *et al.* (2007) and Poletta *et al.* (2007) Do not specify if adjusted for maternal age	Medium
Original articles *n* = 47						
Archer *et al.* (2007), USA	Cohort study	Texas Birth Defect Registry. 1996–2002, denominator all live births but number of total births NA Gastroschisis, *n* = 550 Trisomy 13, *n* = 143 Anencephaly, *n* = 248 Encephalocele, *n* = 118 Trisomy 21, *n* = 1870 Cleft palate, *n* = 2577 Spina bifida, *n* = 564	Paternal age: Gastroschisis: 20–24 years: APR 1.47 (1.12–1.94) Trisomy 21: 20–24 years: APR 1.28 (1.08–1.51 >40 years: APR 1.05 (0.88–1.24) Trisomy 13: >40 years: APR 0.40 (0.16–0.96) Cleft palate: 20–24 years: APR 1.18 (1.00–1.38) >40 years: APR 0.91 (0.71–1.16) Pyloric stenosis >40 years:APR 0.84 (0.72–0.98) Anencephaly, spina bifida, encephalocele, ASD, VSD (NS)	Paternal age 25–29 years	Selected birth defects. Adjusted for maternal age, race/ethnicity, parity Totally 18.6% had missing paternal age	High
Berg *et al.* (2015), Norway	Cohort study	2890 cleft lip (with or without cleft palate) from 2 449 218 births	Paternal age: 30–34 years: ARR 0.89 (0.80–0.98) 35–39 years: ARR 0.91 (0.79–1.04) 40–44: ARR 0.97 (0.80–1.17) 45–49: ARR 1.21 (0.92–1.58) >50: ARR 1.18 (0.78–1.79)	Paternal age 25–29 years Baseline risk 1.15/1000	Cleft lip with or without cleft palate Adjusted for maternal age Interaction analysis showed that the risk was increased only if the age was increased in both parents	High
Bille *et al.* (2005), Denmark	Cohort study	1 489 014 births with 1920 non-syndromic (fewer than 3 associated minor anomalies) cleft lip with or without cleft palate + 956 cleft palate only	Paternal age 20–50 years: per 10 years increase in age AOR 1.12 (1.02–1.22) for cleft lip with or without cleft palate and AOR 1.24 (1.10–1.40) for cleft palate only	No reference group	Cleft lip with or without cleft palate Adjustment for maternal age Both maternal and paternal ages were associated with the risk of cleft lip with or without cleft palate. For cleft palate alone, only paternal age was a risk factor	High
Bunin *et al.* (1997), USA	Case control	89 cases	Paternal age (mean ± SE) 29.9 ± 0.6 Age difference 1.5 years, *P* = 0.07 versus controls 30–34 years OR 1.8 (*P* = 0.05) 35–39 years: OR 0.9 (*P* = 0.82) ≥40 years: OR 2.9 (*P* = 0.07)	178 controls (mean ± SE) 28.3 ± 0.5 Reference group: Paternal age <30 years	Sporadic neurofibromatosis. Two kind of analyses, one with a control group and another with a reference group Adjustment for maternal age or socio-economic status did not change the results	Low
Cross and Hook (1987), USA	Cohort study	35 680 foetuses with prenatal cytogenetic	No statistically significant effect of any paternal age for trisomy 21	None	Trisomy 21 Adjustment for maternal age	High

		analysis (amniocentesis, age indication)				
de Michelena *et al.* (1993), Peru	Case control	318 children and teen agers with trisomy 21	Means of paternal age for all ages, and for maternal age groups <21, 21–29. 30–34, 35–39 and >39 years were similar ($P \geq 0.1$)	1196 controls (4 controls/ cases)	Trisomy 21 Controls were matched on date of birth, sex and maternal age	Low
De Souza *et al.* (2009), UK	Case control	471 cases	No statistically significant association between paternal age and trisomy 21, AOR 1.13 (0.85–1.52) per 10 year increase	456 controls (parents of children with other disabilities)	Trisomy 21 Controls were matched on maternal age (within 3.5 years) and year of birth (within 3 years)	Low
De Souza and Morris (2010), UK	Case control	374 cases with trisomy 13, 929 with trisomy 18, 295 with Klinefelter and 28 with XYY syndrome	Per 10 year increase in paternal age (adjusted for the association of trisomy 21 with paternal age = AOR 1.11 [1.01–1.23]): Relative (adjusted) to the population Trisomy 13: AOR 1.10 (0.83–1.45) Trisomy 18: AOR 1.15 (0.96–1.38) Klinefelter: AOR 1.36 (1.02–1.79) XYY: AOR 1.99 (0.75–5.26)	Population and 5627 controls with trisomy 21	Trisomy 13, trisomy 18, Klinefelter (XXY), XYY syndrome Controls were matched on maternal age (within 6 months)	Low
Dzurova and Pikhart (2005), USA and Czech Republic	Cohort study	Trisomy 21/all births: 593/516 745 (California) and 251/475 834 (Czech Republic)	AOR 0.54–1.02 and NS in California, and AOR 1.49–2.03 and NS in Czech Republic	Paternal age <19 years	Trisomy 21 Adjusted for maternal age, education of mother and sex of infants, 2 years categories Paternal age missing in 17% in Czech Republic	Medium
Erickson and Cohen (1974), USA	Case control	44/56 cases analysed	Mean paternal age in cases with Apert syndrome: 34.8 years 'Increased paternal age'	Mean paternal age 'population' 32.4 years	Apert syndrome, no statistics given	Low
Erickson (1978), USA	Case control	4000 white infants with trisomy 21	No independent effect of paternal age (maternal age and birth order constant), rates at paternal age >45 years were constant	'Some' 86 000 normal white infants	Trisomy 21	Medium
Erickson (1979), USA	Cohort study	2 data sources, Atlanta data: 226 cases and National Centre for Health Statistics (NCHS) data: 1858 cases	Atlanta and NCHS data: no independent paternal age effect using cut off for paternal age ≥40, 45 and 50 years	Atlanta data 161 452 white and 71 193 black controls, NHCS 4597 305 controls	Trisomy 21	Medium
Erickson and Bjerkedal (1981), Norway	Cohort study	693 cases	Small age effect in paternal age ≥50 years	685 000 controls	Trisomy 21 Stratified for maternal age No statistics given	Medium
Finley *et al.* (1990), USA	Case control	14 cases of sporadic blepharophimosis, ptosis, epicanthus inversus, telecanthus complex (BPEI), control data from national means from US statistics	Mean maternal and paternal age higher in cases	US national means 1966–1975	Blepharophimosis, ptosis, epicanthus inversus, telecanthus complex (BPEI), (autosomal dominant disorder) No statistics given	Low

Continued

Table II *Continued*

Author, year, country	Study design	Number of deliveries or children	Result		Outcomes Comments Adjustments	Study quality
			Outcomes (risk estimates)	Reference group/ controls		
Fisch *et al.* (2003), USA	Case series	3419/4387 cases	Effect of paternal age only in mothers >35 years ($P = 0.0023$) and most pronounced in mothers >40 years ($P = 0.0004$)	None	Trisomy 21	Low
Green *et al.* (2010), USA	Case control	Cases with birth defects (if $n \geq 100$), between 102 to 6629 cases	Paternal age 40 years All orofacial clefts: AOR 1.07 (0.94–1.23) Septal defects: AOR 0.98 (0.87–1.10) Spina bifida: AOR 1.03 (0.82–1.28) Omphalocele: AOR 0.92 (0.64–1.33) Gastroschisis: AOR 0.80 (0.54–1.21)	Control group of 5839 normal live born infants. Paternal age 30 years. Maternal age 28 years	Selected birth defects Adjusted for paternal race and ethnicity, paternal education, maternal alcohol, maternal smoking, parity, earlier miscarriage, plurality, paternal drug used during pregnancy, use of ART, maternal BMI, folic acid use	Medium
Grewal *et al.* (2012), USA	Case control	46 114 cases with birth defects	Paternal age: Nervous system anomalies: 38 years: AOR 1.05 (1.00–1.11) 42 years: AOR 1.10 (1.02–1.18) Limb anomalies: 38 years: AOR 1.06 (1.02–1.11) 42 years: AOR 1.11 (1.05–1.18) Integument anomalies: 38 years: AOR 1.05 (1.00–1.09) 42 years: AOR 1.10 (1.03–1.16) For fathers 29 years versus <29 years: Amniotic band syndrome: AOR 0.87 (0.78–0.97) Pyloric stenosis: AOR 0.93 (0.90–0.96) Anomalies of the great veins: AOR 0.93 (0.87–1.00)	Paternal age 29 year A random sample of 36 838 non-malformed births	Selected birth defects Adjusted for maternal age	Medium
Harville *et al.* (2007), Norway	Cohort study	1431 cases	Paternal age: Cleft palate alone: 30–34 years: AOR 1.00 (0.76–1.31) 35–39 years: AOR 0.94 (0.68–1.30) ≥40 years: AOR 1.10 80.76–1.60)	Paternal age 20–24 years 1.8 million controls	Cleft palate alone Stratified for maternal age, 20–29 years	High
Hook *et al.* (1981), USA	Cohort study	551 cases 1952–1963 and 492 cases 1964–1976	For 1952–1963 there was no significant paternal age effect (36.87 versus 36.82 years) For 1964–1976, paternal age was about half a year greater in cases than in controls (34.55 versus 34.09 years, $P < 0.05$)	418 017 births 1952–1963 418 848 births 1964–1976	Trisomy 21 Controlled for maternal age	Medium
Hook and Cross (1982), USA	Case control	98 cases of prenatally detected trisomy 21	Mean difference in paternal age 0.27 (−1.59 to +1.06)	10 239 foetuses with normal karyotype	Trisomy 21 Controlled for maternal age	Medium

Hook and Regal (1984), USA	Case control	2354 cases with trisomy 21, 116 cases with trisomy 13 (including cases prenatally diagnosed)	No effect of paternal age	Controls were from all live births the same year in New York State	Trisomy 21 and trisomy 13 associated with Robertsonian translocations Controlled for maternal age and year of birth	Low
Kazaura and Lie (2002), Norway	Cohort study	1 738 852 infants 1788 trisomy 21	No increase by paternal age AOR 1.11 (0.99–1.22) per 10 year increase in paternal age	None	Trisomy 21 Adjusted for maternal age as a continuous variable, birth calendar year and place of birth	High
Kazaura *et al.* (2004a), Norway	Cohort study	291 cases with gastroschisis	Higher risk at young paternal age AOR 1.6 (1.0–2.4) per 10 year decrease in paternal age after adjustment for maternal age, but was not significant after adjustment for paternal year of birth, AOR per year of father's age: 1.04 (0.99–1.08)	>1.7 million controls	Gastroschisis Adjusted for maternal age, paternal year of birth	High
Kazaura *et al.* (2004b), Norway	Cohort study	1 869 388 births, 42 813 infants with birth defects	Paternal age 45–49 years: CNS defects (not neural tube defects, anencephaly, spina bifida or hydrocephaly) AOR 2.5 (1.2–5.5) Paternal age 20–24 years: Anencephaly AOR 1.4 (1.1–1.8) Neural tube defects. AOR 1.3 (1.1–1.5) Cleft lip: AOR between 0.9–1.2 (NS) Any birth defects: AOR 1.0–1.1 (borderline significant)	Paternal age 25–29 years	Any and selected birth defects Adjusted for maternal age, parity, maternity institution and year of birth	High
Lian *et al.* (1986), USA	Cohort study	7490 infants with a major or serious birth defect	Paternal age ≥35 years versus <35 years: ASD: AOR 1.95 (significant) Paternal age ≥40 years versus <40 years: Any birth defect: AOR 1.20 (significant) VSD: AOR 1.69 (significant) Chondrodystrophy: AOR 13.32 (significant) Situs inversus: AOR 19.27 (significant) Paternal age ≥45 versus <45 years Cleft palate/lip: AOR 2.86 (significant) Trisomy 21: NS any age	333 624 live born control infants without defects	Any and selected birth defects (86 groups of defects) Adjusted for maternal age and race AOR given but no 95% CI.	Medium
Lorda-Sanchez *et al.* (1998), Spain	Case control	14 cases	Associated with increase in: Paternal age (34.5 ± 6.0 versus 29.6 ± 6.0), OR 1.11 (1.02–1.21) but NS after adjustment for maternal age and no of pregnancies	162 controls	Klippel–Trenaunay–Weber syndrome	Low

Continued

Table II *Continued*

Author, year, country	Study design	Number of deliveries or children	Result		Outcomes Comments Adjustments	Study quality
			Outcomes (risk estimates)	Reference group/ controls		
Materna-Kiryluk *et al.* (2009), Polen	Cohort study	8683 infants 0–2 years with birth defects	AOR (per five years increase in paternal age) Heart defects: AOR 1.05 (1.00–1.09) Cleft lip with or without cleft palate: AOR 1.11 (1.02–1.20) Hypospadia: AOR 1.11 (1.03–1.19) Gastroschisis: AOR 0.69 (0.54–0.90)	902 452 population	Selected birth defects Adjusted for maternal age	High
McIntosh *et al.* (1995), USA	Case control	9431 cases with 22 different birth defects (Trisomy 21, $n = 997$, cleft palate, $n = 1489$)	Neural tube defects Paternal age 40–44, >50 years AORs 1.6 and 2.3 (borderline significant) Reduction of upper limbs 35–39, 40–44 years AORs: 2.1 and 2.4 (significant) Trisomy 21: 40–44, 45–49, ≥50 years AORs 1.5 to 2.0 (significant) Cleft palate: AORs 0.8–1.5 (NS)	18 862 controls Paternal age 25–29 years	Selected birth defects Adjusted for maternal age	Medium
Olshan *et al.* (1994), USA	Case control	4110 cases with CHD	General increase by paternal age with trend analysis, NS per age group	8220 controls Paternal age 25–29 years	CHDs Adjusted for maternal age, no of stillbirths, race	Low
Orioli *et al.* (1995), Italy	Case control	78 cases with achondroplasia (AC) 64 cases with thanatophoric dysplasia (TD) 106 cases with osteogenesis imperfecta (OI)	Paternal age >35 years AC: AOR 3.71 (1.7–8.08) (also mother's age < 30 sign) TD: AOR 3.37 (1.43–8.0) OI: AOR 1.44 (0.78–2.64)	2 controls per cases Paternal age <30 years Maternal age >30 years	Achondroplasia (AC), thanatophoric dysplasia (TD), osteogenesis imperfecta (OI), Stratified for maternal age > and <30 years	Low
Polednak (1976), USA	Cohort study	897 orofacial clefts	Total malformation rate: NS Syndactyly: $P < 0.05$ Oral cleft rate 1.13/1000, $P < 0.01$	776 642 population Maternal age 25–29 years	Any and selected birth defects. Stratified for maternal age	Low
Poletta *et al.* (2007), South America	Case control	5128 cleft lip/palate, 1745 cleft palate	Among 3/11 strata (representing 50% of the cases) significant higher risk with paternal age, ORs between 1.42–3.56	3712 controls	Orofacial clefts, probably not adjusted for maternal age	Medium/low
Riccardi *et al.* (1984), USA	Case series	187 cases	Paternal age >35 years: 2-fold increase	Year matched population controls (from general population). Paternal age <35	Neurofibromatosis Controlled for maternal age	Low

Roecker and Huether (1983), USA	Cohort study	1244 cases	No paternal age effect	1 672 210 controls	Trisomy 21 Stratified for maternal age	Low
Roth *et al.* (1983a), France	Case control	118 cases	No effect of paternal age Mean difference in paternal age: 0.46 (−0.84 to +1.76)	6656 prenatal diagnoses (amniocentesis)	Trisomy 21 Controlled for maternal age	Low
Roth *et al.* (1983b), France	Case series Case control	2 studies: 1:611 cases with trisomy 21 2:242 cases with trisomy 21	No effect of paternal age Mean difference in paternal age: 0.46 (−0.34 to +1.26)	2 controls per cases in study 2	Trisomy 21 Controlled for maternal age and time and place of birth	Low
Stene *et al.* (1977), Denmark	Case control	224 cases	Increased risk of trisomy 21 with paternal age >55 years	5619 controls	Trisomy 21 Controlled for maternal age No statistics	Low
Stene *et al.* (1981), Denmark	Case control	117 cases	Increased risk of trisomy 21 by paternal age >41 years	5014 prenatal diagnoses	Trisomy 21 Controlled for maternal age No statistics	Low
Su *et al.* (2015), China	Cohort study (Denmark)	15 216 cases with CHDs	No overall effect of paternal age for CHD PDA (>45 years): AHR 1.69 (1.17–2.43)	1 893 899 population Paternal age 25–29 years	CHDs Controlled for maternal age, family history of CHD, maternal infection, gender, parity, parental age difference	High
Takano *et al.* (1992), Japan	Cohort study	26 cases	No significant effect of paternal age ($P = 0.08$)	Population controls	Neurofibromatosis	Low
Tay *et al.* (1982), Singapore	Case control	100 cases	No effect of paternal age	100 controls	Congenital heart disease	Low
Tellier *et al.* (1996), France	Cohort study	41 cases with CHARGE	Significant higher mean paternal age versus control population Mean paternal age: 33.7+-8 versus 30.8+-5 years ($P < 0.05$)	Control population not described	CHARGE malformations (coloboma, heart malformation, choanal atresia, retarded growth, genital hypoplasia, ear anomalies and deafness etc) No difference in maternal age	Low
Urhoj *et al.* (2015), Denmark	Cohort study	10 817 cases with musculoskeletal congenital abnormalities	AOR 1.06 (1.01–1.11) by 10 years increase for any musculoskeletal congenital abnormalities 26% increase (2–56%) for paternal age >50 versus 30–34 years	1 605 885 population	Musculoskeletal congenital abnormalities Adjusted for maternal age, year of birth, ethnicity and education	High
Vashist *et al.* (2011), India	Case series	200 cases with trisomy 21	Association with paternal age (correlation coeff (r) = 0.04, maternal age constant)	Mean paternal age 31.5 years	Trisomy 21	Low
Wolf (1963), USA	Case control	411 cases with cleft lip and palate	A significant paternal age effect ($P < 0.05$)	411 controls	Cleft lip and palate Controlled for maternal age	Low

Continued

Table II *Continued*

Author, year, country	Study design	Number of deliveries or children	Result		Outcomes Comments Adjustments	Study quality
			Outcomes (risk estimates)	Reference group/ controls		
Yang *et al.* (2007), Canada	Cohort study	77 514 cases with birth defects (Trisomy, *n* = 13 078, cleft palate, *n* = 6049)	Paternal age 35–39, 40–44, 45–49, ≥50 years Any birth defects: AORs: 1.04–1.15 (significant), test for trend $P = 0.015$ Trisomy 21: AORs 1.19–1.45 (significant), test for trend $P < 0.01$ Cleft palate: AOR 0.89–1.23 (NS for any age group)	5 213 248 population Paternal age 25–29 years	Any and selected birth defects Advanced paternal age was associated with: Any birth defects, heart defects, tracheo-oesophageal fistula, oesophageal atresia, musculoskeletal/ integumental anomalies, trisomy 21 and other chromosomal anomalies Paternal age <25 years were associated with: Spina bifida/ meningocele, microcephalus, omphalocele/gastroschisis Adjusted for maternal age, race, education, marital status, parity, prenatal care, smoking, alcohol consumption in woman	High
Zhan *et al.* (1991), China	Case control	497 cases with CHDs	Paternal age <25 years AOR:2.63 (2.12–3.27)	6222 controls Paternal age ≥25 years	Congenital heart disease Controlled for maternal age and birth order	Low
Zhu *et al.* (2005b), USA and Denmark	Cohort study	3910 cases with birth defects (Trisomy 21, *n* = 46 Cleft palate/lip, *n* = 162)	No overall effect for any birth defect Paternal age >50 years: Trisomy 21 AHR: 4.50 (1.0–20.39) Paternal age 35–39 years: Cleft palate: AHR 1.48 (1.02–2.15) Multiple syndromes, extremities, increased by age, test for trend $P <$ 0.001–0.05	71 937 population Paternal age 20–29 years	Any and selected birth defectsAdjusted for maternal age, parity, maternal and paternal income and education, sex of child and year of birth	High

AC, achondroplasia; APR, adjusted prevalence ratio; CHD, congenital heart defects; OI, osteogenesis imperfecta; PDA, persistent ductus arteriosus; TD, thanatophoric dysplasia.

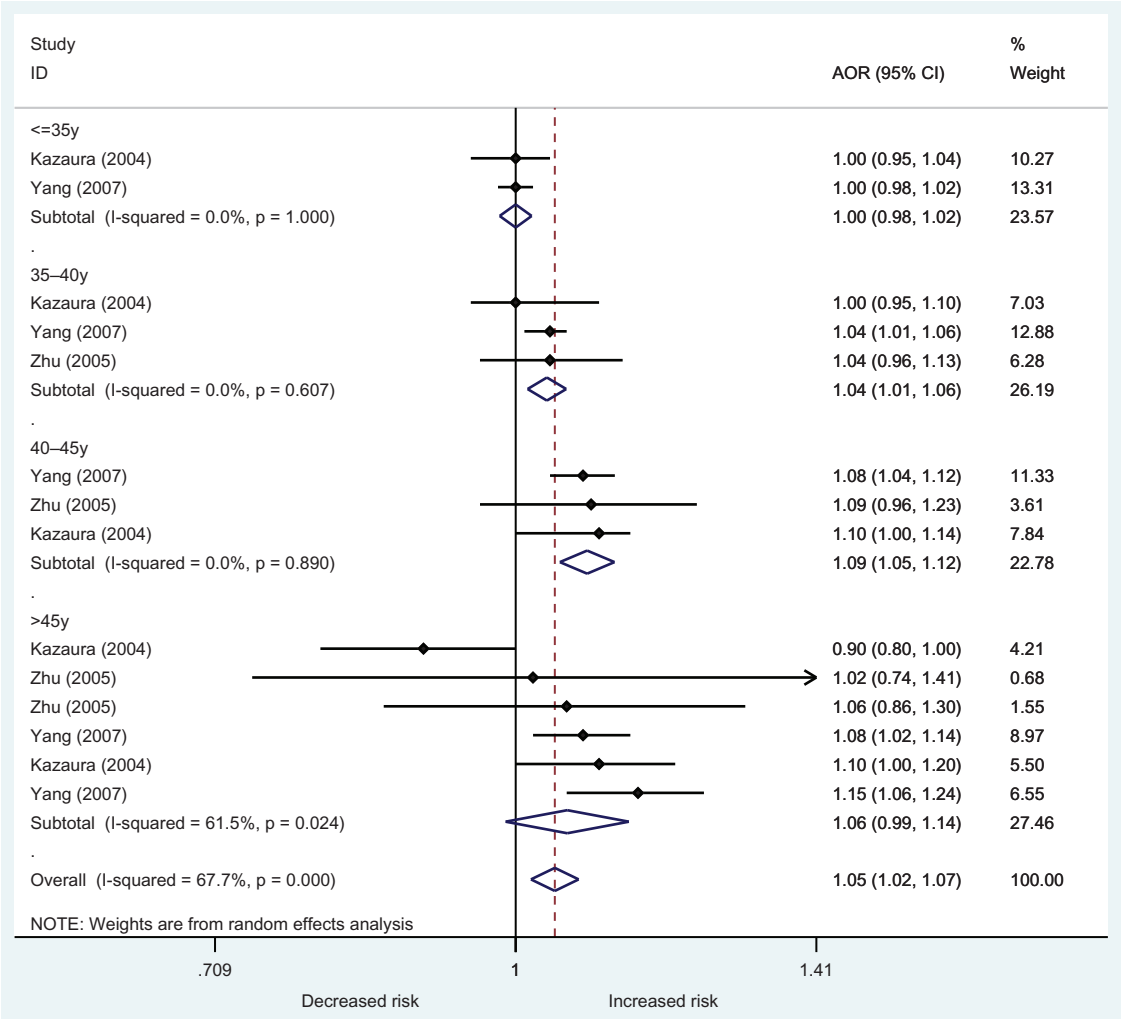

Figure 5 Forest plot describing the association between paternal age and risk for any birth defects in offspring.

(Supplementary Table SI, Table II). Five of these studies were high-quality cohort studies, nine were medium and nine were low quality, mostly case control studies (Supplementary Table SV). Altogether these studies included more than 37 000 (37 513) children with trisomy 21. Six of the studies could be included in a meta-analysis (Fig. 10). The meta-analysis identified a small but significantly increased risk of trisomy 21 associated with paternal age (pooled estimate 1.13, 95% CI 1.05–1.23). The rate was significantly increased at ages 40 years and above (Fig. 10). For other aneuploidies (trisomy 13 and 18), one high quality study could not identify any increase by paternal age.

Conclusion: Higher paternal age is probably associated with a small increase in the incidence of trisomy 21. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

Paternal age at childbirth and long-term outcomes for offspring

Morbidity and mortality

Twenty-two studies assessed the effect of paternal age on childhood morbidity including childhood cancer (13 studies), diabetes and obesity (three studies), developmental disturbances (one study) and mortality (five studies). In addition, one meta-analysis concentrated on the risk of leukaemia (Sergentanis *et al.*, 2015).

Childhood cancer. We identified 13 studies, four of high quality, six of medium quality and three of low quality. They examined childhood cancer in general as well as haematological cancer and leukaemia, retinoblastoma, non-Hodgkin lymphoma, Wilm's tumour and brain tumours in particular (Supplementary Table SI, Table III).

Five studies assessed the effect of paternal age on the incidence of retinoblastoma. Only one study adjusted for maternal age (Yip *et al.*, 2006), and did not report an association between paternal age and retinoblastoma.

In addition, in one systematic review/meta-analysis, the effect of paternal age on the risk of childhood leukaemia was assessed. This showed that higher paternal age was associated with an increased risk of childhood acute lymphoblastic leukaemia (ALL) (RR 1.05, 95% CI 1.01–1.10, per year increments: RR 1.04, 95% CI 1.00–1.08) (Sergentanis *et al.*, 2015).

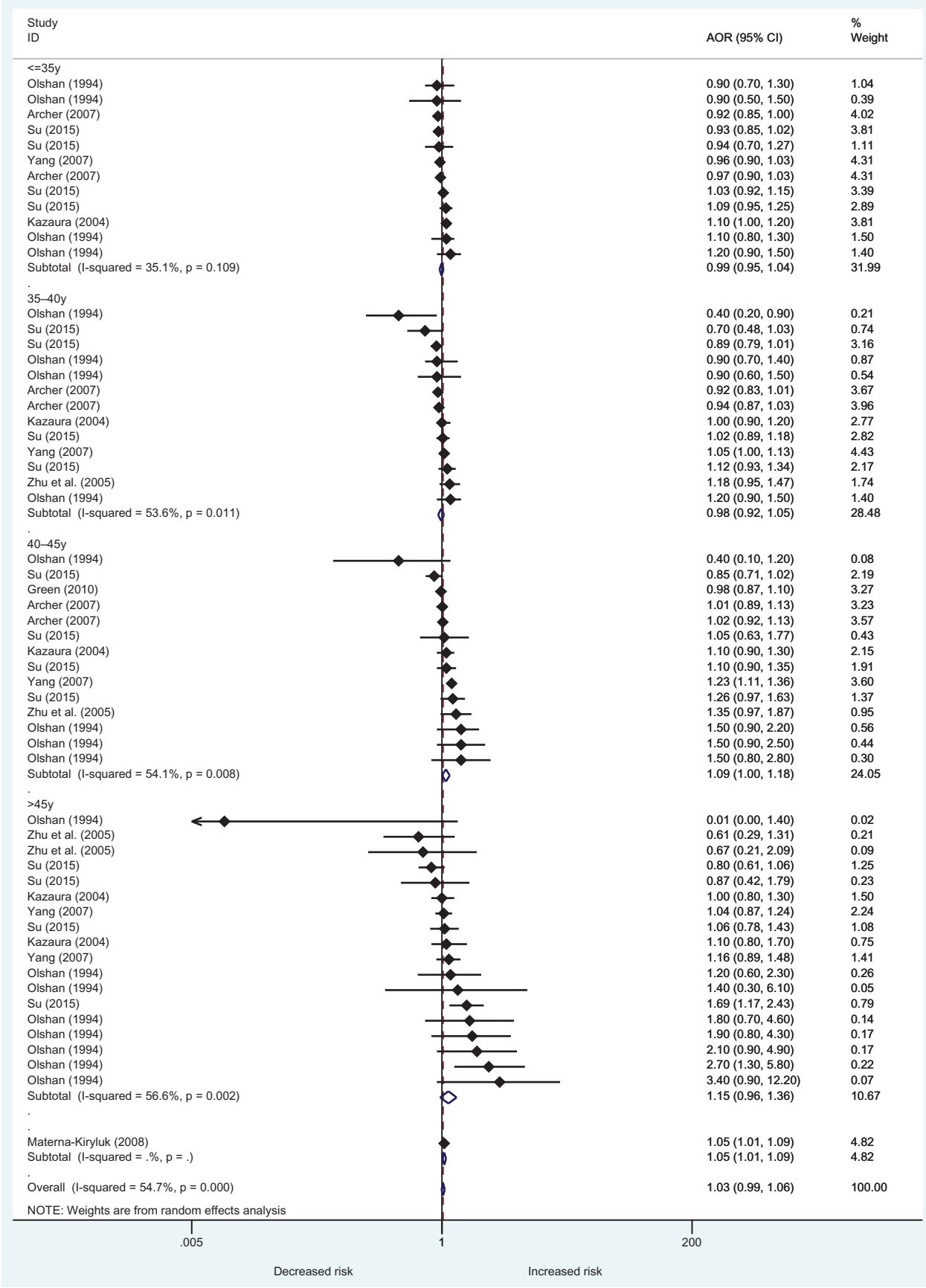

Figure 6 Forest plot describing the association between paternal age and risk for CHDs in offspring,

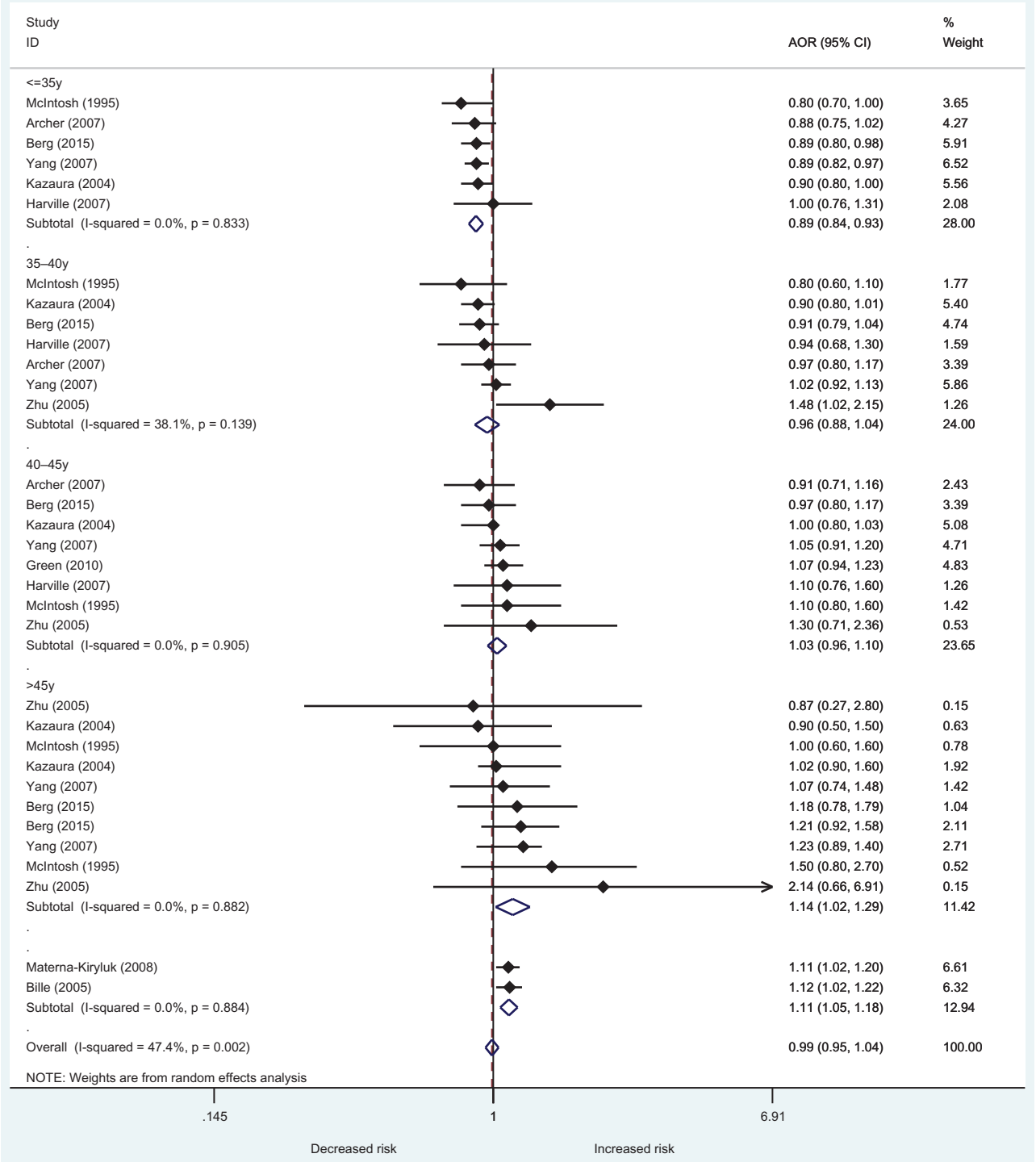

Figure 7 Forest plot describing the association between paternal age and risk for orofacial clefts in offspring.

Two studies adjusted for maternal age and could be included in a meta-analysis (Fig. 11). No overall higher risk of ALL was associated with increasing age (pooled estimate 1.08, 95% CI 0.96–1.21).

Conclusion: Higher paternal age is probably associated with little or no difference in the risk of ALL. Moderate certainty of evidence (GRADE⊕⊕⊕◯). Higher paternal age may be associated with little or no difference in the risk of other childhood cancers. Low certainty of evidence (GRADE⊕⊕◯◯).

Diabetes mellitus type 1 and obesity. Two cohort studies concentrated on paternal age and diabetes mellitus (DM) type 1, and one study on

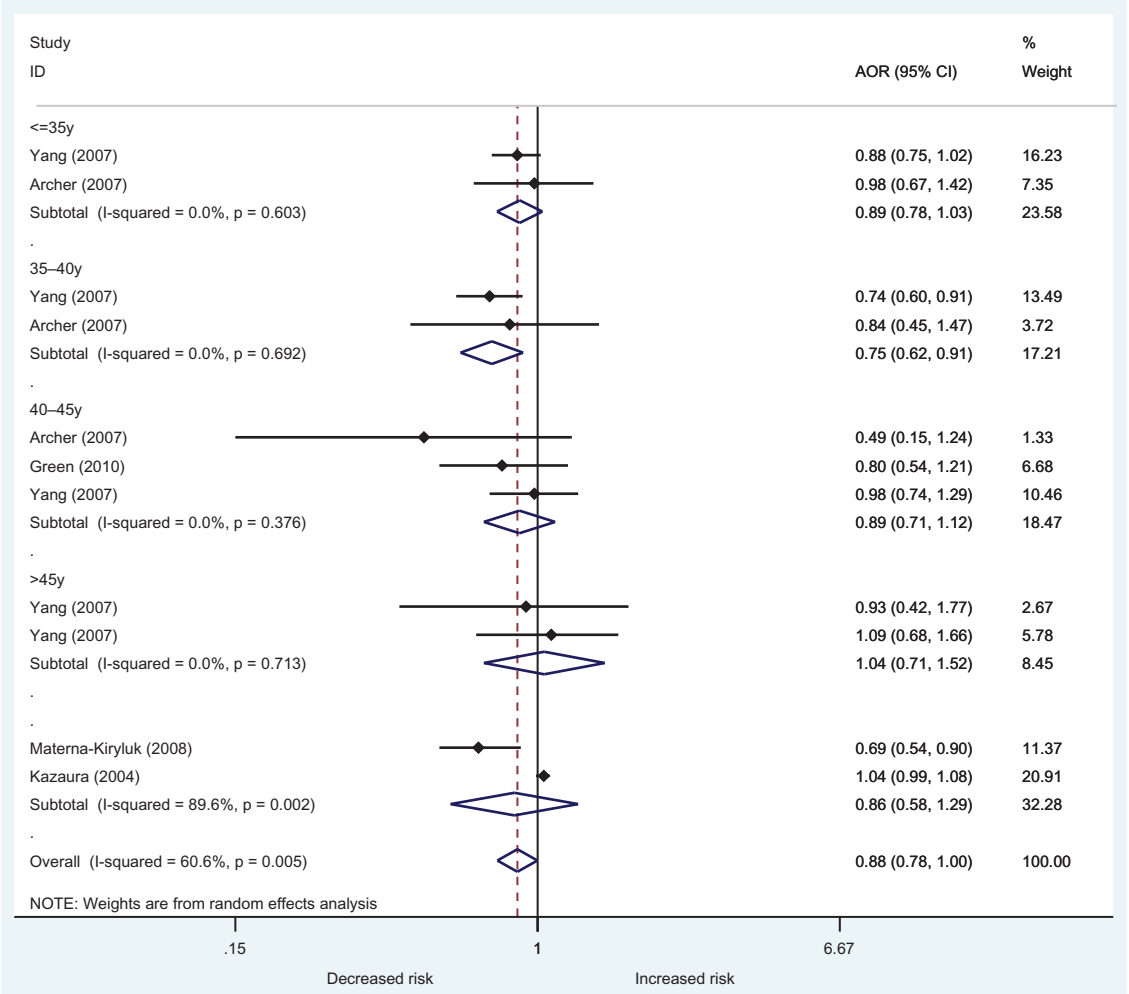

Figure 8 Forest plot describing the association between paternal age and risk for gastroschisis in offspring.

overweight and obesity. Two of these studies were of high quality and one of medium quality (Supplementary Table SI, Table III). In both studies concerning DM, adjustments were made for maternal age. One study (Cardwell *et al.*, 2005) reported an association with paternal age, and the other (Stene *et al.*, 2001) found that paternal age was not significantly associated with DM type 1. One study associated an increased risk of obesity with paternal age > 50 years (Eriksen *et al.*, 2013).

Conclusion: It is uncertain whether paternal age is associated with an increased risk of DM type 1 and obesity in offspring. Very low certainty of evidence (GRADE⊕◯◯◯).

Mortality. Infant mortality during the first year of life and the possible effects of paternal age were studied by Wunsch and Gourbin (2002), while Urhoj *et al.* (2014) looked into mortality before the age of 5 years. Three studies concentrated on mortality up to 18, 39, and 40 years, respectively (Zhu *et al.*, 2008; Miller *et al.*, 2010; Mok *et al.*, 2017) (Supplementary Table SI, Table III). In all studies, except Wunsch and Gourbin (2002), adjustments were made for maternal age. These four studies also reported an association of mortality with higher paternal age. It was not possible to do a meta-analysis because of different length of follow-up in the studies.

Conclusion: Higher paternal age may be associated with a small increase in risk of mortality. Low certainty of evidence (GRADE ⊕⊕◯◯).

Psychiatric diseases/disorders in offspring of older fathers

Autism and ASDs. Two meta-analyses (Hultman *et al.*, 2011; Wu *et al.*, 2017) and 28 original studies assessed the effect of paternal age on autism and ASD (Supplementary Table SI, Table IV). The original articles included 15 cohort studies and 13 case control studies. Five studies were of high quality, 16 of medium quality and seven of low quality. The systematic review/meta-analysis by Hultman *et al.* (2011) included 12 studies from seven different countries. The pooled estimates for autism and ASD were for offspring of fathers between 40 and 49 years old 1.78 (95% CI 1.52–2.07), and for offspring of fathers ≥50 years old 2.46 (95% CI 2.20–2.76). In the meta-analysis by Wu *et al.* (2017) including 27 studies, a significant association between paternal age and the risk of autism in offspring was found (AOR 1.55, 95% CI 1.39–1.73). We included 16 studies in our

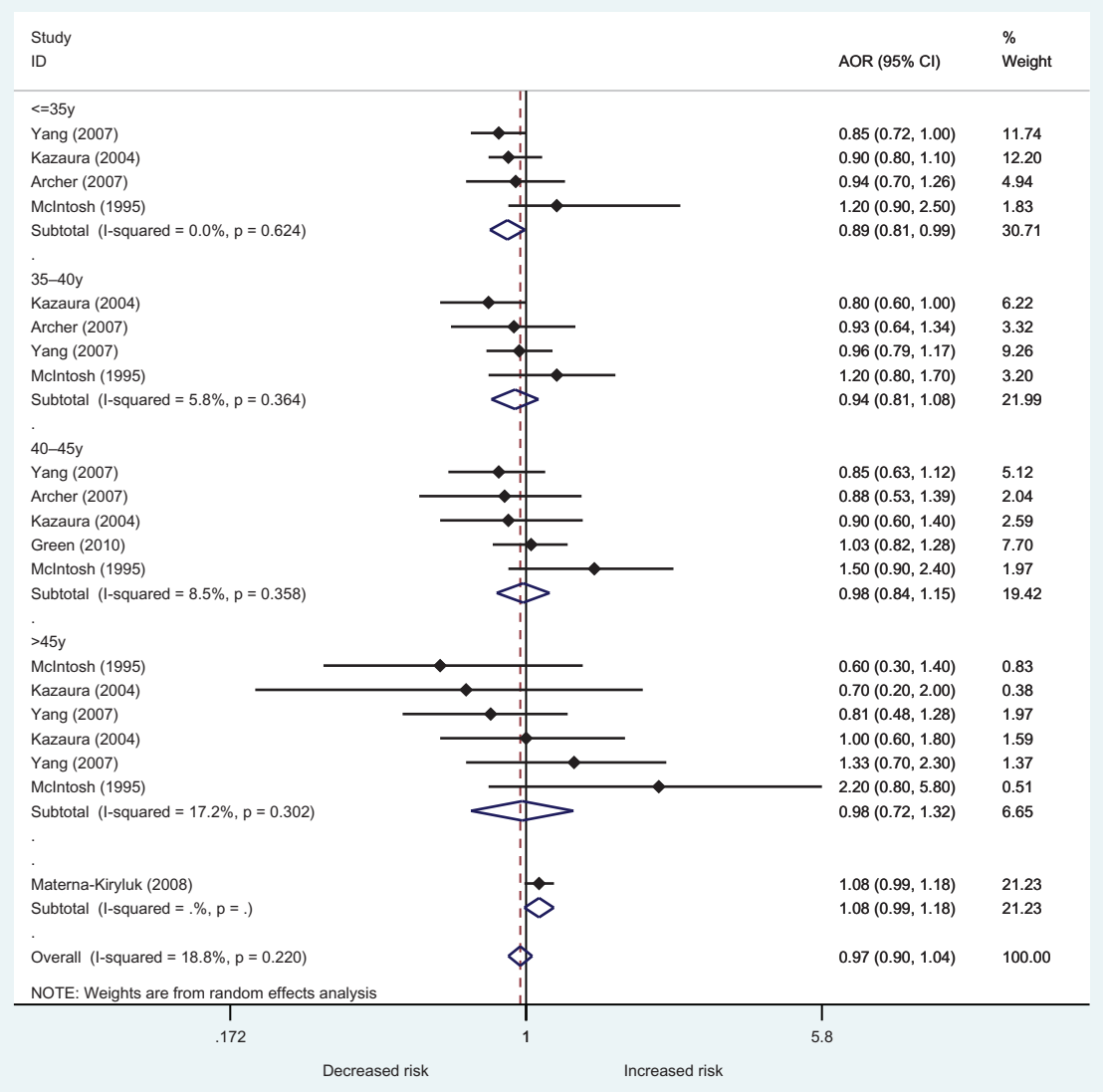

Figure 9 Forest plot describing the association between paternal age and risk for spina bifida in offspring.

meta-analysis (Fig. 12). All of these studies adjusted for maternal age. It was observed that there was a higher risk of autism/ASD with increasing paternal age (pooled estimate 1.25, 95% CI 1.20–1.30).

Conclusion: Higher paternal age is probably associated with an increase in autism/ASD. Moderate certainty of evidence (GRADE⊕⊕⊕◯)

Schizophrenia. Three meta-analyses (Wohl and Gorwood, 2007; Torrey *et al.*, 2009; Miller *et al.*, 2010) and 19 original studies assessed the effect of paternal age on the risk of schizophrenia in offspring. The original articles included 10 cohort studies and 9 case control studies. No studies of high quality, 9 of medium quality and 10 of low quality were included (Supplementary Table SI, Table V). The meta-analysis by Miller *et al.* (2010) included six cohort and six case control studies. In both study designs, a significant increase in the risk of schizophrenia in the offspring of older fathers was found. The relative risk in the oldest fathers (≥50 years) was 1.66 (95% CI 1.46–1.89). The meta-analysis by Torrey *et al.* (2009) included ten studies and found an increased risk of schizophrenia in the offspring of the older fathers. The pooled estimate of risk of schizophrenia in offspring of fathers ≥55 years of age was 2.21 (95% CI 1.46–3.37) and for fathers ≥45 years the pooled estimate was 1.38 (95% CI 0.95–2.01). Wohl and Gorwood (2007) reported an association with paternal age, with higher levels of schizophrenia in the offspring of fathers younger than 20 and older than 35 years.

Fourteen of the original articles were included in a meta-analysis (Fig. 13). All of these studies adjusted for maternal age. Paternal age was categorized as <35, 35–39, 40–45, >45 and >50 years. A higher risk of schizophrenia was associated with increasing paternal age (pooled estimate 1.31, 95% CI 1.23–1.38).

Conclusion: Higher paternal age is probably associated with an increased risk of schizophrenia in offspring. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

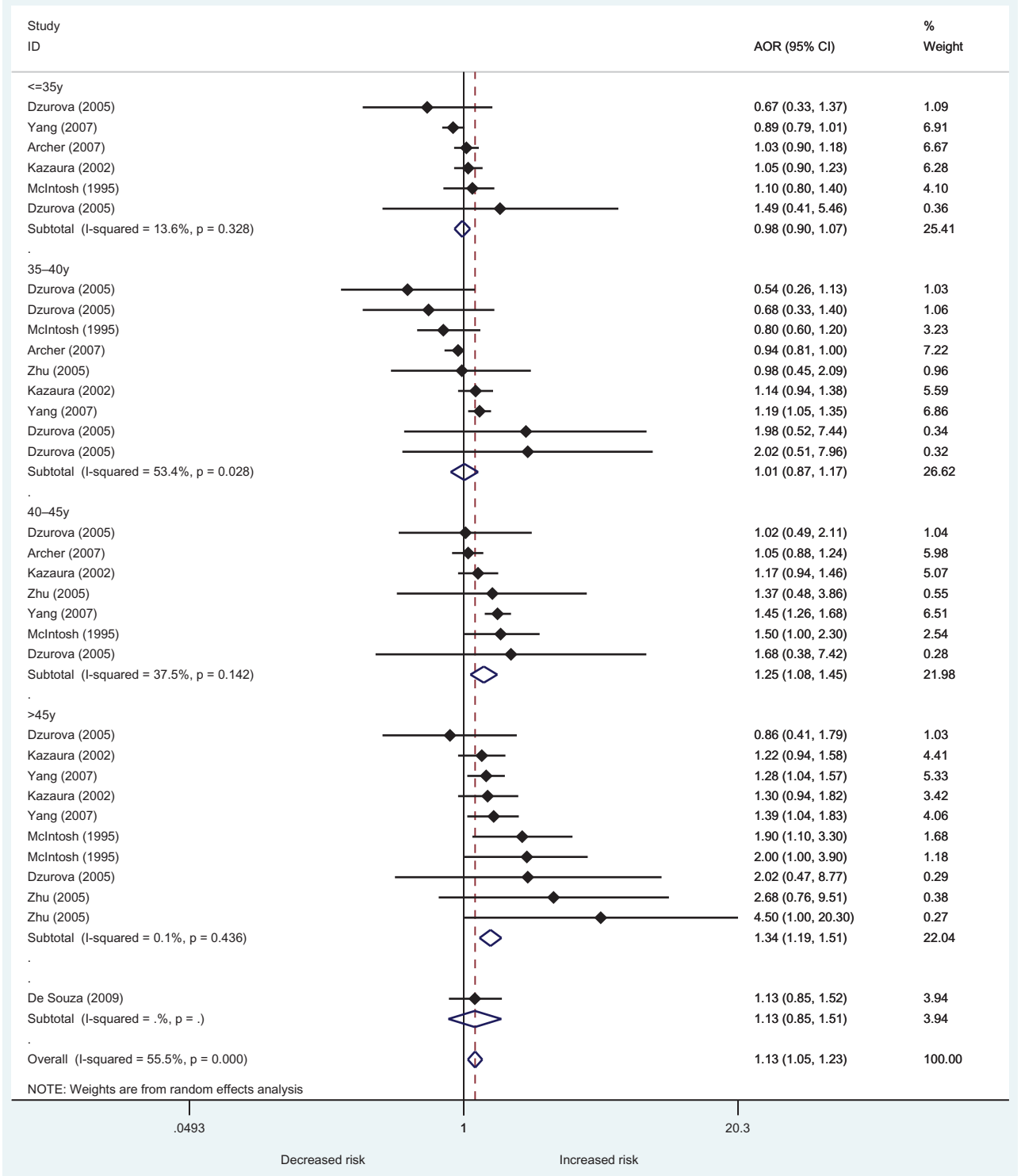

Figure 10 Forest plot describing the association between paternal age and risk for trisomy 21 in offspring.

Other psychiatric disorders. Fifteen studies concentrated on other psychiatric conditions including attention deficit hyperactivity syndrome (ADHD) (three studies), eating disorders (two studies), psychosis (three studies), bipolar disorders (six studies), Tourette disorder (one study) and neurocognitive development (one study) (Supplementary Table SI, Table VI).

ADHD Two studies (D'Onofrio *et al.*, 2014; Hvolgaard Mikkelsen *et al.*, 2016) were of high and one of medium quality (Chudal *et al.*,

Table III Studies on the association of paternal age with childhood morbidity and mortality in offspring.

Author, year, country	Study design	Number of children	Result		Outcomes	Quality
			Outcomes (Risk estimates)	Reference group/ control		
Meta-analysis *n* = 1						
Sergentanis *et al.* (2015), Greece	Systematic review and meta-analysis	Paternal age as categorical variable: 34 case control studies and 4 cohort studies in systematic review As incremental variable: 9 case control studies and 3 cohort studies in systematic review Meta-analysis (incremental analysis): 8 case control studies and 2 cohort studies	ALL: A 5 year increase in paternal age: RR 1.04 (1.00–1.08) 'Oldest versus middle': Increased risk in oldest fathers with RR 1.10 (1.02–1.19) ARR 1.09 (0.90–1.25) 'Youngest versus middle age': increased risk in youngest with RR 1.09 (1.00–1.20) ARR 1.10 (0.81–1.51) AML: No significant associations at incremental analysis or 'oldest versus middle' Increased risk in offspring from 'younger fathers versus middle' with pooled RR 1.28 (1.04–1.59) ARR 0.63 (0.33–1.20)	Paternal age: 'Older': >35 years or >40 years 'Younger': <25 years	Many studies in forest plots did not adjust for maternal age (RR), but sub-analyses regarding degree of adjustments were included (ARR)	Medium
Original articles *n* = 22						
Cardwell *et al.* (2005), UK Northern Ireland	Cohort study	991 children with DM type 1 447 663 cohort	Paternal age: >35 years ARR 1.52 (1.10–2.09)	Paternal age <25 years	Children born 1971–1986 Diagnosed with DM type 1 at the age of 15 years Adjusted for maternal age, birth order, year of birth	Medium
Crump *et al.* (2012), Sweden	Cohort study	936 cases with non-Hodgkin's lymphoma 3 571 574 population	Adjusted risk estimates not mentioned in text, no association, $p_{trend} = 0.31$	Probably paternal age <20 years	Children born 1973–2008 followed through 2009 (ages 0–37 years). Adjusted for perinatal and family variables including maternal age	Medium
Crump *et al.* (2015), Sweden	Cohort study	2809 cases with brain Tumours 3 571 574 population (25–29år)	Paternal age: ≥35 years AIRR 1.24 (0.82–1.85)	Paternal age 25–29 years	Children born 1973–2008 followed through 2010 (max age 38 years) Adjusted for maternal age, birth year, sex, foetal growth, parental country at birth, family history of brain-tumour, maternal education	Medium
DerKinderen *et al.* (1990), the NL	Cohort study	361 sporadic retinoblastoma cases Compared to general population (number NA)	Paternal age: 20–24 years RR 0.4 (no confidence interval available) >50 years: RR 5 (no confidence interval available)	Paternal age 25–34 years	Children born 1945–1970 No information about adjustments	Low
Dockerty *et al.* (2001), UK	Case control	10 162 cases with childhood cancer 10 162 controls	Paternal age: Retinoblastoma: 40–45 years AOR 0.82 (95% CI 0.39–1.75) ≥45 years AOR 0.73 (95% CI 0.26–2.01) ALL: 40–44 years AOR 1.45 (95% CI 1.10–1.92), ≥45 years AOR 1.54 (95% CI 1.06–2.23)	Paternal age 25–29 years	Children born 1968–1981 Not adjusted for maternal age	Medium

Continued

Table III *Continued*

Author, year, country	Study design	Number of children	Result		Outcomes	Quality
			Outcomes (Risk estimates)	Reference group/ control		
Eriksen *et al.* (2013), Norway	Cohort study	346 609 cohort 44 712 cases with overweight 11 091 cases with obesity	Paternal age: Overweight: >50 years ARR 1.15 (0.98–1.35) Obesity: >50 years ARR? 1.55 (1.14–2.10)	Paternal age <20 years	Male conscripts at 18–20 years, born 1967–1984 Overweight defined as BMI 25.0–29.9 kg/m2 Obesity defined as BMI > 30 kg/m2 Adjusted for birth order, birth years, birth season, maternal age, parity of mother, maternal marital status at birth, parental education level	High
Heck *et al.* (2012), USA, California	Case control	609 cases with retinoblastoma 209 051 controls	Paternal age: 30–34 years OR 1.44 (0.99–2.10) ≥35 years OR 1.75 (1.20–2.47)	Paternal age 20–29 years	Children diagnosed with retinoblastoma 1988–2007, children up to 5 years Confounding variables in multivariate models were year of birth, paternal age, urban or rural county of residence, maternal race and maternal place of birth. No information about adjustment for maternal age	Medium
Iwayama *et al.* (2011), Japan	Cohort study	72 268 cohort 16 762 cohort attending check-up	Developmental delay AOR 2.25 (1.33–3.80) (36 cases) No word uttering AOR 2.29 (1.52–3.44) (60 cases) Lack of eye contact AOR 5.16 (1.92–13.8) (6 cases) Unable to walk with support AOR 1.51 (1.21–1.91) (230 cases)	Paternal age was categorized: <20, 20–29, 30–39, 40–49 and ≥50 years. The younger category group was the reference group	Children attending child health check-up at age 12 months during 1987–2003 examining child growth and developmental delay. (Included in obstetric outcome, Table 1a) Adjusted for maternal age	Low
Johnson *et al.* (2009), USA	Case control	17 672 cases with childhood cancer 57 966 controls	Paternal age: Overall cancer AOR 1.01 (0.99–1.03) Leukaemia AOR 1.03 (1.00–1.07)	OR related to a 5-year increase in paternal age	Children 0–14 years diagnosed with cancer 1980–2004 Controls born 1970–2004 Adjusted for maternal age, sex, birth weight, gestational age, birth order, plurality, maternal race, birth year and state	High
Larfors *et al.* (2012), Sweden	Case control	2660 cases (children) with leukaemia (AML and ALL) 28 288 controls	Paternal age: ≥35 years childhood ALL: AHR 1.08 (95% CI 0.95–1.23) ≥35 years childhood AML: AHR 0.89 (95% CI 0.65–1.22)	Paternal age 20–34 years	Born 1932 or later, diagnosed with leukaemia (children and adult leukaemia) during 1962–2008 Adjusted for sex, Down syndrome and chromosomal aberrations, multiple birth, number of siblings, maternal/paternal age	Medium
Matsunaga *et al.* (1990), Japan	Case control	225 bilateral and 408 unilateral cases with retinoblastoma Respective 225 and 408 controls	No risk estimate (OR, RR or HR) Only observed and expected numbers	No specific control group	Born during 1965–1968 or 1975–1982 Adjusted by the birth of the children. No adjustments for maternal age	Low
Maule *et al.* (2007), Italy	Cohort study	229 cases with ALL 284 cases with embryonal tumours 633 155 population	Paternal age: ≥40 years ALL: ARR 0.93 (0.52–1.67) ≥40 years embryonal tumours: 1.50 (0.90–2.48)	25–29 years	Children aged 1–5 years 1980–1997 Adjusted for sex, year of birth, paternal/maternal age	Medium

Miller *et al.* (2010), Finland	Cohort study	10 965 population 318 cases/deaths	Paternal age: All causes mortality: ≥45 years AHR 3.45 (1.85–6.45) Natural death: ≥45 years 2.93 (1.05–8.18)	Paternal age 25–29 years	Mortality in offspring born in 1966 and followed to age 39 Adjusted for age of the other parent, subject age, parent social class, maternal parity	Medium
Mok *et al.* (2017), Denmark	Cohort study	1 793 681 population Cases with premature mortality, psychiatric morbidity and criminality	Paternal age: Natural death: >45 years AIRR 1.28 (1.02–1.59)	Paternal age 25–29 years	Mortality in children born 1966–1998 and followed to their 15th or 40th birthday or until 2011 Article also in Table 2d: other psychiatric disorders Older paternal age not associated with premature mortality after adjustments except for risk of natural death linked with paternal age 45 years and over. Adjusted for other parent's age, offspring age and sex	Medium
Stene *et al.* (2001), Norway	Cohort study	1 382 602 population 1824 with DM type 1	Paternal age: >40 year ARR 1.16 (0.92–1.46)	Paternal age < 25 years	DM type 1 in children born 1974–1998, followed for maximum 15 years until 1989–1998 Adjusted for age group year of birth, maternal age, birth order	High
Teras *et al.* (2015), USA	Cohort study	2532 cases with haematological malignancies 138 003 population	Paternal age: ≥35år AHR 1.20 (1.01–1.42) With no siblings: ≥35 years AHR 1.63 (1.19–2.23)	Paternal age < 25 years	Haematological malignancies diagnosed 1992–2009 No clear linear trend in risk by paternal age Adjusted for age of the other parent and sex	High
Urhoj *et al.* (2014), Denmark	Cohort study	10 855 cases 1 575 521 population	Paternal age: 40–45 years AHR 1.10 (95% CI 1.00–1.21) >45 years AHR 1.16 (95% CI 1.02–1.32)]	Reference group: Paternal age 30–34 years	Mortality before the age of 5 years in children born 1978–2004 Paternal age associated with increased risk of dying in early childhood due to an excess risk of fatal congenital anomalies, malignancies and external causes. Adjusted for maternal age, parity, parental education, year of birth.	High
Urhoj *et al.* (2017b), Denmark	Cohort study	3492 cases 1 904 363 population	Paternal age: ALL: ≥45 years AHR 1.55 (1.02–2.35) Leukaemias overall: ≥45 years AHR 1.58 (1.07–2.32)	Paternal age 30–34 years	Paternal age associated with risk of ALL with 13% higher HR for every 5 years increase in paternal age. No firm conclusions for other specific cancer types Adjusted for maternal age, child's year of birth, parental educational levels, parental ethnic origin and maternal parity	High
Wunsch and Gourbin (2002), Hungary	Cohort study	490 000 population 8300 cases/deaths	Paternal age: 25–34 years: Neonatal mortality: OR 0.83 (0.76–0.89) Post neonatal mortality: OR 0.99 (95% CI 0.95–1.16)	Paternal age 35–44 years	Live births and infant deaths from 1984–1988: Early neonatal: up to 7 days of life Neonatal: up to 28 days of life Post neonatal: 28 days to 1 year of life No adjustments described	Low
Yip *et al.* (2006), Sweden	Cohort study	7844 cases with cancer: Retinoblastoma $n = 226$ Leukaemia $n = 1234$ All CNS tumours $n = 977$ Astrocytoma $n = 316$ Wilm's tumour $n = 348$ non-Hodgkin's lymphoma $n = 218$	Paternal age >40 years: Retinoblastoma: AIRR 0.96 (0.47–1.97) Leukaemia AIRR 1.14 (0.85–1.53) CNS tumours AIRR 1.69 (1.21–2.35) Astrocytoma AIRR 1.95 (1.10–3.45) Wilm's tumour AIRR 1.53 (0.89–2.65) Non-Hodgkin's lymphoma >40 years AIRR 1.09 (0.55–2.16)	Paternal age <25 years	Children (<15 years) born 1961–2000 with childhood cancer. Adjusted for maternal age	High

Continued

Table III *Continued*

Author, year, country	Study design	Number of children	Result		Outcomes	Quality
			Outcomes (Risk estimates)	Reference group/ control		
		Population 4.3 million				
Zhu et al. (2008), Denmark	Cohort study	108 879 population 831 cases/deaths	Paternal age: 45–49 years: infant mortality AMRR 1.77 (1.28–2.45) ≥50år: AMRR 1.59 (1.03–2.46)	Paternal age 25–29 years	Mortality in singletons born 1980–1966 followed up to 18 years Adjusted for maternal age and parity, parental education and income, parental country of origin and calendar period	Medium
Zorlu et al. (2002), Turkey	Case control	116 cases with ALL 400 controls	Paternal age: >40 years ALL AOR 3.30 (1.28–8.51)	Paternal age < 40 years	Diagnosed with leukaemia in 1993–1996, aged 1–14 years. Adjusted for patients' age No adjustments for maternal age (no relationship with maternal age and the risk of ALL was found)	Low

AIRR, adjusted incidence rate ratio; ARR, adjusted rate ratio; AMRR, adjusted mortality rate ratio; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; DM, diabetes mellitus

2015). Chudal *et al.* (2015) reported an association between younger fathers and ADHD (highest risk associated with paternal age 20–24 years). Another study (D'Onofrio *et al.*, 2014) reported an association of ADHD with advanced paternal age, and the third study (Hvolgaard Mikkelsen *et al.*, 2016) found that there was a higher risk of ADHD if both parents were very young.

Eating disorders Two studies reported on eating disorders (one of high and one of low quality) (Racine *et al.*, 2014; Javaras *et al.*, 2017). The high quality study reported an association between advanced paternal age and eating disorders and also an association with anorexia nervosa (Javaras *et al.*, 2017).

Bipolar disorders Six studies have assessed the risk of bipolar disorders in offspring in relation to advanced paternal age, two study of high quality (Brown *et al.*, 2013; D'Onofrio *et al.*, 2014) three of medium quality (Frans *et al.*, 2008; Chudal *et al.*, 2014; Lehrer *et al.*, 2016) and one of low quality (Menezes *et al.*, 2010). Both Brown *et al.* (2013) and D'Onofrio *et al.* (2014) showed that advanced paternal age was a risk factor for bipolar disorders in offspring.

Psychosis and psychotic-like symptoms Three studies, including two case control studies of low quality (Gillberg, 1982; Foutz and Mezuk, 2015) and one study (El-Saadi *et al.*, 2004) which reported results from three different countries, assessed the association between paternal age and psychosis and psychotic-like symptoms in offspring. Two of the studies found an association between advanced paternal age and psychosis (El-Saadi *et al.*, 2004; Foutz and Mezuk, 2015).

Conclusion: It is uncertain whether paternal age is associated with an increased risk of other psychiatric conditions. Very low certainty of evidence (GRADE ⊕◯◯◯)

Paternal BMI, height and/or weight at childbirth and short-term outcomes for offspring

Obstetric outcomes

Altogether 13 cohort studies (mostly of medium quality) have evaluated the effect of paternal BMI, height, and/or weight on obstetric outcomes, in most cases on BW of infants (Supplementary Table SII, Table VII). All studies included in the systematic review had adjusted for maternal factors such as maternal height and BMI. In nine studies the influence of paternal height on BW of the children was studied. In all studies the father´s height correlated significantly with BW of the offspring. The effects of BMI, and the weight of the father at the time of conception, or at the beginning of the pregnancy, on neonatal BW were less clear. In one study from 2012, paternal BMI correlated significantly with BW of the newborn, and biparietal diameter, head circumference and pectoral diameter in male offspring (Chen *et al.*, 2012). However, three of six studies did not find any association between paternal BMI and BW of the babies (Table III). Four studies evaluated the correlation between paternal weight at conception and child BW. In three of these reports no association was found (Wilcox *et al.*, 1995; To *et al.*, 1998; Nahum and Stanislaw, 2003). Two studies compared paternal and child BW, with conflicting results (Klebanoff *et al.*, 1998; L'Abee *et al.*, 2011).

Conclusion: Paternal height is probably associated with BW of the offspring. Moderate certainty of evidence (GRADE⊕⊕⊕◯). There may be little or no association between paternal BMI/paternal weight and the BW of the offspring. Low quality of evidence (GRADE⊕⊕◯◯).

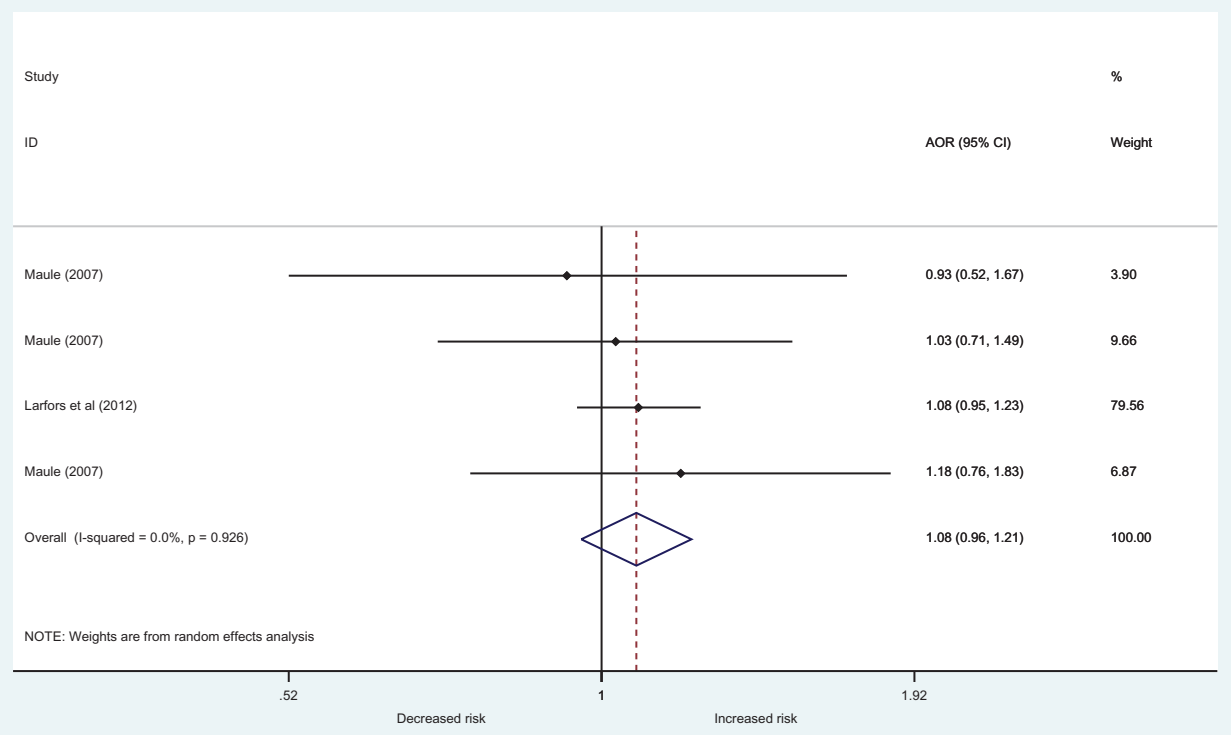

Figure 11 Forest plot describing the association between paternal age and risk for acute lymphoblastic leukaemia in the offspring.

Paternal BMI, height and/or weight at childbirth and long-term outcomes for offspring

Obesity

Paternal anthropometric measurements (BMI, height and/or weight) available at the time of the child's birth were studied in association with childhood outcomes in 13 cohort studies (nine medium and four high quality) and in one medium quality case control study (Supplementary Table SII, Table VIII). In two of the studies paternal height and weight were measured (Durmus *et al.*, 2013; Heppe *et al.*, 2013) and in other studies this information was obtained from questionnaires or records. The outcome was BMI, body fat and/or weight in 11 studies. Paternal anthropometrics at the time of the child's birth were associated with offspring BMI, weight and/or body fat mass in all studies.

Conclusion: High paternal BMI and weight may be associated with a modest increase in BMI, weight and/or body fat mass in offspring. Low certainty of evidence (GRADE⊕⊕◯◯).

ASDs and neurodevelopment

Paternal obesity was an independent risk factor for ASD in children in one medium quality study (Suren *et al.*, 2014) (Supplementary Table SII, Table VIII). In the study of Yeung and co-workers (2017) paternal obesity was associated with delays in personal-social functioning, whereas maternal obesity was associated with delays in fine motor development. Daraki and co-workers (2017) did not find any association between paternal obesity and child neurodevelopment at 4 years of age (Supplementary Table SII, Table IV).

Conclusion: It is uncertain whether there is an association between paternal obesity and ASD and neurodevelopment of the child. Very low certainty of evidence (GRADE⊕◯◯◯).

Paternal smoking at childbirth and short-term outcomes for offspring

Obstetric outcomes

Preterm birth. Three cohort studies including more than 30 000 children found no increased risk of PTB (<37 weeks) in children where fathers smoked (Supplementary Table SIII, Table IX). Two of the studies were adjusted for maternal smoking (Horta *et al.*, 1997; Ko *et al.*, 2014) and in one cohort study analyses were performed on non-smoking mothers (Andriani and Kuo, 2014). We included three studies in a meta-analysis and found a slight but not significant effect of paternal smoking on PTB (pooled estimate 1.16, 95% 1.00–1.35) (Fig. 14).

Conclusion: There may be little or no association between paternal smoking and PTB. Low certainty of evidence (GRADE⊕⊕◯◯).

Low BW. Seven studies (six cohort and one case control), comprising more than 60 000 children, investigated the association between paternal smoking during preconception/pregnancy and BW (Supplementary Table SIII, Table IX). In four cohort studies, all adjusted for maternal smoking, no increased risk of LBW was observed in pregnancies where fathers smoked (Horta *et al.*, 1997; Andriani and Kuo, 2014; Ko *et al.*, 2014; Inoue *et al.*, 2016).

Two cohort studies (Magnus *et al.*, 1984; Martinez *et al.*, 1994) and one case control study (Zhang and Ratcliffe, 1993) explored the association

Table IV Studies on the association of paternal age with autism/ASDs in offspring.

Author, year, country	Study design	Number of children	Result		Outcomes Comment Adjustments	Quality
			Outcome	Reference group/ control		
Systematic review and meta-analysis *n* = 2						
Hultman *et al.* (2011), Sweden	Meta-analysis (For separate cohort study see under original papers below)	11 studies (including 12 cohorts) with paternal age as exposure	Pooled estimates: 30–39 years 1.22 (1.05–1.42) 40–49 years 1.78 (1.52–2.07) ≥50 years 2.46 (2.20–2.76)	Paternal age ≤29 years	Increased risk of autism with increased paternal age	Medium
Wu *et al.* (2017), China	Systematic review and meta-analysis	27 studies (6 cohort and 21 case control studies) with paternal age as exposure	Below reference points: AOR 0.81 (0.73–0.89) Above reference point: AOR 1.55 (1.39–1.73) Overall RR for each 10 year increase in paternal age: 1.21 (1.18–1.24)	Reference point: Midpoint paternal age -age not mentioned	Compared to reference point, lower paternal age was associated with reduced risk and increased paternal age was associated with increased risk of autism	Medium
Original articles *n* = 28						
Ben Itzchak *et al.* (2011), Israel	Cohort study	529 cases with ASD Israeli Newborn data, total population not available (2004)	Paternal age in a cohort with ASD. No risk estimate.	Paternal age 20–29 years	The percentage of fathers in the older age (30–40 years) was significantly higher in the ASD cohort compared to the Israeli newborn data ($P < 0,01$)	Low
Bilder *et al.* (2009), USA	Case control	132 cases with ASD 13 200 controls	Paternal age: OR 1.28 (0.54–3.03)	Paternal age 30–39 years	No effect of paternal age (high or low) Not adjusted for maternal age	Low
Buizer-Voskamp *et al.* (2011), The Netherlands	Case control	14 231 cases (Autism *n* = 2262 Schizophrenia *n* = 2564 8284 Major depression *n* = 8284 Bipolar disease *n* = 1121 9048 controls (56 924 controls in total)	Paternal age ≥40 years: Autism: AOR 1.23 (1.01–1.50)	Paternal age 25–29 years	Adjusted for maternal age <30 years and >30 years, ethnic background and average income of the residential area	Medium
Burd *et al.* (1999a), USA	Case control study	78 cases of autism 390 controls	A one-year decrease in the age of the father decreased the risk of autism by 6% compared to the control OR 1.45 (0.90–2.45)	Paternal age <20 or >30, 20–30 years	Matched controls Increasing father's age associated with increased risk of autism No adjusted risk estimate	Low
Byars and Boomsma (2016), Denmark	Cohort study	10 703 cases with autism (ASD) 20 586 cases with schizophrenia 1 656 795 population	Paternal age: 26–30 years AHR 0.92 (0.86–0.98) 35–39 years AHR 1.10 (1.03–1.18) 40–44 years AHR 1.19 (1.06–1.33) 45–60 years AHR 1.2 (1.04–1.49)	Paternal age 31–34 years	Adjusted for other parent's age (see STable I)	Medium
Croen *et al.* (2007), USA	Case control	593 cases with autism 132 251 population	Paternal age: 35–39 years AOR 1.38 (1.04–1.84) ≥40 years AOR 1.52 (1.10–2.10) With each 10 year increase in paternal age ARR 1.34 (1.06–1.69)	Paternal age 25–29 years	Adjusted for maternal age, birth order, gender, date of birth, parental educational level, ethnicity	Medium

D'Onofrio *et al.* (2014), Sweden	Cohort study	2424 cases with autism Psychosis, bipolar disorder, suicide attempts 900 337 population	Paternal age: >45 years AHR 1.76 (1.36–2.28)	Paternal age 20–24 years	Adjusted for maternal age, sex, year of birth, parental education, history of psychiatric hospitalization	High
Durkin *et al.* (2008), USA	Cohort study	1251 cases with autism 253 347 population	Paternal age: ≥40 years AOR 1.4 (1.1–1.8) With each 10 year increase in paternal age AOR 1.3 (1.1–1.5)	Paternal age 25–29 years	Adjusted for maternal age, birth order, gender, maternal education, ethnicity, multiple birth, gestational age, BW for gestational age	High
Frans *et al.* (2013), Sweden	Case control	5936 cases with autism 30 923 controls	Paternal age: 45–49 years AOR 1.85 (1.47–2.31) ≥50 years AOR 2.23 (1.59–3.12) With each 10 years RR 1.25 (95% CI 1.17, 1.31)	Paternal age 20–24 years	Adjusted for maternal age, birth year, gender, family history, educational level, country	Medium
Grether *et al.* (2009), USA	Cohort study	23 311 cases with autism 7 550 026 population	Paternal age: 50–54 years AOR 1.53 (1.32–1.77) 60–64 years AOR 2.05 (1.38–3.05) With each 10 year increase in paternal age (15–64 years) ARR 1.22 (1.18, 1.25)	Paternal age 25–29 years	Adjusted for maternal age, child's sex, birth weight, ethnicity, education, parity, gestational age, delivery method, birth year	High
Hultman *et al.* (2011), Sweden	Cohort study	883 cases with autism 1 075 588 population	Paternal age: 30–39 years AOR 1.19 (1.00–1.42) 40–49 years AOR 1.42 (1.07–1.87) ≥50 years AOR 2.21 (1.26–3.88) ≥55 years AOR 4.36 (2.09–9.09) With each 10 year increase in paternal age RR 1.21 (1.10, 1.34)	Paternal age <29 years	Adjusted for maternal age, maternal country of birth, birth weight, maternal history of psychiatric illness, paternal country of birth, paternal history of psychiatric illness, BW, being small/large for gestational age, foetal distress, SES, birth order, year of birth of the offspring	Medium
Idring *et al.* (2014), Sweden	Cohort study	4746 cases with ASD 417 303 population	Paternal age: 25–28 years AOR 0.93 (0.90–0.96) 35–39 years AOR 1.07 (1.04–1.10) 55–59 years AOR 1.39 (1.29–1.50)	Paternal age 32 years	Adjusted for maternal age (using generalized additive models - GAMs), birth year, sex, parity, parental psychiatric history, occupational class, family income, maternal region of birth	High
King *et al.* (2009), USA	Cohort study	18 731 cases with autism 4 906 926 population	Paternal age: Risk varies over time: >40 years: lowest risk in 1992: RR 1.29 (1.03–1.60) to highest in 1995: RR 1.71 (1.41–2.08)	Paternal age <30 years	Autism risk is analysed over multiple birth cohorts Not adjusted risk estimates	Medium
Lampi *et al.* (2013), Finland	Case control	4713 cases with ASD 1132 with childhood autism 1785 with Asperger's syndrome 1796 with pervasive development disorder (PDD) 18 777 controls	Paternal age: Autism: 40–49 years AOR 1.6 (1.1–2.3) Asperger: 40–49 years AOR 1.1 (0.5–2.2) PDD: 40–49 years AOR 1.6 (0.8–3.2)	Paternal age 25–29 years	Adjusted for maternal age, number of previous births, weight for gestational age, intellectual disability, maternal SES, paternal psychiatric history.	Medium
Larsson *et al.* (2005), Denmark	Case control	698 cases with autism 17 450 controls	Paternal age: >39 years ARR 1.36 (0.96–1.93)	Paternal age 25–29 years	Adjusted for perinatal factors, maternal age, parental psychiatric history, socio-economic characteristics	Medium

Continued

Table IV *Continued*

Author, year, country	Study design	Number of children	Result		Outcomes Comment Adjustments	Quality
			Outcome	Reference group/ control		
Lauritsen *et al.* (2005) Denmark	Cohort study	818 cases with autism 943 664 population	Paternal age: 40–44 years ARR 1.61 (1.19–2.18) ≥45 years: ARR 1.21 (1.78–1.86)	Paternal age 25–29 years	Adjusted for maternal age, gender, calendar year of diagnosis, paternal history of psychiatric disease, parental country of birth	Medium
Lundstrom *et al.* (2010), Sweden	Cohort (twin cohort) - Sweden and UK	Sweden: 164 cases with ASD 11 122 population UK: 66 cases with ASD 13 524 population	Paternal age in Sweden: 45–50 years AOR 1.90 (1.73–4.92) ≥51 years AOR 3.37 (1.02–11.14) Paternal age in UK: 45–49 years AOR 1.66 (0.47–5.82) ≥51 years AOR 3.59 (0.37–34.46)	Paternal age 25–34 years	Twin cohort Adjusted for maternal age, zygosity and SES	Medium
Maimburg and Vaeth (2006), Denmark	Case control	473 cases with infantile autism 4730 controls	Paternal age: >35 years AOR 0.9 (0.7–1.4)	Paternal age 25–29 years	Adjusted for maternal age, maternal citizenship, BW, gestational age, Apgar score, birth defect, irregular foetal position	Medium
Mamidala *et al.* (2013), India	Case control	471 cases with ASD471 controls	Paternal age: >30 years AOR 1.05 (0.76–1.46)	Paternal age <30 years	Adjusted for maternal age, gender, year of birth	Medium
Parner *et al.* (2012), Denmark	Cohort study (sibling design)	9556 cases with ASD 1 311 736 children	Maternal age < 35 years and paternal age 35–39 years: AHR 1.27 (1.19–1.35) Maternal age < 35 years and paternal age ≥ 40 years: AHR 1.44 (1.31–1.58)	Paternal age <35 years	Combinations of parents' ages: for mothers younger than 35 years, the risk of ASD increased with increasing father's age group. Adjusted for gestational age, birth weight, birth order, sex, parental psychiatric history at birth	Medium
Quinlan *et al.* (2015), USA (New York)	Cohort study	1589 cases with ASD 927 003 population	Paternal age: ≥35 years AOR 1.4 (1.08–1.68)	Paternal age <25 years	Adjusted for parity, sex, race and ethnicity, gestational age, maternal metabolic risk factor, SGA. Not precise whether adjusted for maternal age	Medium
Reichenberg *et al.* (2006), Israel	Cohort study	319 cases with ASD 132 271 population	Paternal age: 40–49 years AOR 5.75 (2.65–12.46) With each 10 year increase in paternal age RR 2.14 (1.44–3.16)	Paternal age 15–29 years	Adjusted for year of birth, SES and maternal age	Medium
Sandin *et al.* (2016), Scandinavia (Danmark, Norge, Sweden), Western Australia and Israel	Cohort study	30 902 cases with ASD 5 776 794 population	Paternal age and risk for ASD: <20 years ARR 1.08 (0.92–1.27) 30–39 years ARR 1.05 (1.02–1.08) 40–49 years ARR 1.28 (1.22–1.34) ≥50 years ARR 1.64 (1.66–1.85)	Paternal age 20–29 years	Joint effect of maternal and paternal age with increasing risk for couples with increasing differences in parental age. Adjusted for site (country), sex, birth year, maternal age	High
Sasanfar *et al.* (2010), Iran	Case control study	179 cases with ASD 1611 controls	Paternal age: ≥40 years AOR 2.03 (1.10–3.73) With each 10 year increase in paternal age a 29% increase in autism risk	Cohort study: Paternal age 25–29 years Case control study: Paternal age 25–29 years	Adjusted for parental education, birth order, sex, consanguinity, urbanism and province. Not precise whether adjusted for maternal age	Low

Shelton *et al.* (2010), USA	Cohort study	4 947 935 population 12 159 cases with autism	Paternal age: >40 years AOR 1.36 (1.26–1.47)	Paternal age 25–29 years	Adjusted for maternal age, parents race/ethnicity, year of birth, insurance type, parental education	Medium
Tsuchiya *et al.* (2008), Japan	Case control	84 cases with high-functioning ASD 208 controls	Paternal age: 29–32 years: AOR 2.28 (1.02–5.11) ≥33 years: AOR 3.09 (1.17–8.16) Paternal age as a continuous variable: AOR 2.54 (0.96–6.72)	Paternal age <29 years	Few cases. Adjusted for maternal age, gender and parity	Low
van Balkom *et al.* (2012), Aruba, The Netherlands	Case control	95 cases with ASD 347 controls	Paternal age: 30–39 years AOR 2.16 (1.15–4.04) 45–49 years AOR 2.67 (1.07–6.68)	Paternal age <30 years	Adjusted for maternal age and PTB	Low
Zhang *et al.* (2010), China	Case control	95 cases with autism 95 controls	Paternal age: >30 years: AOR 2.63 (1.38–5.00)	Paternal age <30 years	Adjusted for paternal age, gender and birth year. No adjustments for maternal age	Low

ASD, autism spectrum disorder; PDD, pervasive development disorder; RR, relative risk; SES, socio-economic status.

between BW and paternal smoking. Martinez *et al.* (1994) showed that the number of cigarettes smoked by the father was associated with lower BW in children with non-smoking mothers (test for linearity $P < 0.03$). This was in line with Zhang, where paternal smoking had a modest effect on BW, the mean BW being 30 grams lower in pregnancies where the fathers smoked (Zhang and Ratcliffe, 1993). In the study by Magnus, paternal smoking had no independent effect on BW in the offspring (Magnus *et al.*, 1984). We performed a meta-analysis including four studies. A small but not significant effect of paternal smoking on the incidence of LBW was found (pooled estimate 1.10, 95% 1.00–1.21) (Fig. 15).

Conclusion: There appears to be little or no association between paternal smoking and LBW. Low certainty of evidence (GRADE⊕⊕◯◯).

SGA/intrauterine growth retardation. Two cohort studies investigated SGA/ IUGR, defined as BW <10th percentile for gestational age and sex (Horta *et al.*, 1997; Ko *et al.*, 2014), comprising more than 27 000 children in total (Supplementary Table SIII, Table IX). In Horta *et al.* (1997) the adjusted risk of SGA/IUGR was significantly increased in pregnancies with paternal smoking, AOR 1.33 (95% CI 1.05–1.68), while in the study by Ko *et al.* (2014) no significant association was found (AOR 1.12 (95% CI 0.90–1.40) for SGA/IUGR. Figures were similar for paternal smoking in the first, second and third trimesters (Ko *et al.*, 2014). A meta-analysis including two studies showed a pooled estimate of 1.21 (95% CI 1.03–1.44) (Fig. 16).

Conclusion: Paternal smoking may be associated with a small increase in SGA/IUGR. Low certainty of evidence (GRADE⊕⊕◯◯).

Perinatal mortality. One cohort study of medium quality from Lithuania (comprising 29 619 births) including 296 perinatal deaths found an increased risk of perinatal death when fathers smoked (AOR 1.72, 95% CI was not available) (Gaizauskiene *et al.*, 2007) (Supplementary Table SIII, Table IX). The probability of foetal and NND was 0.009 in the offspring of fathers who smoked, in comparison with 0.005 in the offspring of non-smoking parents.

Conclusion: It is uncertain whether paternal smoking is associated with perinatal death. Very low certainty of evidence (GRADE⊕◯◯◯).

Birth defects

Eight studies (one cohort and seven case control) reported birth defects in relation to paternal smoking before and during pregnancy (Supplementary Table SIII, Table IX). The cohort study included 14 685 births for analysis and found no significant association between paternal smoking and children with orofacial clefts, hydrocephalus, ventricular septal defect (VSD) and urethral stenosis (Savitz *et al.*, 1991). There were seven case control studies. These included a total of 1977 cases, where four studies reported CHD ($n = 1112$) (Wasserman *et al.*, 1996; Kuciene and Dulskiene, 2010; Cresci *et al.*, 2011; Deng *et al.*, 2013), two studies reported orofacial clefts ($n = 780$) (Krapels *et al.*, 2006; Figueiredo *et al.*, 2015) and one study reported anorectal defects ($n = 85$ cases) (van Rooij *et al.*, 2010). Wasserman *et al.* (1996) also reported neural tube defects ($n = 264$ cases) and limb reduction defects ($n = 178$ cases).

The three CHD studies showed a significantly increased risk associated with paternal smoking with AOR ranging from 1.45 to 3.2 (Kuciene and Dulskiene, 2010; Cresci *et al.*, 2011; Deng *et al.*, 2013), while Wasserman *et al.* (1996) showed no association (AOR 0.93,

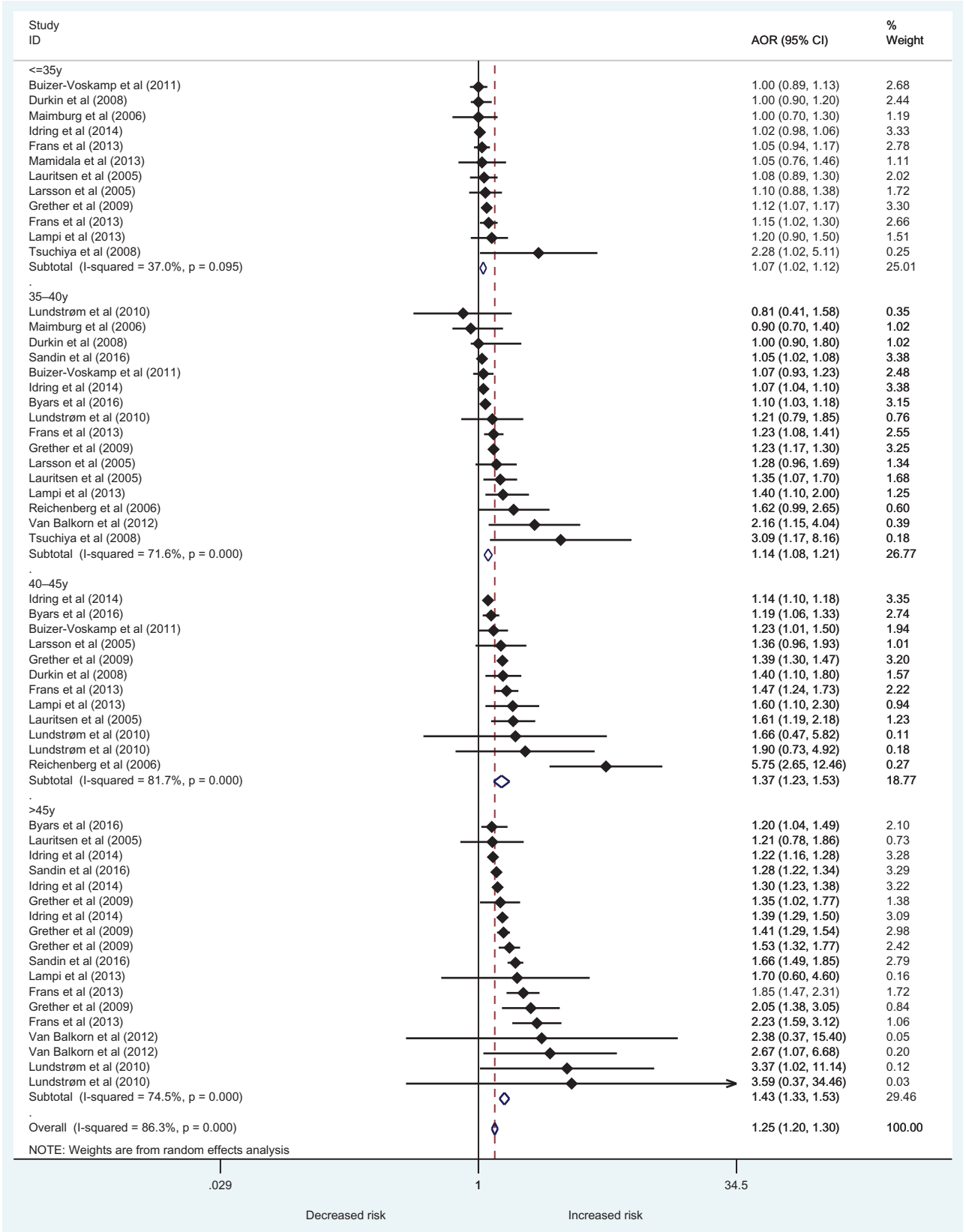

Figure 12 Forest plot describing the association between paternal age and risk for autism/ASDs in the offspring.

Table V Studies on the association of paternal age with schizophrenia and schizophrenia spectrum disorders in offspring.

Author, year, country	Study design	Number of deliveries or children	Result Outcomes (Risk estimates)	Reference group/ Control	Outcomes Comment Adjustments	Quality
Systematic reviews *n* = 3						
Miller *et al.* (2011), Finland	SR (6 cohort and 6 case control studies) and MA	Cohort studies: 14 568 cases and 3 000 729 controls Case control studies; 8733 cases and 1 945 092 controls	Paternal age >50 years: RR 1.66 (1.46–1.89) <25 years: RR 1.08 (1.02–1.14) in male offspring.	Paternal age 25–29 years	Adjusted for maternal age Sub analyses on gender-stratified data	Medium
Torrey *et al.* (2009), USA	MA (10 studies)	10 studies included	Paternal age >45 years: OR 1.38 (0.95–2.02) >55 years: OR 2.22 (1.46–3.37)	NA	Matched for city of birth, season of birth and parental history of treatment for mental disorder	Low
Wohl and Gorwood (2007), France	MA (8 studies)	8 out of 10 studies were included	Paternal age >54 years: OR 1.02 (2.03–17.12)	Paternal age 25–34 years	Adjusted for maternal age Different age categories used as reference	Low
Original articles *n* = 19						
Brown *et al.* (2002), USA	Cohort study	12 094 individuals	73% response rate (146 of 170) Risk for each 10-year increase in paternal age: ARR 1.89 (1.08–3.32), $Z = 2.22$, $P < 0.03$	Paternal age 15–24 years	Adjusted for maternal age Small study size (71 cases) Includes both schizophrenia and other schizophrenia spectrum diseases (SSD)	Low
Buizer-Voskamp *et al.* (2011), The Netherlands	Case control	14 231 cases 56 925 controls	Paternal age >35 age: OR 1.27 (1.05–1.53) Matched controls	Paternal age 25–29 years	Adjusted for maternal age, SES, and ethnic background Separate analyses for male and female offspring	Medium
Byars and Boomsma (2016), Denmark	Cohort study	1 787 447 children	7 out of 15 risk ratios increased in the three age-difference groups Estimates not given	NA	5 categories for schizophrenic disorders U-shaped association	Low
Byrne *et al.* (2003), USA	Case control	7704 cases 192 590 controls	Paternal age >50 years: Sex-specific estimates. Males with fathers >55 years: AIRR 2.10 (1.35–3.28). Females with fathers >55 years: AIRR: 3.53 (1.82–6.83)	Paternal age 20–24 years	Adjusted for maternal age, parental education, wealth, marital status and family history of psychiatric history	Medium
Dalman and Allebeck (2002), Sweden	Case control	420 cases 857 controls	Paternal age >45 years: AOR 2.8 (1.3–6.3)	Paternal age 20–24 years	Brief report. Adjusted for maternal age No adjustment for paternal psychiatric illness	Low
Ek *et al.* (2015), Sweden	Cohort study	3829 cases 2 589 502 individuals	Paternal age >45 years: HR 0.93 (0.72–1.21) 35–39 years: HR 1.37 (1.18–1.58) 40–44 years: HR 1.81 (1.44–2.28)	Paternal age 25–29 years	Adjusted for offspring sex and maternal age Small sample size in the oldest group	Low
Frans *et al.* (2011), Sweden	Cohort study	120 758 individuals	Paternal age >55 years: AOR 1.95 (1.58–2.40)	Paternal age 20–24 years	Adjusted for maternal age, birth year	Medium
Lehrer *et al.* (2016), USA	Case control	5317 cases 7658 controls	Paternal age >45 years: RRR 2.88 (2.65–3.13)	Paternal age 20–24 years	Adjusted for maternal age Self-reporting of paternal age and clinical history	Medium
Malaspina *et al.* (2001), Israel	Cohort	658 cases 89 722 controls	Paternal age 40–44 years: ARR 1.79 (1.25–2.57) 45–49 years: ARR 1.89 (1.24–2.88) >50 years: ARR 2.60 (1.63–4.15)	Paternal age 20–24 years	Adjusted for maternal age, sex and ethnic group	Low
McGrath *et al.* (2014), Denmark	Cohort	2 894 688 people	Paternal age >45 years: IRR 1.54 (1.41–1.69)	Paternal age 25–29 years	The cohort was observed for 42.7 million person-years	Medium

Continued

Table V *Continued*

Author, year, country	Study design	Number of deliveries or children	Result		Outcomes Comment Adjustments	Quality
			Outcomes (Risk estimates)	Reference group/ Control		
Naserbakht *et al.* (2011), Iran	Case control	220 cases 220 controls	Birth rank comparisons: 35% versus 24% of the cases versus the controls were in the third or upper birth rank ($P = 0.01$). Mean age of fathers at birth in cases (30 ± 6.26 years) versus controls (26.45 ± 5.64 years; $P = 0.0001$). Paternal age ≥32 years (at birth) in cases versus controls: AOR 3.8 (1.80 to 4.27)	NA	Paternal age category is not described Matching for sex and maternal age	Low
Petersen *et al.* (2011), Denmark	Cohort	2.2 million people	Paternal age: 45–49 years: AIRR 1.39 (1.13–1.70) 50–54 years: AIRR 1.93 (1.49–2.50) >55 years: AIRR 1.15 (1.12-1-20)	Paternal age 25–29 years	Adjusted for maternal age, proband sex, family psychiatric history in father, mother and siblings The risk of schizophrenia increased with increased paternal age of the father´s first child	Medium
Sipos *et al.* (2004), Sweden	Cohort	754 330 people	For each 10 year increase in paternal age: AHR 1.47 (1.23–1.76)	Paternal age 21–24 years	Separate analysis according to family history of the disorder. Adjusted for maternal age, BW, GA, parity and plurality	Low
Sorensen *et al.* (2014), Denmark	Cohort	176 454 men	Cox regression to estimate the IRR of SSD IRR: 1.32 (1.10–1.60) per 10 years increase in paternal age	Paternal age 25–29 years	SSD Adjusted for maternal age, IQ, birth order and family history of psychiatric disorders	Medium
Torrey *et al.* (2009), USA	Cohort + MA (10 studies)	168 + 88 cases 25 025 controls	Cohort of 88 cases: Paternal age: >35 years: OR 1.35 (0.88–2.06) >40 years: OR 1.33 (0.75–2.37) >45 years: OR 1.32 (0.48–3.63) ≥55 years: MA: pooled OR 2.21 (1.46–3.37)	NA	Matched for city of birth, season of birth and parental history of treatment for mental disorder	Low
Tsuchiya *et al.* (2005), Japan	Case control	99 cases, 381 controls	Paternal age 29–31 years: AOR 2.08 (1.12–3.86) >32 years: AOR 3.00 (1.49–6.04) Test for trend $P = 0.002$	Paternal age < 25 years	Adjusted for age and gender of the subject, parity, family history and maternal age.	Low
Wang *et al.* (2015), Taiwan	Case series	1297 cases	Inverted U-shaped association Onset of schizophrenia was lowered by 1.5 years for paternal age 25–29 years and by 5.5 years for paternal age >55 years Test for trend $P = 0.04$	Paternal age 21–24 years	Study of earlier onset among co-affected sib-pairs with the same familial predisposition. Adjusted for maternal age, gender, education in years and parental education	Low
Wu *et al.* (2012), China	Case control	351 cases 238 controls	351 patients with schizophrenia (167 males, 134 females) Paternal age: <25 years: OR 0.628 (0.350–1.127) 30–34 years: OR 2.660 (1.697–4.169) >35 years: OR 10.183 (4.772–21.729)	Paternal age 25–29 years	Adjusted for participant´s sex, age and maternal age	Low
Zammit *et al.* (2003), Sweden	Cohort	2362 cases 50 087 individuals	For each 10-years increase in paternal age: AOR 1.3 (1.0–1.5); $P = 0.015$ Paternal age: 55 years or more: AOR: 3.8 (1.3–11.8)	Paternal age 15–24 years	Adjusted for maternal age, drug use, poor social integration and place of upbringing.	

BW, birth weight; GA, gestational age; HR, hazard ratio; IQ, intelligence quotient; IRR; incidence rate ratio, MA, meta-analysis; RRR, relative risk ratio; SSD schizophrenia spectrum diseases; SR, systematic review

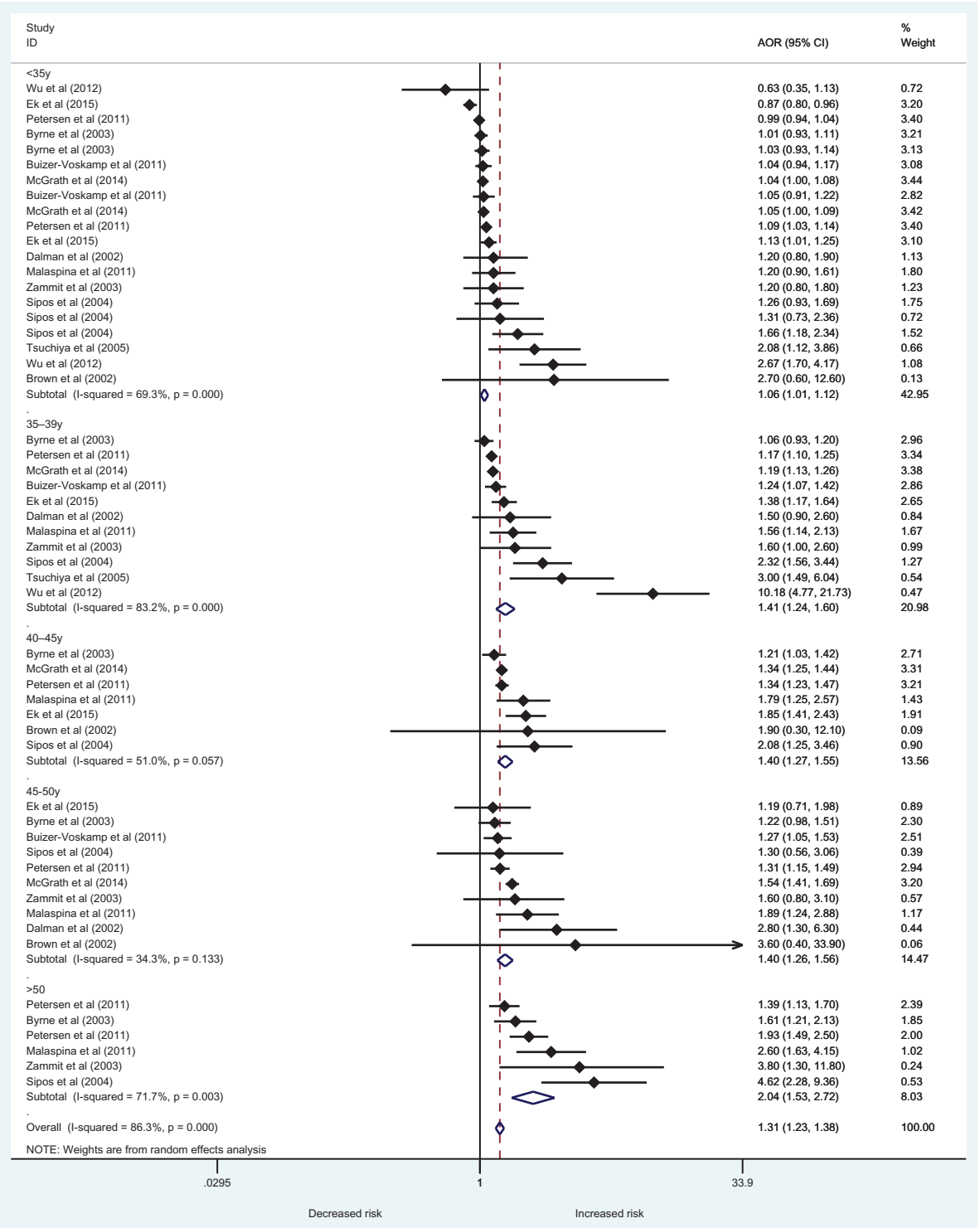

Figure 13 Forest plot describing the association between paternal age and risk for schizophrenia/schizoaffective disorders in the offspring.

95% CI 0.58–1.5). Savitz *et al.* (1991) found no significant association of paternal smoking and VSD (AOR 2.0, 95% CI 0.9–4.3).

We included six studies in a meta-analysis and found a positive association between paternal smoking and CHD (pooled estimate 1.75 (95% CI 1.25–2.44) (Fig. 17).

There was also a positive association between paternal smoking and orofacial clefts in both case control studies (AOR from 1.45 to 1.5) (Krapels *et al.*, 2006; Figueiredo *et al.*, 2015). However, there was no significantly increased risk in the cohort study, with an APOR 1.7 (95% CI 0.5–6.0) (Savitz *et al.*, 1991). Furthermore, there was a

Table VI Studies on the association of paternal age with other psychiatric disorders in offspring

Author, year, country	Study design	Number of deliveries or children	Result		Outcomes Comment Adjustments	Quality
			Outcomes (Risk estimates)	Adjustments Reference group/ Control		
Original articles *n* = 15						
Brown *et al.* (2013), USA	Case control study	94 cases 746 controls	Paternal age: Per 10 year increment of paternal age: AOR 1.04 (0.75–1.44)	Paternal age 20–29 years	Bipolar disorders Measured as 10 years increase in paternal age. Controls were matched on date of birth, sex and residency Adjusted for maternal age	Low
Burd *et al.* (1999b), USA	Case control study	92 cases 460 controls	Paternal age risk for Tourette: β - 0.96, OR 0.909	Each additional year of paternal age decreased the risk of Tourette syndrome by 9.1%	Tourette syndrome Controls matched for sex, year of birth and month of birth	Low
Chudal *et al.* (2014), Finland	Case control study	1861 cases 3643 controls	Paternal age: >50 years AOR 2.84 (1.32–6.12) 30–34 years AOR 1.35 (1.06–1.72)	Paternal age 25–29 years	Bipolar disorders Adjusted for maternal age and additional adjustment for parental psychiatric history, parental educational level and place of birth	Medium
Chudal *et al.* (2015), Finland	Case control study	10 409 cases 39 125 controls	Paternal age: <20 years AOR 1.55 (1.11–2.18) 20–24 years AOR 2.20 (1.07–1.34) 45–49 years AOR 1.26 (1.01–1.58) ≥50 years AOR 1.08 (0.73–1.58)	Paternal age 25–29 years	ADHD in singleton births during 1991–2005, diagnosed 1995–2011 ADHD was associated with young fathers Adjusted for maternal age, paternal psychiatric history, maternal SES, maternal smoking during pregnancy, previous birth, birth weight for gestational age	Medium
D'Onofrio *et al.* (2014), Sweden	Cohort study	2861 cases with ADHD 6819 cases with bipolar disorder 2 615 081 population	Paternal age >45 years ADHD: HR 1.76 (1.36–2.28) Sibling *fixed-effects* model: ADHD: HR 13.13 (6.85–25.16) Bipolar disorders: HR 24.70 (12.12–50.31) Psychosis: HR 2.07 (1.35–3.20)	Paternal age 20–24 years	ADHD, bipolar disorders, psychosis Adjusted for maternal age, sex, year of birth, parental education, history of psychiatric hospitalization. Also sibling-comparison analyses	High
	Cohort study (Denmark)	Denmark: 11 672 cases, 2,3 million population	Paternal age: Denmark:	Paternal age 20–24 years	Psychosis Adjusted for maternal age	Low to medium

El-Saadi *et al.* (2004), Sweden and Australia	Case control (Sweden, Australia)	Sweden: 134 cases and 8687 controls Australia: 119 cases and 141 controls	35–39 years AOR 1.14 (1.05–1.24) 50–54 years: AOR 1.33 (1.33–2.53) ≥35 years: Sweden: AOR 2.42 (1.19–4.89) Australia: AOR 0.77 (0.24–2.46)			depending on study group
Foutz and Mezuk (2015), USA	Cohort study	924 cases 9282 population	Paternal age: 30–34 years: AOR 0,63 (0.25–1.60) ≥35 years: AOR 2.12 (1.08–4.16)	Paternal age 25–29 years	Psychotic-like symptoms Adjusted for demographic characteristics, birth order, lifetime history of depression, anxiety and substance use disorders.	Low
Frans *et al.* (2008), Sweden	Case control study	13 428 cases 67 140 controls	Paternal age: 45–49 years OR 1.14 (1.00–1.30) 50–54 years OR 1.21 (1.00–1.48) >55 years OR 1.37 (1.02–1.84)	Paternal age 20–24 years	Bipolar disorders Adjustment for maternal age, additional adjustment for family history of psychotic disorders, parity and socio-economic status	Medium
Gillberg (1982), Sweden	Cohort study	155 cases: Mental retardation 4 Psychosis 30 Psychogenic psychosis 2 Hyperkinetic disorders 3 Anorexia nervosa 5 Conduct disorders 38 Emotional disorders 64 Others 8 82 570 population	Paternal age: No risk estimate	NA	Psychiatric clinic attenders aged 3–19 years during 1975 Psychotic children and adolescents tended to have mothers and fathers who were older than average No adjustments	Low
Hvolgaard Mikkelsen *et al.* (2016), Denmark	Cohort study	12 294 cases 943 785 singletons	Paternal age: 31–35 years AHR 0.9 (0.77–1.05) ≥35 years AHR 0.74 (0.53–1.02)	Paternal age 26–30 years	ADHD Adjusted for smoking, gender, maternal age	High
Javaras *et al.* (2017), Sweden	Cohort study	2 276 809 population Anorexia nervosa = 8137 Any eating disorder =16 405	Paternal age: Anorexia nervosa: 20–24 years AOR 0.91 (0.80–0.96) ≥45 years AOR 1.32 (1.14–1.53) Any eating disorder: 20–24 years AOR 0.93 (0.87–0.98) ≥45 years AOR 1.26 (1.13–1.40)	Paternal age 25–29 years	Eating disorders (anorexia nervosa and any eating disorder). Adjusted for sex, birth order, maternal age, country of birth, parental highest education level, lifetime psychiatric and criminal history	High
		5317 cases	Paternal age ≥45 years:		Bipolar disorders with or without psychosis	Medium

Continued

Table VI *Continued*

Author, year, country	Study design	Number of deliveries or children	Result		Outcomes Comment Adjustments	Quality
			Outcomes (Risk estimates)	Adjustments Reference group/ Control		
Lehrer *et al.* (2016), USA	Case control study	7658 controls	Bipolar disorder with psychotic features: RRR 1.939 (1.411–2.643) Bipolar disorder without psychotic features: RRR 0.934 (0.536–1.543)	Paternal age 20–24 years	For schizophrenia and schizoaffective disorders see Table 2c	
Menezes *et al.* (2010), Sweden	Cohort study	493 cases 754 330 population	Paternal age: 40–44 years HR 1.85 (1.04–3.30) 45–49 years HR 1.06 (0.39–2.83) >50 years HR 1.43 (0.43–4.76)	Paternal age 21–24 years	Bipolar affective disorders (BPAD) Adjusted for maternal age, SES, family history of psychosis and education Risk of BPAD for each 10-years increase in paternal age	Medium
Racine *et al.* (2014), USA	Cohort study	1722 female twins aged 8–17 years, 11 cases	Paternal age: No risk estimate.	Paternal age ≥40 years was coded as reference group for *t*-test comparisons in categorical paternal age models	Eating disorders Advanced paternal age increased the risk for eating pathology Controlled for maternal age	Low
Saha *et al.* (2009), Australia	Cohort study	33 437 singletons	Paternal age 50 years: OR for being in the lowest decile for each neurocognitive variable was significantly associated with elevated paternal age for three of the neurocognitive measures	Paternal age 20 years	Neurocognitive development Adjusted for maternal age, offspring sex, mother's race, weeks of gestation, child's age at testing, family and SES	Medium

ADHD, attention deficit hyperactivity disorder; BPAD, bipolar affective disorders.

Table VII Studies on the association of paternal BMI, height and weight with obstetric outcomes in offspring.

Author, year, country	Study design	Number of children	Results	Outcomes Comments Adjustments	Quality
Original articles *n* = 13					
Cawley *et al.* (1954), UK	Cohort study	1028 children	The height of the fathers was divided into six groups (under 60 inches up to 72 inches and over). BW of the child increased with increased height of father (6.73, 6.91, 7.31, 7.35, 7.55, and 7.74 pounds respectively)	Birth weight (BW) Adjusted for maternal height	Medium
Chen *et al.* (2012), China	Cohort study	889 children; 492 boys and 407 girls	Association between paternal BMI and foetal growth of male offspring: BW ($P = 0.013$), biparietal diameter ($P = 0.001$), head circumference ($P = 0.006$), abdominal circumference ($P = 0.003$) and pectoral diameter ($P = 0.043$). Paternal BMI was not associated with foetal growth of female offspring.	BW, newborn´s body shape and endocrine system Multivariable regression analysis considering maternal BMI, paternal and maternal age, hypertension during pregnancy, maternal glycated serum protein, parity and gestational age as confounding factors	Low
Klebanoff *et al.* (1998), Denmark	Cohort study	Offspring to girls born in Copenhagen 1959–1961. *n* = 3130	Paternal BW was associated with infant BW ($P = 0.002$). Association between paternal adult height and infant BW ($P = 0.088$) Association between paternal BMI and infant BW ($P = 0.049$)	BW Adjusted for maternal BW; maternal adult height, weight, hypertension, diabetes, smoking, education, employment status, and location of residence; child´s birth order and gender; other paternal characteristics	Medium
L'Abee *et al.* (2011), the Netherlands	Cohort study	2947 singletons born 2006–2007	Paternal BMI and paternal BW were not independent predictors for BW of the offspring	BW Adjusted for maternal factors	Medium
Lawlor *et al.* (2007) Australia	Cohort study	7223 women and their offspring	Paternal pre-pregnancy BMI: borderline significantly positive association with birth weight standardized for sex and gestational age (regression coefficient 0.03)	BW Paternal coefficient adjusted for maternal effect	Medium
Magnus *et al.* (1984), Norway	Cohort study	3130 families	Association between paternal weight and infant BW ($P < 0.01$) and between paternal height and infant BW ($P < 0.05$)	BW Socio-economic status, educational attainment and paternal smoking habit had no independent effects on infant BW	Medium
Morrison *et al.* (1991), Australia	Cohort study	5989 children	Paternal height was significantly associated with BW ($P < 0.0007$) The increase of the BW was up to 152 g with increased height of the father (ranging from 165 cm to 184 cm). Paternal BMI had no significant effect on the BW of the child	BW Adjusted for maternal BMI	Medium
Mutsaerts *et al.* (2014), Australia	Cohort study	2264 children	Paternal pre-pregnancy BMI had no influence on PTB AOR 0.99 (0.93–1.06) or SGA AOR 0.96 (0.91–1.01) In multivariable analysis paternal BMI did not significantly affect the outcomes	Spontaneous PTB, SGA Adjusted for maternal factors	Medium
Nahum and Stanislaw (2003), USA	Cohort study	241 children	Association between paternal height and child BW ($P = 0.02$) The addition in term BW attributable to each unit increase in paternal height was 10 g/cm No significant association between paternal weight and child BW	BW Adjusted for maternal and pregnancy-specific factors	Low
Pritchard *et al.* (1983), UK	Cohort study	5834 children	The SD scores for BW for taller men were constantly higher than for shorter men. The average difference was 0.29 (approx. 115 g) for firstborn boys at 40 weeks gestation	BW Adjusted for maternal height	High

Continued

Table VII *Continued*

Author, year, country	Study design	Number of children	Results	Outcomes Comments Adjustments	Quality
To *et al.* (1998), China	Cohort study	355 children born at term	Association between paternal height and child BW ($P < 0.01$) No association between paternal weight and child ($P = 0.052$) No association between paternal BMI and child BW ($P = 0.329$)	BW Analysis of variance of BW adjusted for gestation and controlled for maternal height and pre-pregnancy weight	Medium
Wilcox *et al.* (1995), UK	Cohort study	571 children	Correlation between paternal height and child BW ($P = 0.0115$) No correlation between paternal weight and child BW ($P = 0.2050$)	BW Adjusted for parental smoking, maternal height, paternal weight	
Winikoff and Debrovner (1981), USA	Cohort study	259 children	Paternal height was significantly associated with variations in child BW ($P < 0.05$)	BW Adjusted for maternal height, paternal weight, maternal pre-pregnancy weight, weight during pregnancy	Medium

significant association between paternal smoking and anorectal malformations (AOR 1.8, 95% CI 1.1–2.9) (van Rooij *et al.*, 2010). Our meta-analysis, including two studies of paternal smoking and orofacial clefts, showed a positive association, with a pooled estimate of 1.51 (95% CI 1.16–1.97) (Fig. 18). However, none of the other birth defects we explored showed a significant association with paternal smoking.

Conclusion: Paternal smoking may be associated with a modest increase in CHD and orofacial clefts. Low certainty of evidence (GRADE⊕⊕◯◯).

Paternal smoking at childbirth and long-term outcomes for offspring

Cancer

Five studies explored the association between paternal smoking during pregnancy and cancers in offspring (Supplementary Table SIII, Table X). Of these, three studies divided smoking into two sharply distinguished classifications, smoking/non-smoking, but only reported dose-response estimates (Ji *et al.*, 1997; Sorahan *et al.*, 2001; Pang *et al.*, 2003). In the use of cigarettes >5 pack-years, Ji *et al.* (1997) found a significant association between paternal smoking and cancer in offspring (AOR 1.7, 95% CI 1.2–2.5). Likewise Sorahan *et al.* (2001) showed a significant association between smoking and cancer: 10 to 19 cigarettes per day (AOR 1.63, 95% CI 1.10–2.41) and 20–29 cigarettes per day (AOR 1.46, (95% CI 1.05–2.03). However, Pang *et al.* (2003) did not show an association between cancer and the father smoking >20 cigarettes per day. In the two studies with the smoking/non-smoking dichotomy, Sorahan and Lancashire (2004) showed a significant association between smoking and cancer in offspring (AOR 1.28, 95% CI 1.15–1.42), while John *et al.* (1991) did not. Childhood acute leukaemia and brain tumours are dealt with in the sections below, while paternal smoking was not associated with any of the specific cancers in any of the studies.

Conclusion: Paternal smoking during pregnancy may be associated with a modest increase in cancer in offspring. Low certainty of evidence (GRADE⊕⊕◯◯).

Acute childhood leukaemia. Out of 19 original studies, two were of medium and 17 of low quality (Supplementary Table SIII, Table X). Studies rated as low quality included only a few cases, and the information on paternal smoking in the preconception period and during pregnancy was collected retrospectively from mothers several years after birth. The majority of studies found no association between maternal smoking and childhood leukaemia, hence they did not adjust for maternal smoking in the analyses of paternal smoking.

Acute lymphoblastic leukaemia. Two meta-analyses on paternal smoking and ALL have been published (Liu *et al.*, 2011; Milne *et al.*, 2012). Milne *et al.* (2012) included both a meta-analysis and original data in their paper (Table X). All 10 studies included in the meta-analysis by Milne *et al.* (2012) were also included in the meta-analysis by Liu *et al.* (2011), except for the original data: the latter meta-analysis included 18 case control studies. Thirteen studies explored paternal smoking during the preconception period (AOR 1.25, 95% CI 1.08–1.46) and eight studies during pregnancy (AOR 1.24, 95% CI 1.07–1.43). Their dose–response analysis estimated a higher risk

Table VIII Studies on the association of paternal BMI, height and weight with long-term outcomes in offspring

Author, year, country	Study design	Number of children	Results	Outcomes Comments Adjustments	Quality
Original studies *n* = 14					
Catalano *et al.* (2009), USA	Case control study	89 children (52 from NGT and 37 from GDM pregnancies	Paternal weight at the time birth was greater in children in tertile 3 of weight percentiles compared to children in tertile 1 at follow-up at 8.8 ± 1.8 years No difference in paternal BMI at the time of child's birth in relation to tertiles of percentage body fat of the child	Childhood weight and body fat (measured by dual energy X-ray absorptiometry) at follow-up Reference: Centers for Disease Control and Prevention (CDC) weight and body fat percentiles Maternal obstetrical data, paternal anthropometric data and neonatal birth data was included to best determine which combination of perinatal factors best modelled the risk of adiposity in child Maternal pre-pregnancy BMI was the strongest predictor of childhood obesity	Medium
Cawley *et al.* (1954), UK	Cohort study	1028 children	Infant weight was more highly correlated with height of mother than father. Correlation of infant height and weight at 24 months; mother 0.21, father 0.13	Weight of 625 children with observations at all intervals (6, 9, 12 and 24 months) Adjusted for maternal height	Medium
Daraki *et al.* (2017), Greece	Cohort study	772 children	Paternal obesity not associated with child neurodevelopment at 4 years of age	Child neurodevelopment Adjusted for maternal BMI	Medium
Davey Smith *et al.* (2007), UK	Cohort study	4654 children	The association between paternal BMI and offspring BMI at 7.5 years of age:0.202 standardised age and sex adjusted coefficient (0.175–0.229), similar to maternal BMI	Childhood BMI Standardised regression coefficients age and sex adjusted Sensitivity analysis for non-paternity performed Maternal and paternal BMI were included in the same model.	High
Durmus *et al.* (2011), The Netherlands	Cohort study	5674 children	Pre-pregnancy paternal BMI was strongly associated with childhood overweight at the age of 4 years The main effects of maternal BMI on childhood BMI were stronger than the main effects of paternal BMI ($P < 0.001$; and $P = 0.013$, respectively) As compared to children from parents with normal BMI, children from two obese parents had an increased risk of overweight at the age of years, OR 6.52 (3.44–12.38)	Childhood height, weight and BMI. Maternal BMI had a significantly stronger effect on childhood BMI Adjusted for maternal BMI	High
Heppe *et al.* (2013), The Netherlands	Cohort study	3610 children	Higher paternal BMI associated with higher risk of preschool overweight: OR 1.35 (1.19–1.53)	Preschool overweight Values reflect the OR and 95% CI for each parental or child characteristics that remained in the backward selection model. Maternal pre-pregnancy BMI in the model	High
Jaaskelainen *et al.* (2011), Finland	Cohort study (NFBC 1986)	4788 children	Paternal pre-pregnancy obesity strongly predicted overweight: At 16 years of age: Father–son OR 3.17 (1.70–5.92) Father–daughter OR 5.58 (3.09–10.07) If both parents obese, overweight of the child at 16 years: Sons OR 5.66 (3.12–10.27) Daughters OR 14.84 (7.41–29.73)	Childhood overweight Long-term overweight of both parents had a greater impact on the risk of offspring overweight than parental weight gain from normal weight to overweight/obesity during the 16-year follow-up period	High
Lawlor *et al.* (2007), Australia	Cohort study	7223 children	The increase in standardized offspring BMI at age 14 for a one SD increase in paternal BMI was 0.239 SD (0.197–0.282)	Childhood BMI The maternal-offspring BMI association was stronger than the paternal-offspring BMI association Paternal coefficient adjusted for maternal effect	Medium

Continued

Table VIII *Continued*

Author, year, country	Study design	Number of children	Results	Outcomes Comments Adjustments	Quality
Lawlor *et al.* (2008), UK	Cohort study	4091 children	As assessed at 9 to 11 years of age, mean difference in offspring sex- and age-standardized fat mass z-score per 1 SD BMI 0.24 (0.22–0.26) for maternal BMI versus 0.13 (0.11–0.15) for paternal BMI	Offspring fat and lean mass (measured by dual energy X-ray absorptiometry) Adjusted for maternal BMI Maternal effect size association was larger	Medium
Linabery *et al.* (2013), USA	Cohort study	912 children	Infants of obese fathers had BMI growth curves distinct from those of normal weight fathers. The p value for the global association between paternal BMI category and infant BMI growth curves (birth-3.5 years) from joint mixed effect model was 0.02	Infant BMI Maternal BMI has a stronger influence on BMI growth than paternal BMI Missing exposure (11% maternal and 26% paternal BMIs) and covariate data were assumed to be missing at random and imputed, outcomes were not imputed Adjusted for maternal BMI in the joint model	Medium
O'Callaghan *et al.* (1997), Australia	Cohort study	4062 children	Paternal BMI is independent predictor of severe and moderate obesity at 5 years of age. Paternal BMI percentiles 85–94: Severe obesity RR 2.8 (1.8–4.5) Moderate obesity RR 1.0 (0.6–1.5) Paternal BMI percentiles >95: Severe obesity RR 2.0 (1.1–3.6) Moderate obesity RR 2.1 (1.4–3.3)	Offspring obesity (BMI class) Reference category: paternal BMI percentiles 15–84	Medium
Reilly *et al.* (2005), UK	Cohort study	7758 children	Paternal obesity was associated with the risk of obesity in children at 7 years of age. Final model AOR: Father (BMI > 30) 2.54 (1.72–3.75) compared to both parents with BMI < 30. As compared to children from parents with normal BMI, children from two obese parents had an increased risk of overweight at the age of 4 years: OR 6.52 (3.44–12.38)	Offspring obesity based on BMI Maternal and paternal BMI were entered in the logistic regression models with risk of severe or moderate obesity as the dependent variable	Medium
Suren *et al.* (2014), Norway	Cohort study	92 909 children	ASD in children at the age of 4.0–13.1 (mean 7.4) years: Paternal BMI > 30: versus BMI < 25 AOR 1.73 (1.07–2.82) Asperger disorder in children aged ≥7 years: Paternal BMI > 30 versus BMI < 25 AOR 2.01(1.13–3.57)	ASDs Adjusted for maternal BMI	Medium
Yeung *et al.* (2017), USA	Cohort study	4821 children	Increased risk of failing the personal-social domain in children up to 3 years of age Paternal BMI > 30 compared with children of normal weight fathers AOR 1.71 (1.08–2.70) Children whose parents both had BMI ≥35 were likely to additionally fail the problem-solving domain	Delays in childhood development Adjusted for maternal obesity	Medium

ASD, autism spectrum disorder; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; RR, relative risk;

Table IX Studies on the association of paternal smoking with obstetric outcomes and birth defects in offspring

Author, year, country	Study design	Number of deliveries or children	Result		Quality
			Outcomes (Risk estimates)	Comment Adjustments	
Obstetric outcomes *n* = 8					
Andriani and Kuo (2014), Taiwan	Cohort 1993–2007	3789 children 71.5% paternal smoking with non-smoking mothers 2.4% only mother smoking	LBW Only father smoking during pregnancy AOR 0.89 (0.51–1.54) 1–10 cig/day AOR 0.81 (0.58–1.14)* 11–20 cig/day AOR 0.66 (0.46–0.94)* ≥20 cig/day AOR 2.09 (1.38–3.17)* PTB Only father smoking during pregnancy AOR 1.16 (0.78–1.71) 1–10 cig/day AOR 0.51 (0.34–0.75)* 11–20 cig/day AOR 0.78 (0.55–1.11)* ≥20 cig/day AOR 2.11 (1.38–3.23)*	Questionnaires to both parents Adjusted for sex, birth order, maternal age, father's education, maternal employment status, parental BMI, household income, urban/rural residence *Only adjusted for birth order	Medium
Gaizauskiene *et al.* (2007), Lithuania	Birth Registry study 2002	296 Perinatal death (199 stillborn + 97 died within the first six days after delivery) Total cohort *N* = 29 619	Perinatal death Paternal smoking AOR 1.6 (1.4–2.2) Paternal smoking without maternal smoking AOR 1.72 (no CI)	Confounders 45 parameters Maternal age < or ≥36 years Education, marriage/cohabiting	Low
Horta *et al.* (1997), Brazil	Cohort 1993	5166 singleton live birth 2237 (43.3%) paternal smoking	LBW: AOR 1.18 (0.94–1.48) PTB: AOR 1.25 (0.99–1.57) IUGR: AOR 1.33 (1.05–1.68)	Mothers interviewed soon after delivery by trained interviewers Adjusted for social class, maternal schooling, parity, birth interval, prior LBW, maternal height, number of antenatal care visits and for maternal smoking	Medium
Inoue *et al.* (2016), Japan	Prospective hospital cohort study 1997–2010	Total 21 855 newborn Present study 16 396 Non-participants 5459 (25%) Smoking: 5905 Mother no/Father yes	LBW Smoking only fathers 502 children with LBW AOR 1.07 (0.94–1.22)	Birth after GA 37 weeks Mothers interviewed in 1. trimester Adjusted for maternal smoking, paternal smoking (or four types of combination of interaction effect), maternal age, paternal age, maternal BMI, maternal occupational status, parity, sex	Medium
Ko *et al.* (2014), Taiwan	Birth Cohort study 2005–2006	Total 24 200 children Interview rate 87.8% Included 21 248 children	LBW, PTB, SGA Preconception >20 cigarettes per day: PTB, *n* = 101/1158 (8.7%) AOR 1.07 (0.84–1.35) LBW, *n* = 84/1158 (7.3%) AOR 1.14 (0.87–1.27) SGA, *n* = 114/1158 (9.8%) AOR 1.12 (0.90–1.40)	Interview 6 months post-partum (mothers) Adjusted for maternal age, nationality, education, parity, total weight gain during pregnancy, gender of infant, multiple birth and maternal smoking in the same period Similar results for smoking in 1. or 2–3 trimester	Medium
Magnus *et al.* (1984), Norway	Cohort study 1967–1979	3130 singletons 11 175 pairs of like-sexed twins born 1915–1960 Singletons born 1967–1979	Birth weight Correlation matrix Paternal smoking Regression coefficients (+/− SE) Bivariate regression −48 (8.9) $P < 0.01$	Paternal height and weight, Maternal height and weight, paternal and maternal education, SES, maternal smoking Correlation matrix	Low

Continued

Table IX *Continued*

Author, year, country	Study design	Number of deliveries or children	Result		Quality
			Outcomes (Risk estimates)	Comment Adjustments	
			Multiple regression −4.9 (9.3) NS		
Martinez *et al.* (1994), USA	Cohort study	1596 eligible children 350 refused (22%) 1219 respondents 191 father smoking 992 mother non-smoking 907 non-smoking mothers in multiple regression analyses	Birth weight Paternal with non-smoking mother: None: 3602 g ± 401 1–10:3573 g ± 388 11–20:3520 g ± 382 >20:3514 g ± 428 *P* for linearity 0.026 88 g adjusted BW difference *P* for linearity = 0.026	Hospital data at birth + questionnaire ≤1 months after birth by parents Multiple regression analysis for non-smoking Mothers. Adjusted for GA, birth order, ethnicity, maternal and paternal education, maternal age, sex	Medium
Zhang and Ratcliffe (1993), Shanghai	Case control 1986–1987	1785 full term singleton live born normal infants of non-smoking mothers 1033 exposed to paternal smoking 752 non-exposed	Birth weight 3236 g versus 3262 g Birth weight diff 26 g (NS) Multiple linear regression 30 g (95% CI = −7.66)	Pretested in-hospital interview to mothers after delivery Adjusted for parity, maternal age, gestational age, maternal occupation. Modestly adverse effect on birth weight	Low
Birth defects *n* = 8					
Cresci *et al.* (2011), Italy	Case control 2008–2010	360 cases 360 controls	CHD Paternal smoking OR 1.7(1.1–2.6) Paternal smoking ≥15 cigarettes per day: OR 2.1 (1.3–3.5)	Questionnaires to both parents. Matched for age range Unconditional regression adjusted for potential confounders but not specified Maternal smoking insignificant but not directly adjusted for	Low
Deng *et al.* (2013), China	Case control 2010–2011	284 cases 422 controls Subgroups Light smoking 1–9 cig/day Medium 10–19 cig/day Heavy ≥ 20 cig/day	Non-syndromic CHD Paternal smoking during peri-conception period (3 months before pregnancy and first trimester) and non-smoking mothers No avoidance behaviour: Septal defects: 37 cases/46 controls AOR 2.52 (1.39–4.59) Cono-truncal defects: 36 cases/46 controls AOR 3.22 (1.75–5.93) Other outcomes listed but less than 20 cases	Maternal face-to-face interview Adjusted for residence, age, education, pre-pregnant BMI, alcohol use, folic acid use, paternal alcohol and family history of CHD	Low
Figueiredo *et al.* (2015), USA	Prospective case control Democratic Republic of Congo, Vietnam, Philippines, Honduras	430 cases 754 controls Fathers smoking 173 cases 245 controls	Orofacial cleft Paternal smoking 3 months before and during pregnancy AOR1.5 (1.1–1.9)	Interview of mothers Age <3 years Adjusted for sex, parental employment and education and age, location at birth rural/city, country Maternal smoking infrequent - only 1.4–1.9%	Medium
Krapels *et al.* (2006), The Netherlands	Case control	350 cases 222 controls Fathers smoking >10 cig/day 62 Cleft lip +/− cleft palate 17 Cleft palate only	Orofacial cleft Univariate analyses paternal smoking: >10 cigarettes per day: Cleft lip with or without cleft palate: OR 1.5 (1.0–2.4) Cleft palate only: OR 1.8 (0.9–3.5)	Questionnaires to both parents Follow-up two years after the peri-conception period Multivariate analyses are not shown for paternal smoking but was not significant	Low
	Case control register study	261 newborns	Congenital heart septal defects		Low

Kuciene and Dulskiene (2010), Lithuania	1995–2005	1122 randomly selected newborns without any defects 106 Only fathers smoking	Only father smoking AOR 1.45(1.03–2.03)	Interviews of both parents, mostly mothersAdjusted for maternal education, social status, and marital status	
Savitz et al. (1991), USA	Cohort study of singleton live births 1959–1966	19 044 live born 14 685 births for analysis Youngest child 5 years of age at update in 1972	Congenital anomalies Paternal smoking Cleft lip with or without cleft palate: POR 1.7 (0.5–6.0) Hydrocephalus: POR 2.4 (0.6–9.3) Ventricular septal defect: POR 2.0 (0.9–4.3) Urethral stenosis: POR 2.0 (0.6–6.4)	Interview by mothers at first prenatal care visit Adjusted for maternal age, race, education and maternal smoking	Medium
van Rooij et al. (2010), The Netherlands	Case control 1996–2008	85 cases 650 controls 41 paternal smoking 3 months before conception	Anorectal malformations Paternal smoking 3 months before conception: OR 1.8 (1.1–2.9)	Questionnaire to parents Median age: 5–6 years Multiple adjustments but estimate not confounded by any covariate Maternal smoking insignificant but not directly adjusted for.	Low
Wasserman et al. (1996), USA	Case control 1987–1988	207 Cono-truncal heart 264 Neural tube 178 Limb reduction defects 481 Controls	Birth defects Father only smokers: Cono-truncal heart: 35/90 OR 0.93 (0.58–1.5) Neural tube: 59/90 OR 1.1 (0.76–1.7) Limb reduction defect: 41/90 OR 1.4 (0.88–2.2)	Telephone interview of mothers Paternal smoking 1 month before through 3 months after conception. Risk estimates were adjusted for selected non-specified covariates did not differ substantially from crude estimates.	Low

IUGR, intrauterine growth retardation; POR, prevalence odds ratio;

associated with an increased number of cigarettes a day (CPD), >20 CPD (AOR 1.30; 95% CI 1.09–1.55) (Liu *et al.*, 2011). Milne *et al.* (2012) also found a significantly increased risk of ALL when fathers smoked around the time of conception (AOR 1.15, 95% CI 1.06–1.24). For >20 CPD their meta-analysis included seven studies (AOR 1.44, 95% CI 1.24–1.68).

Three low quality studies out of the 17 original studies in this systematic review were not included in the meta-analysis. Castro-Jimenez and Orozco-Vargas (2011) included 85 matched pairs and found AOR 1.93 (95% CI 1.06–3.54), Farioli *et al.* (2014) included only risk estimates according to the following categories 1–10 CPD (AOR 0.86, 95% CI 0.58–1.26) and >10 CPD (AOR 0.74 (95% CI 0.51–1.05). The Metayer *et al.* (2013) study was an expansion of Chang's (Chang *et al.*, 2006) (included in both meta-analyses) and found an AOR 0.94 (95% CI 0.69–1.27). Based on the meta-analyses, paternal smoking was associated with a 15–25% increased risk of ALL.

Conclusion: Paternal smoking may be associated with a slightly higher risk of childhood ALL. Low certainty of evidence (GRADE⊕⊕OO).

Acute myeloid leukaemia. Twelve original studies (two of medium quality and 10 of low quality) evaluated the outcome of paternal smoking on acute myeloid leukaemia (AML) (Supplementary Table SIII, Table X). The meta-analysis included eight studies and two unpublished reports. Figures for paternal smoking prior to conception were AOR 1.19 (95% CI 1.00–1.41) and during pregnancy AOR 1.28 (95% CI 1.05–1.57). All original studies in our systematic review are included in the meta-analysis.

Conclusion: There appears to be little or no association between paternal smoking and childhood AML. Low certainty of evidence (GRADE⊕⊕OO).

Brain tumours. Fourteen studies explored the association between paternal smoking prior to and during pregnancy, and brain tumours (Supplementary Table SIII, Table X). All were included in our meta-analysis, which showed a significant association between paternal smoking and brain tumours (pooled estimate 1.12, 95% CI 1.03–1.22) (Fig. 19).

Conclusion: Paternal smoking may be associated with a small increase in childhood brain tumours. Low certainty of evidence (GRADE⊕⊕OO)

Cardio-metabolic outcomes. Nine cohort studies of medium quality assessed paternal smoking and cardio-metabolic outcomes in offspring (Supplementary Table SIII, Table X). Five studies examined BMI (Leary *et al.*, 2006; Kwok *et al.*, 2010; Durmus *et al.*, 2011; Howe *et al.*, 2012; Florath *et al.*, 2014), three studies looked at blood pressure and hypertension (Brion *et al.*, 2007; de Jonge *et al.*, 2013; Taal *et al.*, 2013), and one study explored DM type 1 (Toschke *et al.*, 2007). Due to the heterogeneity of the studies, meta-analyses could not be performed for any of these outcomes.

The BMI of children was measured at various ages in the five studies and the results diverged. In two of the studies, no linear associations were observed between paternal smoking and BMI (Durmus *et al.*, 2011; Howe *et al.*, 2012). However, three studies showed a negative linear association between paternal smoking and BMI in children aged 7 to 10 years (Leary *et al.*, 2006; Kwok *et al.*, 2010; Florath *et al.*, 2014).

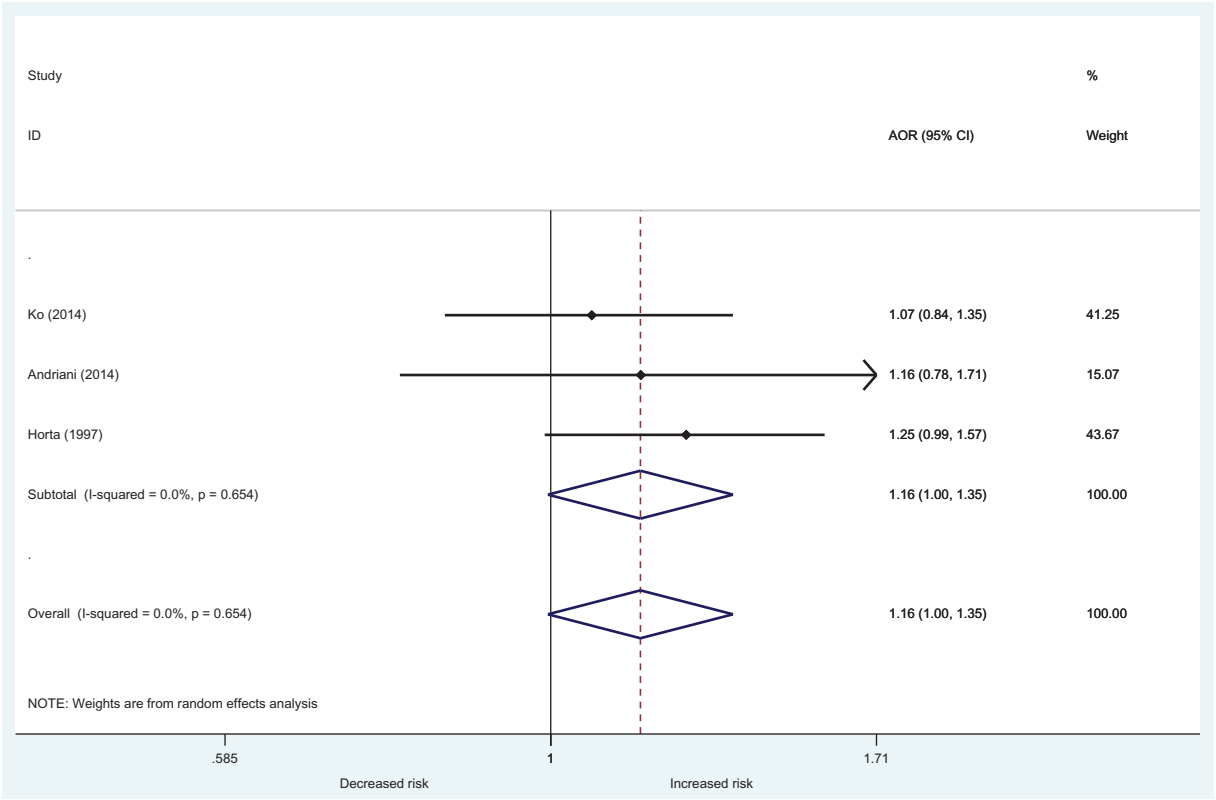

Figure 14 Forest plot describing the association between paternal smoking and risk for PTB.

Brion *et al.* (2007) and Taal *et al.* (2013) showed no association between paternal smoking and diastolic or systolic BP in offspring in the adjusted models, neither did de Jonge *et al.* (2013) show any association between paternal smoking and hypertension in daughters. Toschke *et al.* (2007), in two combined cohorts, showed significantly lower risk estimates of DM type 1 in children where fathers smoked during pregnancy (AOR 0.44, 95% CI 0.25–0.75).

Conclusion: It is uncertain whether there is any association between paternal smoking and BMI in offspring. Very low certainty of evidence (GRADE⊕◯◯◯). There may be little or no association between paternal smoking and blood pressure in offspring. Low certainty of evidence (GRADE⊕⊕◯◯). It is uncertain whether there is any association between paternal smoking and DM type 1 in the offspring. Very low certainty of evidence (GRADE⊕◯◯◯).

Neuro-developmental outcomes

Six cohort studies explored the association between paternal smoking and neuro-developmental outcomes, out of which three cohort studies studied ADHD (Nomura *et al.*, 2010; Langley *et al.*, 2012; Zhu *et al.*, 2014) (Supplementary Table SIII, Table X). All studies were heterogeneous regarding child age, questionnaires used for the parents, and outcome measures. Two of the studies found a significant association between paternal smoking and ADHD (AOR ranging from 1.29–1.42) (Langley *et al.*, 2012; Zhu *et al.*, 2014), while Nomura *et al.* (2010) found no significantly increased risk (AOR 0.31, 95% CI 0.06–1.92). In Langley *et al.* (2012) and Zhu *et al.* (2014) the children were 7 and 8 years of age, while the children in Nomura *et al.* (2010) were only 3 and 4 years old. None of the other studies found any associations between paternal smoking and neuro-developmental outcomes, except Brion *et al.* (2010), who found a significant association between paternal smoking and conduct/externalizing problems (AOR 1.12, 95% CI 1.02–1.24).

Conclusion: Paternal smoking may be associated with a small increase in ADHD. Low certainty of evidence (GRADE⊕⊕◯◯). It is uncertain if there is any association between paternal smoking and other neuro-developmental outcomes. Very low certainty of evidence (GRADE⊕◯◯◯).

Discussion

General discussion

In this systematic review and meta-analysis we have tried to summarize the evidence for the effect of paternal factors on perinatal and paediatric outcomes. Paternal factors investigated in the present paper were paternal age and life-style factors, in particular smoking and BMI/height/weight of the fathers at time of conception. Other exposures, such as male subfertility and teratogenic drugs, have not been included in the present systematic review. Table XI presents a summary of the findings from the meta-analyses.

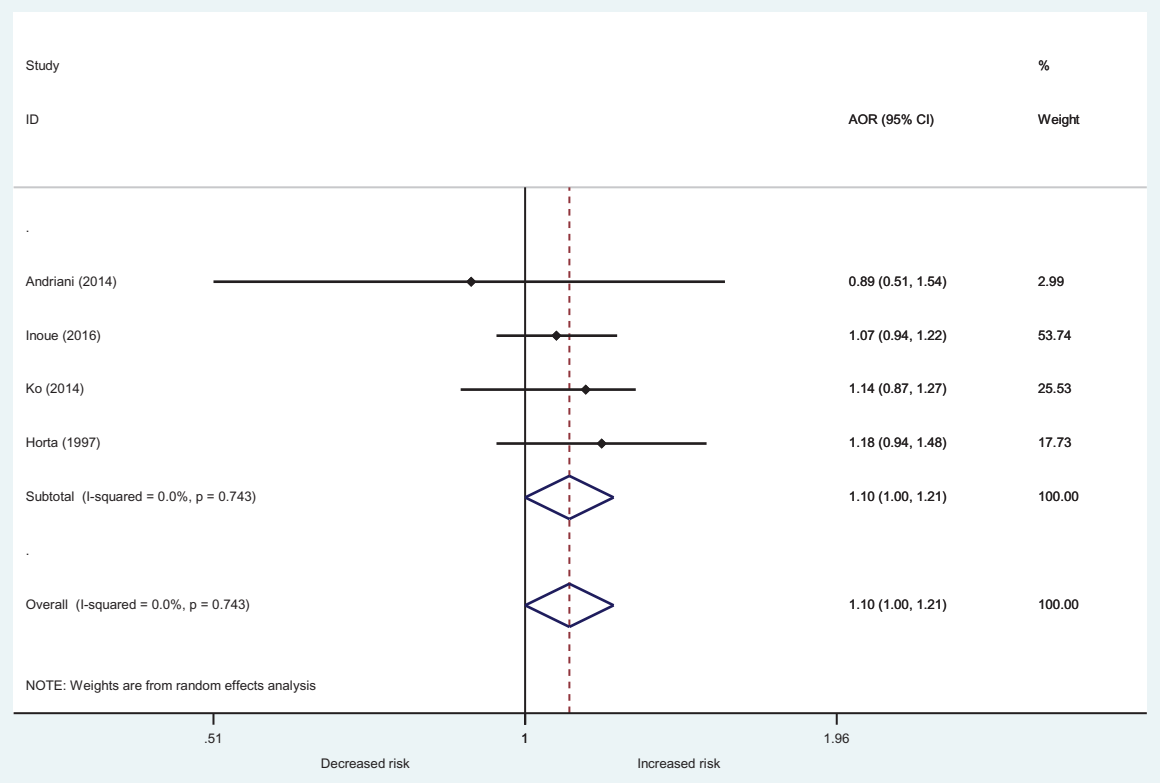

Figure 15 Forest plot describing the association between paternal smoking and risk for LBW in offspring.

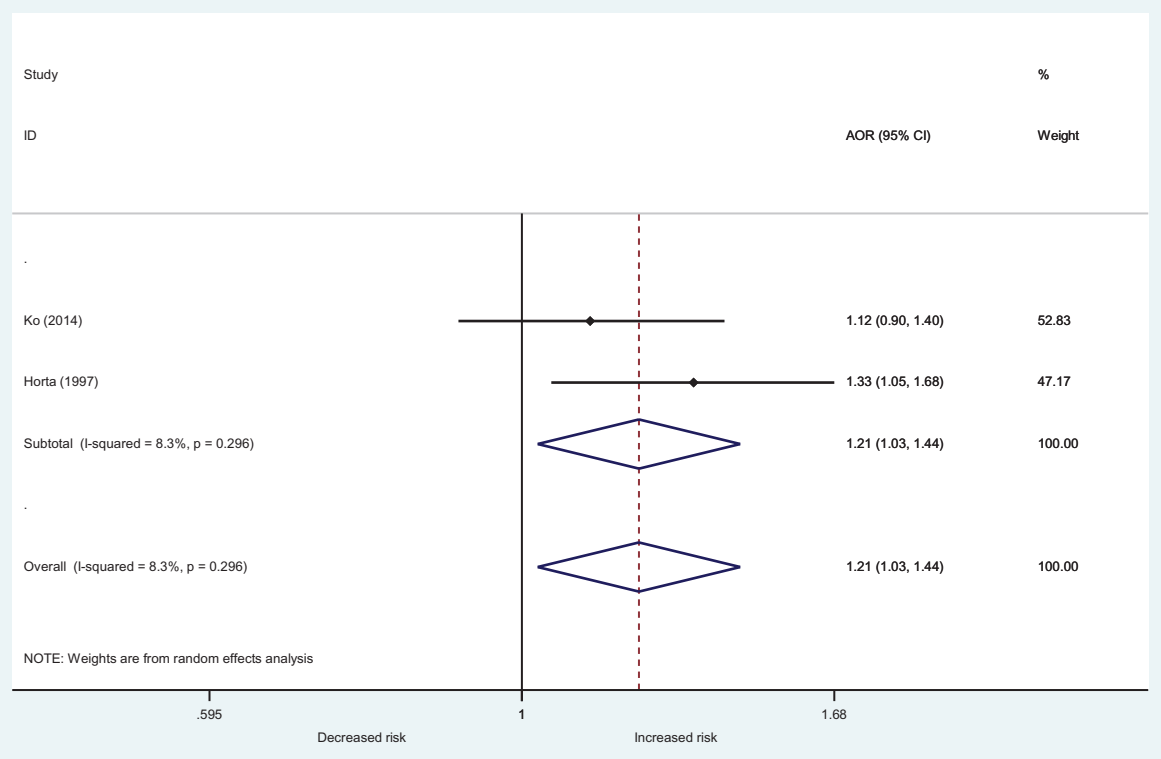

Figure 16 Forest plot describing the association between paternal smoking and risk for SGA in offspring.

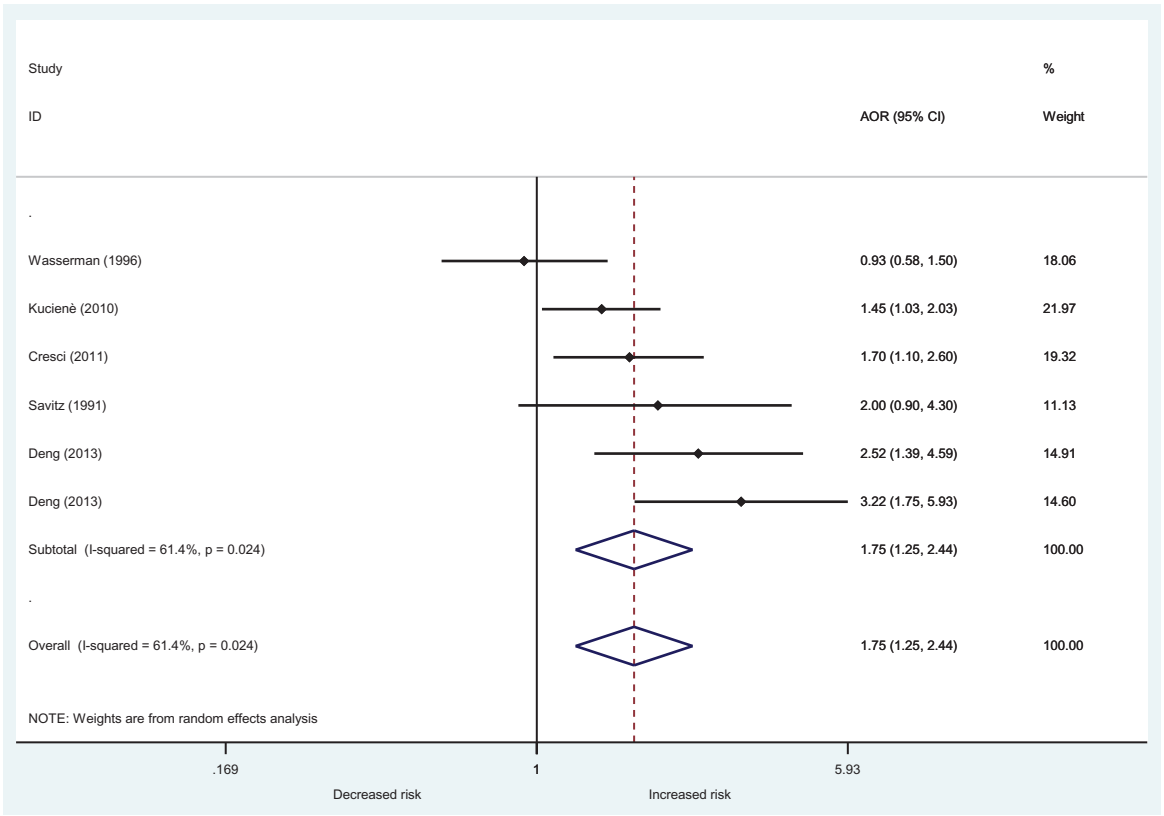

Figure 17 Forest plot describing the association between paternal smoking and risk for CHDs in offspring.

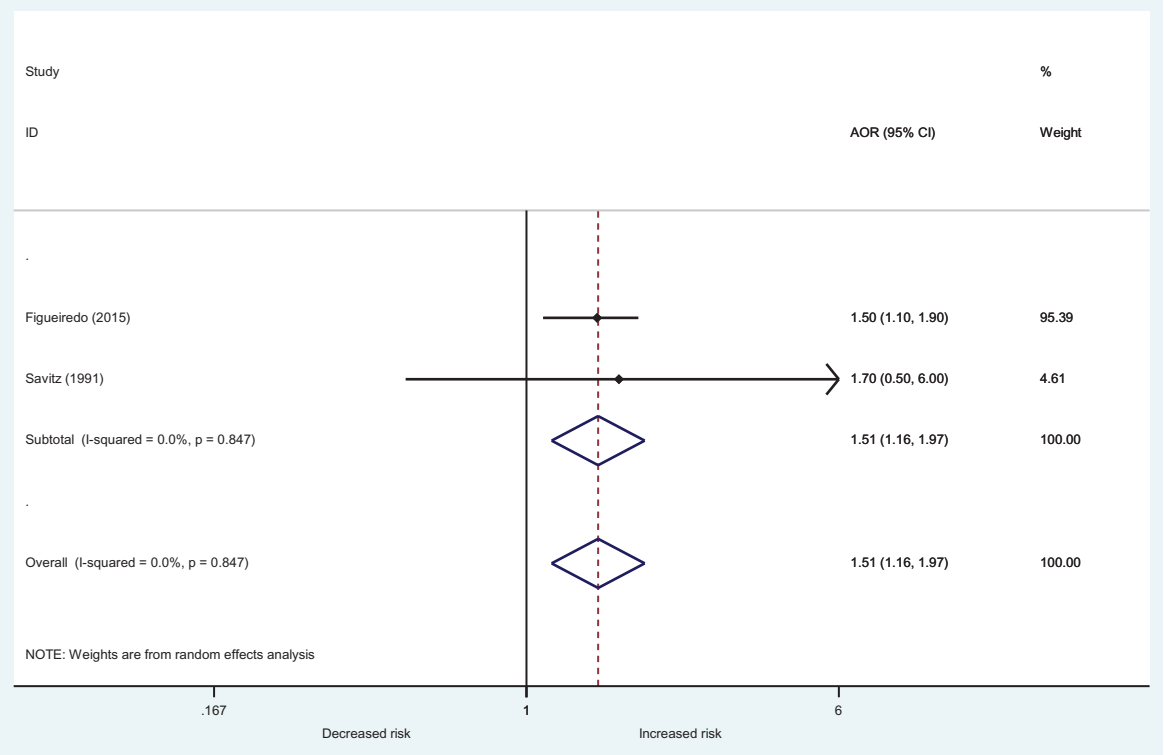

Figure 18 Forest plot describing the association between paternal smoking and risk for orofacial clefts.

Table X Studies on the association of paternal smoking with long-term outcomes in offspring.

Author, year, country	Study design	Number of deliveries and children	Result Outcomes (Risk estimates)	Outcomes Adjustments	Quality assessment
Cancer					
Acute childhood leukaemia **Meta-analyses *n* = 3**					
Metayer *et al.* (2016), USA	SR with meta-analysis Pooled analyses of CLIC studies	Childhood Leukaemia International Consortium (CLIC) studies: Meta-analyses including 6–9 CLIC studies and 3–4 Non-CLIC studies Pooled analysis of 12 case control studies with 1330 AML 13 169 controls	AML Paternal smoking during preconception period MA (CLIC+non-CLIC): AOR 1.19 (1.00–1.41) Pooled CLIC studies: AOR 1.18 (1.01–1.38)* Paternal smoking during pregnancy MA (CLIC+non-CLIC): AOR 1.28 (1.05–1.57) Pooled CLIC studies: AOR 1.24 (1.06–1.46)* Paternal ever smoking MA (CLIC+non-CLCI): AOR 1.18 (0.92–1.51) Pooled CLIC studies: AOR1.34 (1.11–1.62)*	Interview with mothers and/or fathers, age <15 yrs Adjusted for age, sex, ethnicity, paternal education, study centre *Similar results for analyses including only non-smoking mothers (data not shown) Dose-response relationship with paternal smoking Maternal smoking had no effect in pooled CLIC analysis or meta-analysis and is not adjusted for High correlation between pre-and postnatal paternal smoking. Limited ability to identify specific windows of exposure	Medium
Milne *et al.* (2012), Australia	SR and meta-analysis 10 case control studies, including own study	Any versus none:10 studies 5338 cases Controls: NA >20 CPD:7 studies 2118 cases Controls: NA	ALL Paternal smoking around the time of conception: Any versus none: OR 1.15 (1.06–1.24) >20 CPD: OR 1.44 (1.24–1.68)	All studies except own study by Milne *et al.* (2012) are also included in the meta-analysis by Liu *et al.* (2011)	Low
Liu *et al.* (2011), USA	SR and meta-analysis, 18 case control studies	Preconception: 13 studies Cases and controls: NA	ALL Paternal smoking during preconception: AOR 1.25 (1.08–1.46)* Paternal smoking during pregnancy: AOR 1.24 (1.07–1.43) Dose-response a. >10 CPD; b. 10–19; c.>20 a. AOR 1.17 (0.9–1.54) b. AOR 1.25 (1.01–1.55) c. AOR 1.30 (1.09–1.55)	Primarily interviews by mothers Age 18 month to 18 years Most studies matched and adjusted for potential confounders *Only 5 studies included in MA adjusted for maternal smoking Also, a positive association between ALL and paternal ever smoking and at each exposure time period examined	Medium
Original articles *n* = 19					
Brondum *et al.* (1999), USA	Case control (CCG study) 1989–93	1618 ALL 1722 controls 450 AML 523 controls	ALL Paternal smoking 1 month before pregnancy AOR 1.07 (0.90–1.27) Father (not mother) ever smoked (*n* = 1842) AOR 1.04 (0.86–1.26) AML Paternal smoking 1 month before pregnancy AOR 0.87 (0.64–1.18) Father (not mother) ever smoked (*n* = 517) AOR 1.32 (0.91–1.93)	Telephone interview with parents mostly mothers Child age: ALL <15 years, AML <18 years Matched by age, race, telephone code area Adjusted for annual income, father's and mother's exposures, race and education No association with maternal smoking, parental years of smoking, or number of pack-years	Medium
	Case control	85 cases	ALL	Face-to-face interview with parents	Low

Continued

Table X *Continued*

Author, year, country	Study design	Number of deliveries and children	Result Outcomes (Risk estimates)	Outcomes Adjustments	Quality assessment
Castro-Jimenez and Orozco-Vargas (2011), Colombia	2000–2005	85 controls	Paternal preconception smoking AOR 1.93 (1.06–3.54)	Age <15 years Matched control sex, age, region Not adjusted for maternal smoking but of no significance	
Chang *et al.* (2006), USA	Case control 1995–2002 (Northern California Childhood leukaemia study)	281 ALL 46 AML 416 controls Paternal preconception smoking ALL: 74 cases 70 controls AML: 16 cases 8 controls	ALL Paternal preconception smoking AOR 1.32 (0.86–2.04) AML Paternal preconception smoking AOR 3.84 (1.04–14.17)	Self-administered questionnaire/in-person interview of mothers Age <15 years Matched on age, maternal race, and Hispanic ethnicity. Adjusting for household income Maternal smoking was not associated with increased risk of ALL or AML Data included in Metayer *et al.* (2013)	Low
Farioli *et al.* (2014), Italy	Case control 1998–2003 (SETIL study)	557 cases 855 controls 1–10 CPD: 77 cases 108 controls >10 CPD: 151 cases 222 controls	ALL Only paternal smoking 1–10 CPD in conception period AOR 0.86 (0.58–1.26) >10 CPD in conception period AOR 0.74 (0.51–1.05)	Personal interview with parents Age <10 years Mutually adjusted models also including paternal smoking during pregnancy and maternal smoking in first trimester Child second-hand-smoking (SHS), birth order, BW, duration of breast feeding, mat and pat age, educational level, birth year mother, parental exposure benzene	Low
Ji *et al.* (1997), China	Case control 1981–1991	642 cases 642 controls No maternal smoking Acute leukaemia 166 case control pairs Lymphoma 87 case control pairs	Cancer <2 Pack-years (PY) 2–5 PY >5 PY prior to conception Acute leukaemia AOR 2.4 (1.1–5.6)* ALL AOR 3.8 (1.3–12.3)* AML AOR 2.3 (0.4–14.8)* Lymphoma AOR 4.5 (1.2–16.8)* All cancers AOR 1.7 (1.2–2.5)*	Paternal and maternal interviews by trained interviewers Age <15 years. Matched for sex, year of birth Adjusted for BW, income, paternal age, education and alcohol For <5 PY there were no significant risk in any of the cancers	Low
John *et al.* (1991), USA	Case control 1976–83	223 cases 196 controls	Cancer Paternal smoking preconception period, absence of maternal smoking ALL: AOR 1.4 (0.6–3.1) Lymphomas: AOR 1.6 (0.5–5.4) Brain cancer: 1.6 (0.7–3.5) All cancers: AOR 1.2 (0.8–2.1)	Personal interview Prenatal exposure Age 0–14 years Matched for age, sex, area Absence of maternal smoking: Adjusted for father's education.	Low
Lee *et al.* (2009), Chorea	Case control 2003–2005	164 cases leukaemia 106 ALL 164 controls	All leukaemia and ALL PY before pregnancy All leukaemia: >10 PY: AOR 1.7 (0.9–3.3) ALL: >10 PY: AOR 1.6 (0.8–3.5)	Interview with mothers (93.5%) Age 0–18 years Matched for age and sex. Adjusted for age, gender, father's education and birth weight Maternal smoking was too small (6.1% in controls) to be evaluated in childhood leukaemia risk and was not considered further	Low
	Case control	399 cases	Acute leukaemia	Personal interviews with each child parents	Low

MacArthur *et al.* (2008), Canada	(the cross-Canada childhood leukaemia study) 1990–1994	399 controls 109 cases 96 controls	Paternal smoking before pregnancy: <10 CPD 10–19 CPD ≥20 CPD All leukaemia: AOR 0.99 (0.50–1.99) AOR 1.18 (0.70–1.20) AOR 1.14 (0.79–1.64) ALL: APR 0.87 (0.42–1.81) AOR 1.21 (0.70–2.08) AOR 1.15 (0.79–1.67) AML AOR 2.98 (0.70–12.75) AOR 0.93 (0.25–3.45) AOR 0.90 (0.34–2.38)	Age 0–14 years Matched for age, gender, area Conditional logistic regression Maternal age, mat education, household income, ethnicity, and no of residences since birth Not directly adjusted maternal Smoking, but maternal risk estimates did not change when paternal smoking patterns were considered	
Magnani *et al.* (1990)	Case control 1974–1980 1981–1984	142 ALL 22 AnLL 19 (NHL) 307 controls	Leukaemia and lymphoma Paternal smoking preconception and up to childbirth: ALL AOR 0.90 (0.57–1.42) AnLL AOR 0.9 (0.3–2.1) Lymphoma AOR 6.7 (1.0–43.4)	Personal Interview Mean age: Cases 6.1 (3.6) Control 6.6 (3.5) Four residence strata Adjusted for socio-economic status	Low
Mattioli *et al.* (2014), Italy	Case control (SETIL study) 1998–2003	82 AnLL cases 916 ALL cases 1044 controls (128 matched to AnLL and 916 matched to ALL cases)	Acute non-Lymphatic Leukaemia (AnLL) Paternal smoking in the conception period 1–10 CPD: AOR 1.34 (0.65–2.76) ≥11 CPD: AOR 1.79 (1.01–3.15)	Personal interview of parents Age 0–10 years Matched for date of birth, sex, residence Inverse probability weighting adjusting for sex, provenience, birth order, BW, breast feeding, parental educational level, age, birth year, occupational exposure to benzene Not directly adjusted maternal smoking but no association on AnLL and maternal smoking during pregnancy	Low
Menegaux *et al.* (2007), France	Case control 1995–1998	472 cases 407 ALL 62 AML 3 other 567 controls	Childhood acute leukaemia (ALL and AML) Paternal smoking 3 months before pregnancy All acute leukaemia ≤20 CPD: AOR 1.2 (0.9–1.6) >20CPD: AOR 1.0 (0.6–1.7) ALL ≤20 CPD: AOR 1.2 (0.9–1.6) >20 CPD: AOR 1.2 (0.7–2.0) AML ≤20 CPD: AOR 0.9 (0.5–1.7) >20 CPD: AOR 0.2 (0.02–1.7)	Standardised self- administered questionnaire to mothers Age <15 years Matched for age, gender, region Adjusted for matched age, gender, region, socio-professional category, birth order Not directly adjusted for maternal smoking but not significant	Low
Metayer *et al.* (2013), USA	Case control (NCCLS study) 1996–2008	767 ALL 135 AML 1139 controls	ALL and AML Paternal prenatal smoking (3 month before and/or during pregnancy) ALL: AOR 1.17 (0.91–1.50)* AML: AOR 1.36 (0.82–2.24)* Paternal prenatal smoking and child's passive smoking ALL: AOR 0.94 (0.69–1.27)** AML: AOR 1.14 (0.55–2.39)**	Phase 1: Self-administered questionnaire/ Phase 2: In-person interview of mainly mothers Age < 15 years Matched on age, maternal race, and Hispanic ethnicity Adjusting for matching variables and household income *Not adjusted for maternal smoking but no significant association with ALL or AML **adjusted for maternal prenatal smoking Expansion of Chang *et al.* (2006)	Low
Milne *et al.* (2012), Australia	Case control (Aus-ALL study) 2003–2006	388 cases 868 controls	ALL Paternal smoking during conception year: Any: AOR 1.22 (0.92–1.61) 1–14 CPD: AOR 1.00 (0.66–1.52)	Self-administered questionnaires from both parents Age <15 years Matched by age, sex, state of residence	Low

Continued

Table X *Continued*

Author, year, country	Study design	Number of deliveries and children	Result Outcomes (Risk estimates)	Outcomes Adjustments	Quality assessment
			>15 CPD: AOR 1.35 (0.98–1.86)	Adjusted for matching variables, paternal age, parental education, ethnicity Maternal smoking was not associated with ALL and paternal smoking unchanged when adjusted for maternal smoking (data not shown)	
Orsi *et al.* (2015), France	Case control (ESTELLE study) 2010–2011	747 CL 636 ALL 100 AML 1421 controls	All leukaemia (AL), ALL, AML Paternal preconception smoking: AL: AOR 1.3 (1.0–1.6) ALL: AOR 1.2 (0.9–1.6) AML: AOR 1.6 (1.0–2.8) Paternal smoking during pregnancy: AL: AOR 1.3 (1.1–1.6) ALL: AOR 1.3 (1.0–1.6) AML: AOR 1.6 (1.0–2.5)	Telephone interview with parents, mostly mothers Age <15 years Matched for age, sex Adjusted for age, sex, mother's age and education, birth order and maternal smoking	Low
Pang *et al.* (2003), UK	Case control (UKCCS) 1991–96	3585 case fathers 6987 control fathers	Leukaemia Paternal preconception smoking 1–19 CPD: AOR 1.12 (0.96–1.32) 20+ CPD: AOR 1.01 (0.87–1.17) ALL: AOR 1.04 (0.91–1.18) AML: AOR 1.07 (0.80–1.43)	Personal interview with parents Age <15 years Matched for sex, age, region Adjusted for matching variables, parental age, deprivation score	Medium
Rudant *et al.* (2008), France	Case control (ESCALE study) 2003–4	647 ALL 102 AML 1681 controls 128 HL 848 controls 164 NHL 1312 controls	Hematopoietic malignancies Paternal smoking from the year prior to the child's birth to the interview ALL: AOR 1.4 (1.1–1.7) AML: AOR 1.5 (1.0–2.3) Hodgkin's lymphoma (HL): AOR 1.2 (0.8–1.7) Non-Hodgkin's lymphoma (NHL): AOR 1.6 (1.1–2.3) <10 CPD: ALL: AOR 1.2 (0.8–1.6) AML: AOR 1.4 (0.7–2.9) HL: AOR 1.4 (0.7–2.6) NHL: AOR 1.5 (0.8–2.6) 10–19 CPD: ALL: AOR 1.2 (0.9–1.6) AML: AOR 1.3(0.7–2.4) HL: AOR 0.8 (0.4–1.6) NHL: AOR 1.7 (1.1–2.7) 20+ CPD: ALL: AOR 1.7 (1.3–2.1)* AML: AOR 1.7(1.0–2.9)** HL: AOR 1.2 (0.7–2.0) NHL: AOR 1.7 (1.1–2.6)***	Telephone interview of mothers Age <15 years Matched for age, gender Adjusted for age. Gender, parental professional category, maternal age at the time of birth Maternal smoking was not associated with significant increased risk Trend analyses: *$P < 0.0001$ **$P < 0.045$ ***$P < 0.01$	Low
Schuz *et al.* (1999), Germany	Case control (NW and NI study)	2354 cases 2588 controls	Acute leukaemia and NHL Paternal smoking before pregnancy	Questionnaire followed by telephone interview by parents Age <15years	Medium

	NW: 1992–97 NI: 1980–94	955 Acute leukaemia 955 controls 221 NHL 2540 controls	Acute leukaemia (ALL and AnLL) 1–10 CPD AOR 1.1 (0.8–1.5) 11–20 CPD AOR 1.0 (0.8–1.2) >20 CPD AOR 0.9 (0.7–1.2) NHL 1–10 CPD AOR 1.6 (1.0–2.5) 11–20 CPD AOR 1.1(0.7–1.6) >20 CPD AOR 1.1 (0.7–1.8)	Matched for gender, age, region Adjusted for socio-economic status Not adjusted for maternal smoking, but no association with maternal smoking Study also includes estimates on CNS tumours, neuroblastoma, nephroblastoma, bone tumour, soft tissue sarcoma and no associations was found	
Shu *et al.* (1996), USA	Case control 1983–88 (CCG study)	302 cases 203 ALL 88 AML 11 other leukaemia 558 controls Paternal smoking: 191 ALL 79 AML	ALL and AML Only paternal smoking 1 month prior to pregnancy (A) and during pregnancy (B) A: ALL: AOR 1.56 (1.03–2.36) 1–10 CPD AOR 2.40 (1.00–5.72) 11–20 CPD AOR 1.33 (0.79–2.34) >20 CPD AOR 1.51 (0.82–2.77) AML: AOR 0.75 (0.35–1.62) 1–10 CPD AOR 0.42 (0.09–1.95) 11–20 CPD AOR 0.73 (0.27–1.94) >20 CPD AOR 1.29 (0.44–3.74) B: ALL: AOR 1.45 (0.95–2.19) AML: AOR 0.82 (0.38–1.78)	Telephone interview with mothers and fathers (71%) Age ≤18 months Matched by age, region. Adjusted for sex, paternal age, education, maternal alcohol consumption during pregnancy Maternal smoking 1 month prior to pregnancy and during pregnancy was not associated with increased risk of ALL or AML	Low
Sorahan *et al.* (2001), UK	Case control (OSCC study) 1980–83	555 cases 555 controls (GP) Cases/controls: 7/9 18/16 36/35 9/5 12/3	ALL Paternal smoking before the pregnancy <10 CPD: GP: 0.99 (0.35–2.85) 10–19 CPD GP:1.34 (0.62–2.91) 20–29 CPD GP: 1.32 (0.72–2.45) 30–39 CPD GP: 2.33 (0.71–7.63) 40+ CPD GP: 5.29 (1.31–21.30) *P* for trend $P = 0.06$	Interview of parents Child age <15 years Matched on region, sex, date of birth Adjusted for maternal age, paternal age, SES, ethnicity	Low
Other cancers *n* = 19					
Barrington-Trimis *et al.* (2013), USA	Case control 1984–1991	202 cases 286 controls Only paternal smoking: 25 cases 27 controls	Brain tumours Only paternal smoking during pregnancy AOR 1.24 (0.66–2.35)	In-person maternal interview Age ≤10 years Matched by age, sex, study centre Adjusted for race, sex, age at diagnosis, maternal education, birth year, centre	Low
Bunin *et al.* (1994), USA	Case control 1986–1989	155 AP 166 PNET 321 Controls 64/63 60/58 86/82 85/88	Astrocytic gliomas (AG) Primitive neuroectodermal tumours (PNET) Paternal smoking during pregnancy AG: AOR 1.0 (0.6–1.7) PNET: AOR 1.0 (0.6–1.7) Paternal smoking ever AG: AOR 1.1 (0.7–18.0) PNET: AOR 0.9 (0.6–1.5)	Trained interviewers with parents Child age <6 years Matched on race, year of birth, telephone area code and prefix AG: Adj. income level PNET: No adjustment	Low
	SEARCH program	1218 cases	Brain tumours	Nine centres in 7 countries	Medium

Continued

Table X *Continued*

Author, year, country	Study design	Number of deliveries and children	Result Outcomes (Risk estimates)	Outcomes Adjustments	Quality assessment
Filippini *et al.* (2002), Italy	1980–1992	2223 controls 633/1190	AOR 1.1 (0.9–1.2)	In-person interview of mostly mothers Child age 0–19 years Post hoc strata matched on age, sex and centre Adjusted for matched variables and maternal level of education	
Gold *et al.* (1993), USA	Case control 1977–81	361 cases 1083 controls Only paternal smoking: 81 cases 247 controls	Brain tumours Only paternal smoking during year index child was born: AOR 0.94 (0.66–1.33)	Structured interview from each parent Age <18 years Matched for age, sex, maternal race Cases represent 85% of cases identified by the registries	Medium
Hu *et al.* (2000), China	Case control 1991–1996	82 cases 246 controls Paternal smoking + no maternal smoking: 44 cases 124 controls	Brain tumours Smoking PY AOR 1.16 (0.65–2.08)	During hospitalization, paternal and maternal interviews by trained interviewers Age <19 years Matched for sex, age, area of residence Adjusted for maternal education, family income	Low
Ji *et al.* (1997), China	Case control 1981–1991	1981–91 642 cases 642 controls Brain tumours 107 pairs Acute leukaemia, 166 pairs Lymphoma 87 pairs	Brain tumours Paternal smoking before conception <2 PY All cancers: AOR 1.2 (0-8-1.8) Brain tumours: AOR 1.5 (0.5–4.4) 2–5 PY All cancers: AOR 1.3 (0.9–2.0) Brain tumours: AOR 1.7 (0.5–5.8) >5 PY prior to conception All cancers: AOR 1.7 (1.2–2.5) Brain tumours: AOR 2.7 (0.8–9.9)	Paternal and maternal interviews by trained interviewers Age <15 years Matched for sex, year of birth Adjusted for BW, income, paternal age, education and alcohol	Low
John *et al.* (1991), USA	Case control 1976–83	1976–1983 223 cases 196 controls 60 exposed cancers 45 exposed controls	Brain tumours Paternal smoking in preconception period in the absence of maternal smoking Brain tumours: AOR 1.6 (0.7–3.5) All cancers: AOR 1.2 (0.8–2.1)	Personal interview Prenatal exposure Matched for age, sex, area Absence of maternal smoking: Adjusted for father's education	Low
Johnson *et al.* (2013)USA	Case control 2000–2008 (Cases) 1994–2008 (controls)	383 cases 387 controls A: Paternal smoking within the year before pregnancy: 115 cases, 84 controls B: Paternal smoking during pregnancy 95 cases, 69 controls	Hepatoblastoma Paternal smoking the year before pregnancy A: AOR 1.4 (1.0–2.0) B: AOR 1.4 (0.9–2.0)	Maternal telephone interviews Age <6 years Matched for BW, gender, birth year and region Adjusted for BW, year of birth, sex, maternal race and education Not directly adjusted for maternal smoking had no influence and therefore not adjusted for	Medium
McCredie *et al.* (1994), Italy + Australia	Case control Population-based 1985–1989	82 cases 164 controls Ever smoking 23 cases, 28controls During pregnancy 41cases, 49controls	Malignant brain tumours Paternal smoking ever (at least 3 months at any time before pregnancy) AOR 2.0 (1.0–4.1)* Paternal smoking during pregnancy AOR 2.2 (1.2–3.8)	Structured at home interviews with mothers Child age up to 14 years Matched on sex and age *Ever smoked is adjusted for fathers schooling	Low
	Case control	302 cases	Brain tumours	Questionnaire to parents	Medium

Milne *et al.* (2013), Australia	(Aus-CBT study) 2005–2010	941 controls Preconception: 74 cases 222 controls During pregnancy 71 cases 202 controls	Paternal smoking preconception AOR 0.99 (0.71–1.38) 1–14 CPD: AOR 1.31 (0.82–2.11) 15+ CPD: AOR 0.83 (0.55–1.24) Paternal smoking during pregnancy* AOR 1.04 (0.74–1.46) 1–14 CPD: AOR 1.30 (0.79–2.13) 15+ CPD: AOR 0.92 (0.61–1.38)	Age <15 years Matched for age, sex, state of residence Adjusted for matching variables, ethnicity, year of birth group, parental age, household income *Results shown are not adjusted for maternal smoking, but no association was found with maternal smoking Similar results when analysis was restricted to children whose other parent did not smoke (data not shown)	
Norman *et al.* (1996), USA	Case control Population-based 1984–1991	540 cases 801 controls Ever smoked: 262 cases, 380 controls During pregnancy: 174 cases, 238 controls	Childhood brain tumours Ever smoked AOR 1.1 (0.84–1.3) Paternal smoking during pregnancy and no maternal smoking AOR 1.2 (0.95–1.6)	In-person or telephone interviews of mothers and fathers (77%) Child age <20 years Matched on birth year, sex, age at diagnosis Adj. matching criteria + maternal race/ethnicity	Medium
Pang *et al.* (2003), UK	Case control (UKCCS) 1991–1996	3585 case fathers 6987 control fathers Paternal preconception smoking All cancers 583 cases, 1003 controls 757 cases, 1440 controls CNS tumours 101 cases, 1003 controls 138 cases, 1440 controls	Cancer Paternal smoking during the year before birth All cancers 1–19 CPD: AOR 1.11 (0.98–1.25) 20+ CPD: AOR 1.01 (0.90–1.12) CNS tumours 1–19 CPD: AOR 1.08 (0.85–1.38) 20+ CPD: AOR 1.03 (0.82–1.28)	Personal interview with parents Age <15 years Matched for sex, age, region Adjusted for matching variables, parental age, deprivation score	Medium
Plichart *et al.* (2008), France	Case control (ESCALE study) 2003–2004	209 cases 1681 controls Paternal smoking + non-smoking mother 74 cases, 516 controls	CNS tumours Only paternal smoking in the year prior the child's birth AOR 1.3 (1.0–1.9)	Maternal telephone interview Age <15 years Matched for age, sex and number of children <15 years of age in the household Adjusted for age, gender No association between maternal smoking during pregnancy and CNS tumours.	Low
Sorahan *et al.* (1997a), UK	Case control (OSCC study) 1953–1955	1549 cases 1549 controls 655 cases, 618 controls	Death of childhood cancer Paternal smoking at death of child, father only ARR 1.30 (1.10–1.53)	Interview parents, usually mothers (response rate 88%) Matched for sex, date of birth and region Adjusted for social class, parental age at birth, sib-ship position, obstetric radiography	Medium
Sorahan *et al.* (1997b), UK	Case control (OSCC study) 1971–1976	2587 cases 2587 controls 630 cases 573 controls	Death of childhood cancer Paternal smoking at death of child, father only 14% of the cancers could be related to paternal smoking (all cancer and onset at all ages) ARR 1.29 (1.10–1.51)	Interview of parents, usually mothers Child age <16 years Matched for sex, date of birth, region Adjusted for social class, parental age at birth, sib-ship position, obstetric radiography	Medium
Sorahan *et al.* (2001), UK	Case control (OSCC study) 1980–83	555 cases 555 controls (hospital) 555 controls (GP) Cases/GP/Hospital 26/34/27 79/60/70 114/122/121 23/32/48	Childhood cancer Paternal smoking before the pregnancy ARR: <10 CPD: GP: 0.94 (0.53–1.66); Hospital: 0.92 (0.51–1.65) 10–19 CPD	Interview of parents Child age <15 years Matched on region, sex, date of birth Adjusted for maternal age, paternal age, SES, ethnicity	Low

Continued

Table X *Continued*

Author, year, country	Study design	Number of deliveries and children	Result Outcomes (Risk estimates)	Outcomes Adjustments	Quality assessment
		28/21/40	GP: 1.63 (1.10–2.41); Hospital: 1.06 (0.72–1.56) 20–29 CPD GP: 1.46 (1.05–2.03); Hospital: 1.11 (0.80–1.53) 30–39 CPD GP: 0.95 (0.52–1.73); Hospital: 0.45 (0.26–0.77) 40+ CPD GP: 1.77 (0.94–3.34); Hospital: 0.66 (0.39–1.11) *P* for trend GP $P = 0.02$; Hospital $P = 0.16$ CNS tumours also stratified on CPD, but no total ARR *P* for trend 0.67 Data adjusted for maternal smoking is not shown but with a significant positive trend ($P = 0.03$) between cancer and paternal smoking compared to GP controls		
Sorahan and Lancashire (2004), UK	Case control (OSCC study) Deaths 1953–55 1971–76 1977–81	5777 case control matched pairs Paternal smoking only: All cancers 1637 cases 1545 controls Hepatoblastoma 43 cases 8 cases 1545 controls	Death of childhood cancer and hepatoblastoma All cancers ARR 1.28 (1.15–1.42) Hepatoblastoma ARR 1.23 (0.46–3.28)	Interview parents, usually mother Child age <16 years Matched for sex, age at death, year of death Adjusted for sex, age at death, year of death, social class, sib-ship position, maternal age, paternal age, obstetric radiography	Medium (all cancers) Low (hepatoblastoma)
Schuz *et al.* (1999), Germany	Case control (NW and NI study) NW:1992–97 NI:1980–94	NW:1992–97 NI:1980–94 2358 cases 2588 controls 385 CNS tumours 155 neuroblastomas 2540 nephroblastomas 95 bone tumours 133 soft tissue sarcomas	CNS tumour, Neuroblastoma, Nephroblastoma, Bone tumour, Soft tissue sarcoma Paternal smoking before pregnancy 1-10 CPD: CNS tumour: AOR 0.8 (0.5–1.2) Neuroblastoma: AOR 0.6 (0.3–1.1) Nephroblastoma: AOR 0.8 (0.4–1.4) Bone tumour: AOR 0.5 (0.2–1.2) Soft tissue sarcoma: AOR 0.8 (0.4–1.6) 11–20 CPD: CNS tumour: AOR 1.1 (0.8–1.4) Neuroblastoma: AOR 1.1 (0.7–1.6)	Questionnaire followed by telephone interview by parents Age <15years Matched for gender, age, region Adjusted for socio-economic status Not adjusted for maternal smoking, but no association with maternal smoking. Study also includes estimates on Acute leukaemia and NHL	Low

			Nephroblastoma: AOR 0.8 (0.5–1.3) Bone tumour: AOR 0.8 (0.4–1.3) Soft tissue sarcoma: AOR 1.2 (0.8–1.8) >20CPD CNS tumour: AOR 1.0 (0.7–1.4) Neuroblastoma: AOR 1.2 (0.7–2.1) Nephroblastoma: AOR 0.9 (0.5–1.6) Bone tumour: AOR 0.9 (0.4–1.8) Soft tissue sarcoma: AOR 0.9 (0.4–1.6)		
Yang *et al.* (2000), USA & Canada	Case control (CCG and POG studies) 1992–94	504 cases 504 controls Preconception 137 cases, 122 controls	Neuroblastoma Paternal smoking one month before conception AOR 1.2 (0.8–1.6)	Telephone interview with parents Child age <19 years Matched for date of birth Adjusted for gender, mother's race, father's education, household income in birth year Not directly adjusted maternal smoking, but no association with risk of neuroblastoma	Medium
Cardio-metabolic outcomes (n = 9)					
Brion *et al.* (2007), UK	Cohort study Avon longitudinal study	6396 children (Model 1) 3736 children (Model 5)	Blood pressure at 7 years Systolic blood pressure: Model 1: Beta 0.44 (−0.07–0.95) $P = 0.09$ Model 5: Beta 0.17 (−0.52–0.86) $P = 0.6$ Diastolic blood pressure: Model 1: Beta 0.10 (−0.26–0.47) $P = 0.6$ Model 5: Beta −0.25 (−0.72–0.22) $P = 0.3$	Questionnaires sent to partners at 18 weeks gestation on if they had smoked regularly in the last 9 months Model 1: Child age, sex Model 5: Additionally, adjusted for maternal/partner factors, social factors, breast feeding	Medium
de Jonge *et al.* (2013), US	Nurse's Health Study II and Nurses' Mothers' cohort 1989–2007	5777 non-smoking mothers 3078 paternal smoking 2699 no paternal smoking	Hypertension in daughters in adulthood (self-reported physician diagnosed) Paternal smoking during pregnancy Maternal age: ARR 1.12 (1.06–1.18) + perinatal variables: ARR 1.09 (1.03–1.15) + BW: ARR 1.08 (1.03–1.14) + adult life variables: ARR 1.08 (1.02–1.14) + body shape and weight until age: ARR 18:1.07 (1.01–1.13) + current BMI: 1.04 (0.99–1.10)	Self-administered questionnaires to nurse's mothers 2001 Cox proportion hazard models Multiple adj. and additional adj. for perinatal variables, adult life variables, body shape and weight until age 18 years, current BMI	Medium
Durmus *et al.* (2011), The Netherlands	Prospective cohort study 2002–2006	4028 non-Smoking mothers Paternal smoking during pregnancy: 1397 fathers 0–4 CPD: 607 fathers ≥5 CPD: 753 fathers 2572 no paternal smoking	BMI at 3, 6, 12, 24, 36, 48 months Paternal smoking during pregnancy and difference in BMI at 12 months: Standardized coefficients (95% CI): 0.06 (−0.01, 0.13) 0–4 CPD 0.04 (−0.05, 0.13) ≥5 CPD 0.08 (−0.01, 0.17) P for trend $P = 0.01$ Similar no difference in BMI at 3, 6, 24, 36 and 48 months and no trend	Postal questionnaires to mothers Linear mixed models Adj. Child's age at visit, sex, paternal ethnicity and education, paternal height and weight and breast feeding (yes/no) Reporting bias Similar information completed by the fathers in 3358 participants – good agreement between mat and pat assessment	Medium
Florath *et al.* (2014), Germany	Prospective cohort Born 2000–2001	609 healthy mature newborns	BMI at child age 8 years Smoking during pregnancy BMI at 8 years	During hospitalization after delivery standardized maternal interviews by trained interviewers. Follow-up to age 8 years Linear regression	Medium

Continued

Table X *Continued*

Author, year, country	Study design	Number of deliveries and children	Result Outcomes (Risk estimates)	Outcomes Adjustments	Quality assessment
		Paternal smoking during pregnancy in non-smoking mothers 157 paternal smoking 401 no paternal smoking	Adjusted regression coefficient: 0.34 (0.01–0.66)	Adjusted for paternal BMI and education, maternal pre-pregnancy BMI, BW, monthly weight gain, exclusive breast feeding, body height, TV consumption, sports activities, diet score at 8 years and age at anthropometric measurements. Conclusion: Residual confounding conditions in smoking families by living rather than specific intrauterine exposure may account for the increased risk of offspring overweight	
Howe *et al.* (2012), UK	Cohort study Avon longitudinal study	Height: 4832 children PI: 4777 children BMI: 4534 children	Growth 29–120 months Girls: 0.0012 (0.0021), $P = 0.01$ Boys: −0.0012 (0.0020), $P = 0.8$ Ponderal index 2–24 months: Girls: 0.0043 (0.0078), $P = 0.35$ Boys: −0.0011 (0.0069), $P = 0.73$ BMI 103–120 months: Girls: 0.0042 (0.0036), $P = 0.54$ Boys: 0.0033 (0.0021), $P = 0.77$	Self-reported data Height 0–10 years Ponderal index 0–2 years BMI 2–10 years Maternal education, household social class, parity, maternal age, maternal height, maternal BMI, gestational age, breast feeding	Medium
Kwok *et al.* (2010), Hong Kong	Birth Cohort study 1997	Non-smoking mothers: 7924 children 6710 children with BMI at 7 years 6519 children with BMI at 11 years of age	BMI and height at child age 7 and 11 years Daily prenatal and early postnatal paternal smoking: BMI, Z-score difference, mean (95%CI) Child age 7 years: 0.10 (0.02–0.19) Child age 11 years: 0.16 (0.07–0.26) No difference in height Z scores	Standardized self- administered questionnaire at maternal and child-health centres Daily prenatal and early postnatal paternal smoking in non-smoking women Adjusted for gender, birth order, highest parental education, mother's place of birth, pubertal status (for 11 years) highest parental occupation, household income per person, breast feeding history, number of hospital admissions attributable to infections at 0 to 6 months	Medium
Leary *et al.* (2006), UK	Cohort study Avon longitudinal study	Examination at 9 years 6470 children 5615 children* 3649 children**	BMI, total fat, truncal fat, total lean (DXA scanner) at mean child age 9.9 years Paternal smoking during pregnancy *BMI: beta 0.11 (0.05, 0.17) < 0.001 *Total fat: beta 0.08 (0.03–0.13) $P = 0.001$	Questionnaires to mothers Adjusted for maternal smoking *Sex, child age at DXA-scan, **Additionally adjusted for maternal, partner, social and infant feeding factors	Medium
Taal *et al.* (2013), The Netherlands	Prospective cohort study 2008–2012	Non-smoking mothers during singleton pregnancy 4070 cases Fathers smoking 1298 cases Fathers non-smoking 2369 controls	Stroke, volume, cardiac output, larger AOD (aortic root diameter), fractional shortening at child age 6 years Regression coefficients Mean Systolic blood pressure (mmHg) −0.18 (−0.69–0.33) test for trend over smoking cat. 0.741 Mean diastolic blood pressure (mmHg) 0.12 (−0.39–0.52) test for trend over smoking cat. 0.702 Aortic root diameter (mm) Difference 0.17 (0.05–0.28)	Questionnaires in second and third trimester Mixed models and multiple linear regression models Adjusted for maternal age, parity, mixed educational level, pre-pregnancy BMI, BP at intake, sex, GA, BW, breast feeding status, current age and BMI	Medium

Toschke *et al.* (2007), UK	Cohort study NCDS: 1958 BCS70:1970	Two birth cohorts Total: 11 282 children NCDS: 5214 children BCS70: 6068 children	Diabetes Mellitus Type 1 Paternal smoking OR 0.48 (0.29–0.80) Combined OR: AOR 0.44 (0.25–0.75) NCDS: AOR 0.37 (0.18–0.75) BCS70: AOR 0.54 (0.24–1.27)	Interview of mothers NCDS: Up 16 years BCS70:5 and 10 years Adjusted for maternal smoking, sex, maternal age, paternal age, number of sibling, social class, cohort (NCDS, BCS70)	Medium
Neuro-developmental *n* = 6					
Brion *et al.* (2010), UK	Birth cohorts Avon Longitudinal study of Parents and Children (ALSPAC), UK 1991–1992 Pelotas, Brazil 1993	ALSPAC: 6735 children Strength and difficulties questionnaire (SDQ) to parents Pelotas: 509 children Child Behaviour Checklist (CLBL) followed up by a psychologist	Psychological problems Paternal smoking during pregnancy Hyperactivity/attention problem** ALSPAC AOR 1.03 (0.91–1.17) Pelotas AOR 1.04 (0.71–1.50) Emotional/Internalizing problem** ALSPAC AOR 0.93 (0.82–1.06) Pelotas AOR 0.85 (0.58–1.24) Conduct/Externalizing problems** ALSPAC AOR 1.11 (0.98–1.26) Pelotas AOR 0.96 (0.66–1.41) Peer/social problems** ALSPAC AOR 1.01 (0.89–1.15) Pelotas AOR 0.98 (0.67–1.45)	4-years of age, Smoking information at perinatal visit Adjusted in 5 levels for: Unadjusted Maternal and paternal education, income, social class Mediators Parental psychological **Mutually adj. model incl. maternal and paternal smoking with adjustment for one another	Medium (ALSPAC) Low (Pelotas)
Langley *et al.* (2012), UK	Longitudinal cohort study Pregnant women 1991–2000	Fathers only smoking 6478 children ADHD diagnosis 5719 children	ADHD Paternal smoking during pregnancy 0, 1–9, 10–19, >=20 cig per day Paternal smoking and mother non-smoking Adjusted beta=0.12 (0.04–0.20) AOR 1.42 (1.04–1.93)	Self-reported questionnaire (mother) Child age 7–8 years Linear regression F-statistics Adjusted for sex, ethnicity, multiple pregnancy, maternal alcohol during, education, pregnancy, parental social class, maternal education	Medium
Nomura *et al.* (2010), USA	Cohort study	209 children Fathers only smoking 40	ADHD AOR 0.31 (0.06–1.92) ODD Not estimable ADHD and ODD AOR 0.85 (0.13–5.55)	Interview of parents Age 3–4 years Adjusted for gender, age, race and BW of the child, maternal drinking during pregnancy, family SES, mother's ADHD symptoms, father's ADHD symptoms, mother and father's smoking history	Low
Tang (2006), Hong Kong	Case control 2003–2004	392 children newly diagnosed with developmental delay 393 controls	Developmental delay Prenatal paternal smoking AOR 1.18 (0.86–1.63) ≤5 CPD AOR 1.15 (0.74–1.77) >5 CPD AOR 1.39 (0.75–2.58)	Self-administered questionnaire parents mostly mothers Age 2–3 years Matched for age and region Adjusted for environmental tobacco smoke (ETS) due to other household smoking other than paternal smoking, child sex, BW, breast feeding history, housing type, parents educational level and occupation	Medium
Tiesler *et al.* (2011), Germany	Cohort study Delivery 1997–1999	3097 children 1654 ETS at 10 years 40 paternal smoking or ETS only	Behavioural problems Prenatal paternal smoking and environmental tobacco smoking (persons other than mothers smoking at home, ETS) Total difficult score (5/40) APOR 1.21 (0.45–3.27) Hyperactivity/inattention (8/40) APOR 2.03 (0.86–4.81)	Self-administered questionnaires mothers 10 years follow-up Adjusted for sex, study centre, parental education, maternal age at birth, time in front of screen, single mother/father	Low

Continued

Table X *Continued*

Author, year, country	Study design	Number of deliveries and children	Result Outcomes (Risk estimates)	Outcomes Adjustments	Quality assessment
Zhu *et al.* (2014), Denmark	Birth cohort and discharge diagnosis from Medication Registry	50 870 mothers participated in 7-years questionnaire 14 004 singletons with paternal smoking only 360 (2.6%) singletons with ADHD Both non-smokers ADHD: 892/49 072 (1.8%)	ADHD Paternal smoking with no maternal smoking AHR 1.29 (1.14–1.47)	Questionnaire during pregnancy and at follow-up 7- years of age (mother) Cox regression adjusted for maternal age, parity, alcohol, SES, psychopathology, sex, diagnosis, education (registry)	Medium

AG, astrocytic gliomas; AnLL, acute non-lymphoblastic leukaemia; APOR, adjusted proportional odds ratio; CPD, cigarette per day; ETS, environmental tobacco smoke; HL, Hodgkin's lymphoma; NA, not available; NHL, non-Hodgkin's lymphoma; ODD oppositional defiant disorder; PNET, primitive neuroectodermal tumours; PY, pack-years.

The systematic literature search revealed a huge number of articles which were scrutinized, and 238 of these publications were selected for inclusion. Although the quality of included articles varied, several large cohort studies of high quality were identified.

A majority of the included publications investigated the effect of paternal age on the health of children. A previous systematic review concerning the effect of paternal factors on obstetric outcomes found that extremes in paternal age were associated with an increase in LBW, and there was also an association between paternal height and BW of offspring (Shah, 2010). Another recent report summarized the association between paternal age and health of offspring in a narrative way (Nybo Andersen and Urhoj, 2017). They reported a strong association between paternal age and some specific congenital syndromes, namely cleft palate, acute lymphatic leukaemia, ASD and schizophrenia.

While no clear definition seems to exist for advanced paternal age, many studies have used 40 years and above as an age limit. A common problem for many studies of paternal factors, particularly paternal age, is the strong and well-known confounding factor, namely the effect of maternal age on obstetric and child outcome. A similar influence is true for other exposures, such as smoking and BMI. In our meta-analyses we therefore only included publications which had adjusted for maternal age or smoking, or where it was clear that the reference group was young mothers or non-smoking mothers, respectively. We also included some studies in which univariate analysis of maternal smoking was insignificant, and thus did not adjust for maternal smoking in the multivariate analyses.

Paternal age

Among obstetric outcomes, we found a small but significantly increased risk of stillbirth associated with paternal age. We also found significantly higher risks of birth defects, and specifically of orofacial clefts and trisomy 21. For other obstetric outcomes and selected birth defects we could not identify any increased risks. For gastroschisis, there seems to be evidence of an increased risk associated with younger fathers (Kazaura *et al.*, 2004a, Archer *et al.*, 2007, Yang *et al.*, 2007, Materna-Kiryluk *et al.*, 2009). The mechanism behind such an association is suggested to be of socio-economic origin, with certain life-style factors more common among young fathers (drugs, smoking, etc) while the increase in risk associated with higher paternal age is possibly of genetic origin, depending on a higher frequency of *de novo* mutation in sperm of older fathers.

Children born to older fathers have been reported as having a higher risk of various cancer types (Sartorius and Nieschlag, 2010). A meta-analysis (Sergentanis *et al.*, 2015) reported an increased risk of childhood leukaemia associated with higher parental ages. For the risk of ALL, they reported an association with both increased maternal and paternal age. In our meta-analysis we did not find an association between ALL and advanced paternal age. A possible explanation for our result could be that we only included studies that adjusted for maternal age. For other cancer types, it was not possible to carry out meta-analysis, either because the studies were too few, of too low quality, or did not adjust for maternal age.

Psychiatric disorders and diseases like autism/ASD (Hultman *et al.*, 2011; Wu *et al.*, 2017) and schizophrenia (Miller *et al.*, 2010) have been associated with advanced paternal age. From earlier studies, the risk seems to increase linearly without any particular threshold. This

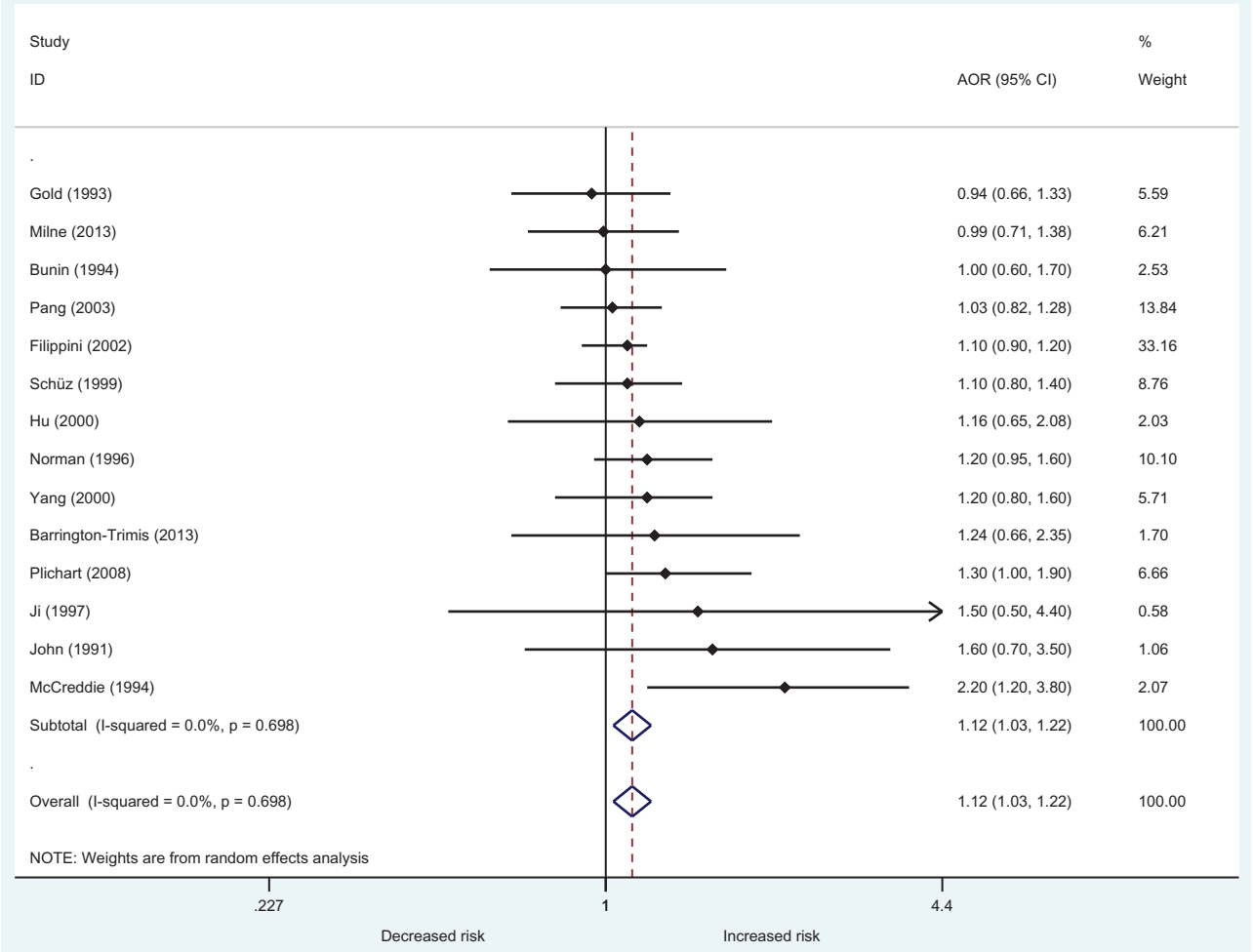

Figure 19 Forest plot describing the association between paternal smoking and risk for brain tumours in the offspring.

link with advanced paternal age has been found in studies from different countries although the magnitude of the associations varies.

ASD is a chronic disease and includes different conditions such as infantile autism, Asperger's syndrome, atypical autism and pervasive development disorder. There are different theories explaining the aetiology. The genetics of ASD seem complex and may involve genetic, epigenetic and environmental factors (Waye and Cheng, 2017). The mean number of *de novo* mutations in human spermatozoa has been found to increase by around two per year (Kong *et al.*, 2012). This increased frequency of *de novo* mutations of older men may result in both gain and loss of DNA region copy numbers, and may explain some of the effects associated with increased paternal age. Other explanations for the paternal effects may include the fact that these men are more often in the higher or lower socio-economic groups, they are more likely to be overweight and obese, and they are more likely to smoke and have a higher alcohol intake. Furthermore, these men more often suffer from diverse physical and mental health problems (Nilsen *et al.*, 2013).

In our meta-analysis of autism, 16 studies were included and a higher risk of autism/ASD was associated with increasing paternal age (pooled estimate 1.25, 95% CI 1.20–1.30). All studies adjusted for maternal age. This finding is in line with previous meta-analyses (Hultman *et al.*, 2011; Wu *et al.*, 2017).

Our meta-analysis of schizophrenia included 11 original articles, all of these studies adjusted for maternal age. A higher risk of schizophrenia was observed in the children of older men (pooled estimate 1.31, 95% CI 1.24–1.38). The previous meta-analysis by Miller *et al.* (2010) found a higher level of risk in the oldest fathers (≥50 years), of AOR 1.66 (95% CI 1.46–1.89). Similarly, the meta-analyses by Torrey *et al.* (2009) and Wohl and Gorwood (2007) found a strong association between advanced paternal age and an increased risk of schizophrenia in offspring. Limitations in some of the studies include few outcomes of interest, and poorly defined classification of diagnosis. Another limitation is that it is not possible to adjust for genetic and environmental factors that could be important confounders in the association between advanced paternal age and adverse outcomes in offspring. Furthermore, there is a heterogeneity of different age categories that complicates comparison between studies. Our results are in line with previous studies and indicate an association between advanced paternal age and increased risk of autism, schizophrenia and other psychiatric diseases.

Table XI Summary results of the meta-analyses of the association between paternal factors and perinatal and paediatric outcomes.

Exposure	Outcome	Pooled estimate (with 95% CI)	Certainty of evidence GRADE
Paternal age	PTB	1.02 (1.00–1.05)	⊕⊕◯◯
	Low BW	1.00 (0.97–1.03)	⊕⊕◯◯
	Stillbirth	1.19 (1.10–1.30)	⊕⊕◯◯
	Children with any birth defects	1.05 (1.02–1.07)	⊕⊕⊕◯
	CHDs	1.03 (0.99–1.06)	⊕⊕⊕◯
	Orofacial clefts	0.99 (0.95–1.04)	⊕⊕◯◯
		1.14 (1.02–1.29)*	
	Gastroschisis	0.88 (0.78–1.00)	⊕⊕⊕◯
	Spina bifida	0.97 (0.90–1.04)	⊕⊕⊕◯
	Trisomy 21	1.13 (1.05–1.23)	⊕⊕⊕◯
	Acute lymphoblastic leukaemia	1.08 (0.96–1.21)	⊕⊕⊕◯
	Autism and ASDs	1.25 (1.20–1.30)	⊕⊕⊕◯
	Schizophrenia	1.31 (1.23–1.38)	⊕⊕⊕◯
Paternal BMI	No meta-analysis		
Paternal smoking	PTB	1.16 (1.00–1.35)	⊕⊕◯◯
	Low BW	1.10 (1.00–1.21)	⊕⊕◯◯
	SGA	1.22 (1.03–1.44)	⊕⊕◯◯
	CHDs	1.75 (1.25–2.44)	⊕⊕◯◯
	Orofacial clefts	1.51 (1.16–1.97)	⊕⊕◯◯
	Brain tumours	1.12 (1.03–1.22)	⊕⊕◯◯

*Exposure: Paternal age >45 years.

Paternal, BMI, height and/or weight. There are only limited data on the impact of paternal obesity at the time of conception on short and long-term health outcomes for children. Information on the father´s weight and BMI was often documented after the birth of the child, and those studies were excluded from the analysis. Paternal obesity has been connected to infertility, a reduced rate of live birth per cycle in ART, and increased risk of pregnancy non-viability (Campbell *et al.*, 2015). Obese men have an increased amount of sperm with low mitochondrial membrane potential, DNA fragmentation, and abnormal morphology, all of which may have harmful effects on fertility (Campbell *et al.*, 2015). However, if the pregnancy starts, pre-pregnancy paternal BMI does not seem to exert any independent effect on the risk of PTB or SGA (Mutsaerts *et al.*, 2014). Actually, with regard to short-term outcomes, only the height of the father correlated significantly with the BW of the offspring. On the other hand, paternal anthropometrics at the time of the child's birth were associated with childhood BMI, weight and/or fat mass. However, paternal height and weight were usually either self-reported, or reported by the mother, and not measured, which increases the risk of bias. The majority of studies reported a stronger effect of maternal BMI than paternal BMI. In one study, Patro and co-workers systematically evaluated the associations of offspring BMI, or adiposity, with pre-pregnancy BMI (or adiposity) of the mother and the father (Patro *et al.*, 2013). They hypothesized that the intrauterine environment is an independent factor in obesity development, and thus the maternal effect is likely to be stronger ('foetal overnutrition hypothesis'), but found only limited evidence to support the hypothesis.

Paternal smoking. Our meta-analyses on short-term outcomes demonstrated a small but significant increased risk of SGA if fathers smoked, but non-significant increased risks of PTB and LBW. While the effect of maternal smoking on obstetric outcomes is evident, the effect of paternal smoking on obstetric outcomes is still equivocal. Paternal smoking significantly increased CHD and orofacial clefts, with pooled estimates of 1.75 and 1.50 respectively. The occurrence of CHD and orofacial clefts is a result of the interaction of genetic and environmental risk factors and cigarette smoke comprises numerous chemical carcinogens. These chemicals have a teratogenic effect on oocytes and sperm DNA or interfere with foetal cardiac development and other foetal structures (Deng *et al.*, 2013; Figueiredo *et al.*, 2015). The existing literature is not able to clarify if the increased risk of CHD associated with paternal smoking is due to a direct effect on sperm, or the result of passive smoking on oocytes or the foetus: an effect of the latter should be weaker than that of maternal smoking. The effect of maternal smoking on orofacial cleft risk is relatively well demonstrated, but an effect on cardiovascular defects is more dubious or perhaps restricted to only some forms. Thus, the effect of paternal smoking on orofacial clefts may be due to maternal passive smoking, and why the effect on CHD is more likely to be due to paternal smoking *per se*. Our meta-analysis of data on brain tumours showed a small but significant increased risk of brain tumours if fathers smoked, with pooled estimate of 1.12. The previous meta-analyses on data on leukaemia demonstrated an association between paternal smoking at pregnancy for AML (AOR 1.19–1.28) and for ALL (1.15–1.25) (Liu *et al.*, 2011; Milne *et al.*, 2012; Metayer *et al.*, 2016). Tobacco smoke is known to be leukomogenic, to introduce oxidative damage in sperm cells resulting in DNA fragmentation, and it may also cause persistent changes in miRNA (Liu *et al.*, 2011; Milne *et al.*, 2012).

The association between paternal smoking and childhood cancer could hardly be due to maternal passive smoking as maternal smoking is not with certainty associated with childhood cancer. However, if the infant or young child has been exposed for passive smoking that may explain the increased cancer risk, if passive smoking has a carcinogenic effect. Most of the studies on the effects of exposure to paternal smoking during pregnancy had matched control groups, and risk estimates were adjusted for relevant confounding factors. Nevertheless, none of the studies were assessed as being of high quality. Most studies were retrospective case control studies with a limited number of cases and controls, where fathers but not mothers smoked.

In the majority of studies, the information on paternal smoking was gained from interviews with, or questionnaires from, the mothers, thus introducing recall and selection bias. Obviously, recall bias is of most concern in long-term outcomes where information on paternal smoking is obtained several years after childbirth. The extent of under reporting of paternal smoking is unknown, which may introduce some non-differential misclassification bias. Furthermore, the dissemination of information on the adverse consequences of smoking in pregnancy may have discouraged some parents from disclosing it. Even in some studies of short-term outcomes, information on BW and gestational age came in the form of maternal self-reported data rather than hospital files or national registries, meaning that accuracy is less certain. Most studies of long-term outcomes involved univariate analyses of

maternal smoking, and if not significant, the final results were not adjusted for maternal smoking. Further differentiation between the impact on long-term outcomes of paternal smoking in the preconception stage, and during and after pregnancy, is a challenge. Exposure of pregnant women to tobacco smoke in the environment may be a confounding factor and likewise, second-hand smoke after delivery is a confounder when examining long-term outcomes.

Strengths and limitations

The major strength of this systematic review is the comprehensive literature search, identifying a huge number of relevant publications, from the beginning of the 1950s up to 2017. Another strength is the fact that it is possible to perform meta-analyses, making interpretation of the summarized literature much easier for the reader. The main limitation is the heterogeneity within the meta-analyses e.g. differences in paternal age groups, reference groups, outcome measures and statistical methods used in the studies included. This heterogeneity may, however, be of less importance since this systematic review/meta-analysis is based solely on observational studies and not on interventional trials. All estimates are thus limited to associations. Another limitation which has to be observed is that most of the estimates and 95% CI for the estimates are close to 1.00. Despite adjusting for confounders, for example maternal age, residual confounders might well exist, which could explain the association between paternal age and several of the outcomes.

Conclusion

This systematic review and meta-analysis investigating paternal age, smoking and BMI/weight/height as risk factors for adverse outcome in offspring, found elevated risks for selected birth defects and psychiatric disorders as well as for selected cancers and metabolic disturbances. Although these risks represent serious health effects for the children, the magnitude of these effects seems modest.

Supplementary data

Supplementary data are available at *Human Reproduction* Update online.

Acknowledgements

We thank Therese Svanberg, librarian at Sahlgrenska University Hospital, Sweden, for performing the literature search, Annette Nattland for secretary assistance and Gwyneth Olofsson for language correction.

Authors' roles

A.L., A.P., C.B., H.L., L.B.R., N.B.O., U.B.W. and V.S.A. contributed to the design of the study, screened articles, selected articles, performed data extraction, interpreted the data and wrote the manuscript. MP performed the statistical analyses. All authors approved the final version for submission.

Funding

The Nordic Expert group's research work was unconditionally supported by Gedeon Richter Nordics in Finland, Norway and Denmark and by an agreement concerning research and the education of doctors in Gothenburg, Sweden (ALFGBG-70 940). V.S.A. was supported by a personal grant from the medical society 'Life and Health' in Finland.

Conflict of interest

None of the authors has any conflicts of interest to declare.

References

Abel EL, Kruger M, Burd L. Effects of maternal and paternal age on Caucasian and Native American preterm births and birth weights. *Am J Perinatol* 2002;**19**:49–54.

Alio AP, Salihu HM, McIntosh C, August EM, Weldeselasse H, Sanchez E, Mbah AK. The effect of paternal age on fetal birth outcomes. *Am J Mens Health* 2012; **6**:427–435.

Andriani H, Kuo HW. Adverse effects of parental smoking during pregnancy in urban and rural areas. *BMC Pregnancy Childbirth* 2014;**14**:414.

Archer NP, Langlois PH, Suarez L, Brender J, Shanmugam R. Association of paternal age with prevalence of selected birth defects. *Birth Defects Res A Clin Mol Teratol* 2007;**79**:27–34.

Astolfi P, De Pasquale A, Zonta LA. Late paternity and stillbirth risk. *Hum Reprod* 2004;**19**:2497–2501.

Astolfi P, De Pasquale A, Zonta LA. Paternal age and preterm birth in Italy, 1990 to 1998. *Epidemiol* 2006;**17**:218–221.

Barrington-Trimis JL, Searles Nielsen S, Preston-Martin S, Gauderman WJ, Holly EA, Farin FM, Mueller BA, McKean-Cowdin R. Parental smoking and risk of childhood brain tumors by functional polymorphisms in polycyclic aromatic hydrocarbon metabolism genes. *PLoS One* 2013;**8**:e79110.

Basso O, Wilcox AJ. Paternal age and delivery before 32 weeks. *Epidemiol* 2006; **17**:475–478.

Ben Itzchak E, Lahat E, Zachor DA. Advanced parental ages and low birth weight in autism spectrum disorders–rates and effect on functioning. *Res Dev Disabil* 2011;**32**:1776–1781.

Berg E, Lie RT, Sivertsen A, Haaland OA. Parental age and the risk of isolated cleft lip: a registry-based study. *Ann Epidemiol* 2015;**25**:942–947.e941.

Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. *Pediatrics* 2009;**123**: 1293–1300.

Bille C, Skytthe A, Vach W, Knudsen LB, Andersen AM, Murray JC, Christensen K. Parent's age and the risk of oral clefts. *Epidemiol* 2005;**16**:311–316.

Brion MJ, Leary SD, Smith GD, Ness AR. Similar associations of parental prenatal smoking suggest child blood pressure is not influenced by intrauterine effects. *Hypertension* 2007;**49**:1422–1428.

Brion MJ, Victora C, Matijasevich A, Horta B, Anselmi L, Steer C, Menezes AM, Lawlor DA, Davey Smith G. Maternal smoking and child psychological problems: disentangling causal and noncausal effects. *Pediatrics* 2010;**126**:e57–e65.

Brondum J, Shu XO, Steinbuch M, Severson RK, Potter JD, Robison LL. Parental cigarette smoking and the risk of acute leukemia in children. *Cancer* 1999;**85**: 1380–1388.

Brown A, Bao Y, McKeague I, Shen L, Schaefer C. Parental age and risk of bipolar disorder in offspring. *Psychiatry Res* 2013;**208**:225–231.

Brown AS, Schaefer CA, Wyatt RJ, Begg MD, Goetz R, Bresnahan MA, Harkavy-Friedman J, Gorman JM, Malaspina D, Susser ES. Paternal age and risk of schizophrenia in adult offspring. *Am J Psychiatry* 2002;**159**:1528–1533.

Buizer-Voskamp JE, Laan W, Staal WG, Hennekam EA, Aukes MF, Termorshuizen F, Kahn RS, Boks MP, Ophoff RA. Paternal age and psychiatric disorders: findings from a Dutch population registry. *Schizophr Res* 2011;**129**:128–132.

Bunin GR, Buckley JD, Boesel CP, Rorke LB, Meadows AT. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children:

a report from the Children's Cancer Group. *Cancer Epidemiol, Biomarkers Prev* 1994;**3**:197–204.

Bunin GR, Needle M, Riccardi VM. Paternal age and sporadic neurofibromatosis 1: a case-control study and consideration of the methodologic issues. *Genet Epidemiol* 1997;**14**:507–516.

Burd L, Severud R, Kerbeshian J, Klug MG. Prenatal and perinatal risk factors for autism. *J Perinat Med* 1999a;**27**:441–450.

Burd L, Severud R, Klug MG, Kerbeshian J. Prenatal and perinatal risk factors for Tourette disorder. *J Perinat Med* 1999b;**27**:295–302.

Byars SG, Boomsma JJ. Opposite differential risks for autism and schizophrenia based on maternal age, paternal age, and parental age differences. *Evol Med Public Health* 2016;**2016**:286–298.

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.

Campbell JM, Lane M, Owens JA, Bakos HW. Paternal obesity negatively affects male fertility and assisted reproduction outcomes: a systematic review and meta-analysis. *Reprod Biomed Online* 2015;**31**:593–604.

Cardwell CR, Carson DJ, Patterson CC. Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. *Diabet Med* 2005;**22**:200–206.

Castro-Jimenez MA, Orozco-Vargas LC. Parental exposure to carcinogens and risk for childhood acute lymphoblastic leukemia, Colombia, 2000–2005. *Prev Chronic Dis* 2011;**8**:A106.

Catalano PM, Farrell K, Thomas A, Huston-Presley L, Mencin P, de Mouzon SH, Amini SB. Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr* 2009;**90**:1303–1313.

Cawley RH, Mc KT, Record RG. Parental stature and birth weight. *Am J Hum Genet* 1954;**6**:448–456.

Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. *Am J Epidemiol* 2006;**163**:1091–1100.

Chen XK, Wen SW, Krewski D, Fleming N, Yang Q, Walker MC. Paternal age and adverse birth outcomes: teenager or 40+, who is at risk? *Hum Reprod* 2008;**23**:1290–1296.

Chen YP, Xiao XM, Li J, Reichetzeder C, Wang ZN, Hocher B. Paternal body mass index (BMI) is associated with offspring intrauterine growth in a gender dependent manner. *PLoS One* 2012;**7**:e36329.

Chudal R, Gissler M, Sucksdorff D, Lehti V, Suominen A, Hinkka-Yli-Salomaki S, Brown AS, Sourander A. Parental age and the risk of bipolar disorders. *Bipolar Disord* 2014;**16**:624–632.

Chudal R, Joelsson P, Gyllenberg D, Lehti V, Leivonen S, Hinkka-Yli-Salomaki S, Gissler M, Sourander A. Parental age and the risk of attention-deficit/hyperactivity disorder: a nationwide, population-based cohort study. *J Am Acad Child Adolesc Psychiatry* 2015;**54**:487–494.e481.

Cresci M, Foffa I, Ait-Ali L, Pulignani S, Gianicolo EA, Botto N, Picano E, Andreassi MG. Maternal and paternal environmental risk factors, metabolizing GSTM1 and GSTT1 polymorphisms, and congenital heart disease. *Am J Cardiol* 2011;**108**:1625–1631.

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.

Cross PK, Hook EB. An analysis of paternal age and 47,+21 in 35,000 new prenatal cytogenetic diagnosis data from the New York State Chromosome Registry: no significant effect. *Hum Genet* 1987;**77**:307–316.

Crump C, Sundquist K, Sieh W, Winkleby MA, Sundquist J. Perinatal and family risk factors for non-Hodgkin lymphoma in early life: a Swedish national cohort study. *J Natl Cancer Inst* 2012;**104**:923–930.

Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K. Perinatal and familial risk factors for brain tumors in childhood through young adulthood. *Cancer Res* 2015;**75**:576–583.

D'Onofrio BM, Rickert ME, Frans E, Kuja-Halkola R, Almqvist C, Sjolander A, Larsson H, Lichtenstein P. Paternal age at childbearing and offspring psychiatric and academic morbidity. *JAMA Psychiatry* 2014;**71**:432–438.

Dalman C, Allebeck P. Paternal age and schizophrenia: further support for an association. *Am J Psychiatry* 2002;**159**:1591–1592.

Daraki V, Roumeliotaki T, Koutra K, Georgiou V, Kampouri M, Kyriklaki A, Vafeiadi M, Papavasiliou S, Kogevinas M, Chatzi L. Effect of parental obesity and gestational diabetes on child neuropsychological and behavioral development at 4 years of age: the Rhea mother-child cohort, Crete, Greece. *Eur Child Adolesc Psychiatry* 2017;**26**:703–714.

Davey Smith G, Steer C, Leary S, Ness A. Is there an intrauterine influence on obesity? Evidence from parent child associations in the Avon Longitudinal Study of Parents and Children (ALSPAC). *Arch Dis Child* 2007;**92**:876–880.

de Jonge LL, Harris HR, Rich-Edwards JW, Willett WC, Forman MR, Jaddoe VW, Michels KB. Parental smoking in pregnancy and the risks of adult-onset hypertension. *Hypertension* 2013;**61**:494–500.

de Michelena MI, Burstein E, Lama JR, Vasquez JC. Paternal age as a risk factor for Down syndrome. *Am J Med Genet* 1993;**45**:679–682.

De Souza E, Alberman E, Morris JK. Down syndrome and paternal age, a new analysis of case-control data collected in the 1960s. *Am J Med Genet A* 2009;**149a**:1205–1208.

De Souza E, Morris JK. Case-control analysis of paternal age and trisomic anomalies. *Arch Dis Child* 2010;**95**:893–897.

Deng K, Liu Z, Lin Y, Mu D, Chen X, Li J, Li N, Deng Y, Li X, Wang Y *et al*. Periconceptional paternal smoking and the risk of congenital heart defects: a case-control study. *Birth Defects Res A Clin Mol Teratol* 2013;**97**:210–216.

DerKinderen DJ, Koten JW, Tan KE, Beemer FA, Van Romunde LK, Den Otter W. Parental age in sporadic hereditary retinoblastoma. *Am J Ophthalmol* 1990;**110**:605–609.

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.

Durkin MS, Maenner MJ, Newschaffer CJ, Lee LC, Cunniff CM, Daniels JL, Kirby RS, Leavitt L, Miller L, Zahorodny W *et al*. Advanced parental age and the risk of autism spectrum disorder. *Am J Epidemiol* 2008;**168**:1268–1276.

Durmus B, Kruithof CJ, Gillman MH, Willemsen SP, Hofman A, Raat H, Eilers PH, Steegers EA, Jaddoe VW. Parental smoking during pregnancy, early growth, and risk of obesity in preschool children: the Generation R Study. *Am J Clin Nutr* 2011;**94**:164–171.

Durmus B, Arends LR, Ay L, Hokken-Koelega AC, Raat H, Hofman A, Steegers EA, Jaddoe VW. Parental anthropometrics, early growth and the risk of overweight in pre-school children: the Generation R Study. *Pediatr Obes* 2013;**8**:339–350.

Dzurova D, Pikhart H. Down syndrome, paternal age and education: comparison of California and the Czech Republic. *BMC Public Health* 2005;**5**:69.

Ek M, Wicks S, Svensson AC, Idring S, Dalman C. Advancing paternal age and schizophrenia: the impact of delayed fatherhood. *Schizophr Bull* 2015;**41**:708–714.

El-Saadi O, Pedersen CB, McNeil TF, Saha S, Welham J, O'Callaghan E, Cantor-Graae E, Chant D, Mortensen PB, McGrath J. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. *Schizophr Res* 2004;**67**:227–236.

Erickson JD. Down syndrome, paternal age, maternal age and birth order. *Ann Hum Genet* 1978;**41**:289–298.

Erickson JD. Paternal age and Down syndrome. *Am J Hum Genet* 1979;**31**:489–497.

Erickson JD, Cohen MM Jr. A study of parental age effects on the occurrence of fresh mutations for the Apert syndrome. *Ann Hum Genet* 1974;**38**:89–96.

Erickson JD, Bjerkedal TO. Down syndrome associated with father's age in Norway. *J Med Genet* 1981;**18**:22–28.

Eriksen W, Sundet JM, Tambs K. Paternal age at birth and the risk of obesity in young adulthood: a register-based birth cohort study of Norwegian males. *Am J Hum Biol* 2013;**25**:29–34.

Farioli A, Legittimo P, Mattioli S, Miligi L, Benvenuti A, Ranucci A, Salvan A, Rondelli R, Conter V, Magnani C. Tobacco smoke and risk of childhood acute lymphoblastic leukemia: findings from the SETIL case-control study. *Cancer Causes Control* 2014;**25**:683–692.

Figueiredo JC, Ly S, Magee KS, Ihenacho U, Baurley JW, Sanchez-Lara PA, Brindopke F, Nguyen TH, Nguyen V, Tangco MI *et al*. Parental risk factors for oral clefts among Central Africans, Southeast Asians, and Central Americans. *Birth Defects Res A Clin Mol Teratol* 2015;**103**:863–879.

Filippini G, Maisonneuve P, McCredie M, Peris-Bonet R, Modan B, Preston-Martin S, Mueller BA, Holly EA, Cordier S, Choi NW *et al*. Relation of childhood brain tumors to exposure of parents and children to tobacco smoke: the SEARCH international case-control study. Surveillance of Environmental Aspects Related to Cancer in Humans. *Int J Cancer* 2002;**100**:206–213.

Finley WH, Callahan A, Thompson JN. Parental age in the blepharophimosis, ptosis, epicanthus inversus, telecanthus complex. *Am J Med Genet* 1990;**36**:414–417.

Fisch H, Hyun G, Golden R, Hensle TW, Olsson CA, Liberson GL. The influence of paternal age on down syndrome. *J Urol* 2003;**169**:2275–2278.

Florath I, Kohler M, Weck MN, Brandt S, Rothenbacher D, Schottker B, Moss A, Gottmann P, Wabitsch M, Brenner H. Association of pre- and post-natal parental smoking with offspring body mass index: An 8-year follow-up of a birth cohort. *Pediatr Obes* 2014;**9**:121–134.

Foutz J, Mezuk B. Advanced paternal age and risk of psychotic-like symptoms in adult offspring. *Schizophr Res* 2015;**165**:123–127.

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.

Frans EM, McGrath JJ, Sandin S, Lichtenstein P, Reichenberg A, Langstrom N, Hultman CM. Advanced paternal and grandpaternal age and schizophrenia: a three-generation perspective. *Schizophr Res* 2011;**133**:120–124.

Frans EM, Sandin S, Reichenberg A, Langstrom N, Lichtenstein P, McGrath JJ, Hultman CM. Autism risk across generations: a population-based study of advancing grandpaternal and paternal age. *JAMA Psychiatry* 2013;**70**:516–521.

Frans E, MacCabe JH, Reichenberg A. Advancing paternal age and psychiatric disorders. *World Psychiatry* 2015;**14**:91–93.

Gaizauskiene A, Padaiga Z, Starkuviene S, Mizeriene R. Prediction of perinatal mortality at an early stage of pregnancy. *Scand J Public Health* 2007;**35**:564–569.

Gillberg C. Parental age in child psychiatric clinic attenders. *Acta Psychiatr Scand* 1982;**66**:471–478.

Gold EB, Leviton A, Lopez R, Gilles FH, Hedley-Whyte ET, Kolonel LN, Lyon JL, Swanson GM, Weiss NS, West D *et al*. Parental smoking and risk of childhood brain tumors. *Am J Epidemiol* 1993;**137**:620–628.

Goriely A, Wilkie AOM. Paternal age effect mutations and selfish spermatogonial selection: causes and consequences for human disease. *Am J Hum Genet* 2012; **90**:175–200.

Green RF, Devine O, Crider KS, Olney RS, Archer N, Olshan AF, Shapira SK. Association of paternal age and risk for major congenital anomalies from the National Birth Defects Prevention Study, 1997 to 2004. *Ann Epidemiol* 2010;**20**: 241–249.

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.

Grewal J, Carmichael SL, Yang W, Shaw GM. Paternal age and congenital malformations in offspring in California, 1989–2002. *Matern Child Health J* 2012;**16**:385–392.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–926.

Harville EW, Wilcox AJ, Lie RT, Abyholm F, Vindenes H. Epidemiology of cleft palate alone and cleft palate with accompanying defects. *Eur J Epidemiol* 2007;**22**: 389–395.

Heck JE, Lombardi CA, Meyers TJ, Cockburn M, Wilhelm M, Ritz B. Perinatal characteristics and retinoblastoma. *Cancer Causes Control* 2012;**23**:1567–1575.

Heppe DH, Kiefte-de Jong JC, Durmus B, Moll HA, Raat H, Hofman A, Jaddoe VW. Parental, fetal, and infant risk factors for preschool overweight: the Generation R Study. *Pediatr Res* 2013;**73**:120–127.

Herkrath AP, Herkrath FJ, Rebelo MA, Vettore MV. Parental age as a risk factor for non-syndromic oral clefts: a meta-analysis. *J Dent* 2012;**40**:3–14.

Hook EB, Cross PK, Lamson SH, Regal RR, Baird PA, Uh SH. Paternal age and Down syndrome in British Columbia. *Am J Hum Genet* 1981;**33**:123–128.

Hook EB, Cross PK. Paternal age and Down's syndrome genotypes diagnosed prenatally: no association in New York state data. *Hum Genet* 1982;**62**:167–174.

Hook EB, Regal RR. A search for a paternal-age effect upon cases of 47, +21 in which the extra chromosome is of paternal origin. *Am J Hum Genet* 1984;**36**:413–421.

Horta BL, Victora CG, Menezes AM, Halpern R, Barros FC. Low birthweight, preterm births and intrauterine growth retardation in relation to maternal smoking. *Paediatr Perinat Epidemiol* 1997;**11**:140–151.

Howe LD, Matijasevich A, Tilling K, Brion MJ, Leary SD, Smith GD, Lawlor DA. Maternal smoking during pregnancy and offspring trajectories of height and adiposity: comparing maternal and paternal associations. *Int J Epidemiol* 2012;**41**: 722–732.

Hu J, Mao Y, Ugnat AM. Parental cigarette smoking, hard liquor consumption and the risk of childhood brain tumors–a case-control study in northeast China. *Acta Oncol* 2000;**39**:979–984.

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.

Hvolgaard Mikkelsen S, Olsen J, Bech BH, Obel C. Parental age and attention-deficit/hyperactivity disorder (ADHD). *Int J Epidemiol* 2016;**46**:409–420.

Idring S, Magnusson C, Lundberg M, Ek M, Rai D, Svensson AC, Dalman C, Karlsson H, Lee BK. Parental age and the risk of autism spectrum disorders: findings from a Swedish population-based cohort. *Int J Epidemiol* 2014;**43**:107–115.

Inoue S, Naruse H, Yorifuji T, Kato T, Murakoshi T, Doi H, Subramanian SV. Impact of maternal and paternal smoking on birth outcomes. *J Public Health (Oxf)* 2016;**39**:1–10.

Iwayama M, Kira R, Kinukawa N, Sakai Y, Torisu H, Sanefuji M, Ishizaki Y, Nose Y, Matsumoto T, Hara T. Parental age and child growth and development: child health check-up data. *Pediatr Int* 2011;**53**:709–714.

Jaaskelainen A, Pussinen J, Nuutinen O, Schwab U, Pirkola J, Kolehmainen M, Jarvelin MR, Laitinen J. Intergenerational transmission of overweight among Finnish adolescents and their parents: a 16-year follow-up study. *Int J Obes (Lond)* 2011;**35**:1289–1294.

Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. *Obstet Gynecol* 2004;**104**:727–733.

Javaras KN, Rickert ME, Thornton LM, Peat CM, Baker JH, Birgegard A, Norring C, Landen M, Almqvist C, Larsson H *et al*. Paternal age at childbirth and eating disorders in offspring. *Psychol Med* 2017;**47**:576–584.

Ji BT, Shu XO, Linet MS, Zheng W, Wacholder S, Gao YT, Ying DM, Jin F. Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers. *J Natl Cancer Inst* 1997;**89**:238–244.

John EM, Savitz DA, Sandler DP. Prenatal exposure to parents' smoking and childhood cancer. *Am J Epidemiol* 1991;**133**:123–132.

Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, Mueller BA, Puumala SE, Reynolds P, Von Behren J *et al*. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiol* 2009;**20**:475–483.

Johnson KJ, Williams KS, Ross JA, Krailo MD, Tomlinson GE, Malogolowkin MH, Feusner JH, Spector LG. Parental tobacco and alcohol use and risk of hepatoblastoma in offspring: a report from the children's oncology group. *Cancer Epidemiol, Biomarkers Prev* 2013;**22**:1837–1843.

Kazaura MR, Lie RT. Down's syndrome and paternal age in Norway. *Paediatr Perinat Epidemiol* 2002;**16**:314–319.

Kazaura MR, Lie RT, Irgens LM, Didriksen A, Kapstad M, Egenaes J, Bjerkedal T. Increasing risk of gastroschisis in Norway: an age-period-cohort analysis. *Am J Epidemiol* 2004a;**159**:358–363.

Kazaura M, Lie RT, Skjaerven R. Paternal age and the risk of birth defects in Norway. *Ann Epidemiol* 2004b;**14**:566–570.

Khandwala YS, Zhang CA, Lu Y, Eisenberg ML. The age of fathers in the USA is rising: an analysis of 168 867 480 births from 1972 to 2015. *Hum Reprod* 2017;**32**: 2110–2116.

King MD, Fountain C, Dakhlallah D, Bearman PS. Estimated autism risk and older reproductive age. *Am J Public Health* 2009;**99**:1673–1679.

Klebanoff MA, Mednick BR, Schulsinger C, Secher NJ, Shiono PH. Father's effect on infant birth weight. *Am J Obstet Gynecol* 1998;**178**:1022–1026.

Ko TJ, Tsai LY, Chu LC, Yeh SJ, Leung C, Chen CY, Chou HC, Tsao PN, Chen PC, Hsieh WS. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatr Neonatol* 2014;**55**:20–27.

Kong A, Frigge ML, Masson G, Besenbacher S, Sulem P, Magnusson G, Gudjonsson SA, Sigurdsson A, Jonasdottir A, Jonasdottir A *et al*. Rate of de novo mutations and the importance of father's age to disease risk. *Nature* 2012;**488**:471–475.

Krapels IP, Zielhuis GA, Vroom F, de Jong-van den Berg LT, Kuijpers-Jagtman AM, van der Molen AB, Steegers-Theunissen RP. Periconceptional health and lifestyle factors of both parents affect the risk of live-born children with orofacial clefts. *Birth Defects Res A Clin Mol Teratol* 2006;**76**:613–620.

Kuciene R, Dulskiene V. Parental cigarette smoking and the risk of congenital heart septal defects. *Medicina (Kaunas)* 2010;**46**:635–641.

Kwok MK, Schooling CM, Lam TH, Leung GM. Paternal smoking and childhood overweight: evidence from the Hong Kong 'Children of 1997'. *Pediatrics* 2010; **126**:e46–e56.

L'Abee C, Vrieze I, Kluck T, Erwich JJ, Stolk RP, Sauer PJ. Parental factors affecting the weights of the placenta and the offspring. *J Perinat Med* 2011;**39**:27–34.

Lampi KM, Hinkka-Yli-Salomaki S, Lehti V, Helenius H, Gissler M, Brown AS, Sourander A. Parental age and risk of autism spectrum disorders in a Finnish national birth cohort. *J Autism Dev Disord* 2013;**43**:2526–2535.

Langley K, Heron J, Smith GD, Thapar A. Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: testing for intrauterine effects. *Am J Epidemiol* 2012;**176**:261–268.

Larfors G, Hallbook H, Simonsson B. Parental age, family size, and offspring's risk of childhood and adult acute leukemia. *Cancer Epidemiol, Biomarkers Prev* 2012; **21**:1185–1190.

Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, Schendel D, Thorsen P, Mortensen PB. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. *Am J Epidemiol* 2005;**161**: 916–925; discussion 926–918.

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.

Lawlor DA, Smith GD, O'Callaghan M, Alati R, Mamun AA, Williams GM, Najman JM. Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the mater-university study of pregnancy and its outcomes. *Am J Epidemiol* 2007; **165**:418–424.

Lawlor DA, Timpson NJ, Harbord RM, Leary S, Ness A, McCarthy MI, Frayling TM, Hattersley AT, Smith GD. Exploring the developmental overnutrition hypothesis using parental-offspring associations and FTO as an instrumental variable. *PLoS Med* 2008;**5**:e33.

Leary SD, Smith GD, Rogers IS, Reilly JJ, Wells JC, Ness AR. Smoking during pregnancy and offspring fat and lean mass in childhood. *Obesity (Silver Spring)* 2006; **14**:2284–2293.

Lee KM, Ward MH, Han S, Ahn HS, Kang HJ, Choi HS, Shin HY, Koo HH, Seo JJ, Choi JE *et al*. Paternal smoking, genetic polymorphisms in CYP1A1 and childhood leukemia risk. *Leuk Res* 2009;**33**:250–258.

Lehrer DS, Pato MT, Nahhas RW, Miller BR, Malaspina D, Buckley PF, Sobell JL, Walsh-Messinger J, Cohort Consortium GP, Pato CN. Paternal age effect: replication in schizophrenia with intriguing dissociation between bipolar with and without psychosis. *Am J Med Genet B Neuropsychiatr Genet* 2016;**171**:495–505.

Lian ZH, Zack MM, Erickson JD. Paternal age and the occurrence of birth defects. *Am J Hum Genet* 1986;**39**:648–660.

Linabery AM, Nahhas RW, Johnson W, Choh AC, Towne B, Odegaard AO, Czerwinski SA, Demerath EW. Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. *Pediatr Obes* 2013;**8**:159–169.

Liu R, Zhang L, McHale CM, Hammond SK. Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. *J Oncol* 2011; **2011**:854584.

Lorda-Sanchez I, Prieto L, Rodriguez-Pinilla E, Martinez-Frias ML. Increased parental age and number of pregnancies in Klippel-Trenaunay-Weber syndrome. *Ann Hum Genet* 1998;**62**:235–239.

Lowe X, Eskenazi B, Nelson DO, Kidd S, Alme A, Wyrobek AJ. Frequency of XY sperm increases with age in fathers of boys with Klinefelter syndrome. *Am J Hum Genet* 2001;**69**:1046–1054.

Lundstrom S, Haworth CM, Carlstrom E, Gillberg C, Mill J, Rastam M, Hultman CM, Ronald A, Anckarsater H, Plomin R *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.

MacArthur AC, McBride ML, Spinelli JJ, Tamaro S, Gallagher RP, Theriault G. Risk of childhood leukemia associated with parental smoking and alcohol consumption prior to conception and during pregnancy: the cross-Canada childhood leukemia study. *Cancer Causes Control* 2008;**19**:283–295.

Magnani C, Pastore G, Luzzatto L, Terracini B. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case-control study. *Tumori* 1990;**76**:413–419.

Magnus P, Berg K, Bjerkedal T, Nance WE. Parental determinants of birth weight. *Clin Genet* 1984;**26**:397–405.

Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. *Acta Psychiatr Scand* 2006;**114**:257–264.

Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, Susser ES. Advancing paternal age and the risk of schizophrenia. *Arch Gen Psychiatry* 2001; **58**:361–367.

Mamidala MP, Polinedi A, P T V PK, Rajesh N, Vallamkonda OR, Udani V, Singhal N, Rajesh V. Prenatal, perinatal and neonatal risk factors of Autism Spectrum Disorder: a comprehensive epidemiological assessment from India. *Res Dev Disabil* 2013;**34**:3004–3013.

Martinez FD, Wright AL, Taussig LM. The effect of paternal smoking on the birthweight of newborns whose mothers did not smoke. Group Health Medical Associates. *Am J Public Health* 1994;**84**:1489–1491.

Materna-Kiryluk A, Wisniewska K, Badura-Stronka M, Mejnartowicz J, Wieckowska B, Balcar-Boron A, Czerwionka-Szaflarska M, Gajewska E, Godula-Stuglik U, Krawczynski M *et al*. Parental age as a risk factor for isolated congenital malformations in a Polish population. *Paediatr Perinat Epidemiol* 2009;**23**:29–40.

Matsunaga E, Minoda K, Sasaki MS. Parental age and seasonal variation in the births of children with sporadic retinoblastoma: a mutation-epidemiologic study. *Hum Genet* 1990;**84**:155–158.

Mattioli S, Farioli A, Legittimo P, Miligi L, Benvenuti A, Ranucci A, Salvan A, Rondelli R, Magnani C. Tobacco smoke and risk of childhood acute non-lymphocytic leukemia: findings from the SETIL study. *PLoS One* 2014;**9**: e111028.

Maule MM, Vizzini L, Merletti F, Magnani C, Pastore G, Richiardi L. Parental age and risk of acute lymphocytic leukaemia and embryonal tumours in the Piedmont Region, Italy. *Int J Epidemiol* 2007;**36**:691–692.

McCredie M, Maisonneuve P, Boyle P. Antenatal risk factors for malignant brain tumours in New South Wales children. *Int J Cancer* 1994;**56**:6–10.

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.

McIntosh GC, Olshan AF, Baird PA. Paternal age and the risk of birth defects in offspring. *Epidemiol* 1995;**6**:282–288.

Menegaux F, Ripert M, Hemon D, Clavel J. Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: a French population-based case-control study. *Paediatr Perinat Epidemiol* 2007;**21**:293–299.

Menezes PR, Lewis G, Rasmussen F, Zammit S, Sipos A, Harrison GL, Tynelius P, Gunnell D. Paternal and maternal ages at conception and risk of bipolar affective disorder in their offspring. *Psychol Med* 2010;**40**:477–485.

Metayer C, Zhang L, Wiemels JL, Bartley K, Schiffman J, Ma X, Aldrich MC, Chang JS, Selvin S, Fu CH *et al*. Tobacco smoke exposure and the risk of childhood acute lymphoblastic and myeloid leukemias by cytogenetic subtype. *Cancer Epidemiol, Biomarkers Prev* 2013;**22**:1600–1611.

Metayer C, Petridou E, Arangure JM, Roman E, Schuz J, Magnani C, Mora AM, Mueller BA, de Oliveira MS, Dockerty JD *et al*. Parental tobacco smoking and acute myeloid leukemia: the Childhood Leukemia International Consortium. *Am J Epidemiol* 2016;**184**:261–273.

Miller B, Alaraisanen A, Miettunen J, Jarvelin MR, Koponen H, Rasanen P, Isohanni M, Kirkpatrick B. Advanced paternal age, mortality, and suicide in the general population. *J Nerv Ment Dis* 2010;**198**:404–411.

Miller B, Messias E, Miettunen J, Alaraisanen A, Jarvelin MR, Koponen H, Rasanen P, Isohanni M, Kirkpatrick B. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring. *Schizophr Bull* 2011;**37**:1039–1047.

Milne E, Greenop KR, Scott RJ, Bailey HD, Attia J, Dalla-Pozza L, de Klerk NH, Armstrong BK. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. *Am J Epidemiol* 2012;**175**:43–53.

Milne E, Greenop KR, Scott RJ, Ashton LJ, Cohn RJ, de Klerk NH, Armstrong BK. Parental smoking and risk of childhood brain tumors. *Int J Cancer* 2013;**133**: 253–259.

Mok PL, Antonsen S, Pedersen CB, Webb RT. Younger or older parental age and risk of suicidality, premature death, psychiatric illness, and criminality in offspring. *J Affect Disord* 2017;**208**:130–138.

Morrison J, Williams GM, Najman JM, Andersen MJ. The influence of paternal height and weight on birth-weight. *Aust N Z J Obstet Gynaecol* 1991;**31**:114–116.

Mutsaerts MA, Groen H, Buiter-Van der Meer A, Sijtsma A, Sauer PJ, Land JA, Mol BW, Corpeleijn E, Hoek A. Effects of paternal and maternal lifestyle factors on pregnancy complications and perinatal outcome. A population-based birth-cohort study: the GECKO Drenthe cohort. *Hum Reprod* 2014;**29**:824–834.

Nahum GG, Stanislaw H. Relationship of paternal factors to birth weight. *J Reprod Med* 2003;**48**:963–968.

Naserbakht M, Ahmadkhaniha HR, Mokri B, Smith CL. Advanced paternal age is a risk factor for schizophrenia in Iranians. *Ann Gen Psychiatry* 2011;**10**:15.

National Institute for Health and Welfare. Nordic perinatal statistics 2014. Helsinki, Finland. https://www.thl.fi/en/web/thlfi-en/statistics/statistics-by-topic/sexual-and-reproductive-health/parturients-deliveries-and-births/nordic-perinatal-statistics.

Nilsen AB, Waldenstrom U, Rasmussen S, Hjelmstedt A, Schytt E. Characteristics of first-time fathers of advanced age: a Norwegian population-based study. *BMC Pregnancy Childbirth* 2013;**13**:29.

Nomura Y, Marks DJ, Halperin JM. Prenatal exposure to maternal and paternal smoking on attention deficit hyperactivity disorders symptoms and diagnosis in offspring. *J Nerv Ment Dis* 2010;**198**:672–678.

Norman MA, Holly EA, Ahn DK, Preston-Martin S, Mueller BA, Bracci PM. Prenatal exposure to tobacco smoke and childhood brain tumors: results from the United States West Coast childhood brain tumor study. *Cancer Epidemiol, Biomarkers Prev* 1996;**5**:127–133.

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.

Nybo Andersen AM, Urhoj SK. Is advanced paternal age a health risk for the offspring? *Fertil Steril* 2017;**107**:312–318.

O'Callaghan MJ, Williams GM, Andersen MJ, Bor W, Najman JM. Prediction of obesity in children at 5 years: a cohort study. *J Paediatr Child Health* 1997;**33**:311–316.

Olshan AF, Schnitzer PG, Baird PA. Paternal age and the risk of congenital heart defects. *Teratology* 1994;**50**:80–84.

Olshan AF, Ananth CV, Savitz DA. Intrauterine growth retardation as an endpoint in mutation epidemiology: an evaluation based on paternal age. *Mutat Res* 1995;**344**:89–94.

Orioli IM, Castilla EE, Scarano G, Mastroiacovo P. Effect of paternal age in achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta. *Am J Med Genet* 1995;**59**:209–217.

Orsi L, Rudant J, Ajrouche R, Leverger G, Baruchel A, Nelken B, Pasquet M, Michel G, Bertrand Y, Ducassou S *et al*. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: the ESTELLE study. *Cancer Causes Control* 2015;**26**:1003–1017.

Pang D, McNally R, Birch JM. Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. *Br J Cancer* 2003;**88**:373–381.

Parner ET, Baron-Cohen S, Lauritsen MB, Jorgensen M, Schieve LA, Yeargin-Allsopp M, Obel C. Parental age and autism spectrum disorders. *Ann Epidemiol* 2012;**22**:143–150.

Patro B, Liber A, Zalewski B, Poston L, Szajewska H, Koletzko B. Maternal and paternal body mass index and offspring obesity: a systematic review. *Ann Nutr Metab* 2013;**63**:32–41.

Perrin MC, Brown AS, Malaspina D. Aberrant epigenetic regulation could explain the relationship of paternal age to schizophrenia. *Schizophr Bull* 2007;**33**:1270–1273.

Petersen L, Mortensen PB, Pedersen CB. Paternal age at birth of first child and risk of schizophrenia. *Am J Psychiatry* 2011;**168**:82–88.

Plichart M, Menegaux F, Lacour B, Hartmann O, Frappaz D, Doz F, Bertozzi AI, Defaschelles AS, Pierre-Kahn A, Icher C *et al*. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE). *Eur J Cancer Prev* 2008;**17**:376–383.

Poledna AP. Paternal age in relation to selected birth defects. *Hum Biol* 1976;**48**:727–739.

Poletta FA, Castilla EE, Orioli IM, Lopez-Camelo JS. Regional analysis on the occurrence of oral clefts in South America. *Am J Med Genet A* 2007;**143a**:3216–3227.

Pritchard CW, Sutherland HW, Carr-Hill RA. Birthweight and paternal height. *Br J Obstet Gynaecol* 1983;**90**:156–161.

Quinlan CA, McVeigh KH, Driver CR, Govind P, Karpati A. Parental Age and Autism Spectrum Disorders Among New York City Children 0–36 Months of Age. *Matern Child Health J* 2015;**19**:1783–1790.

Racine SE, Culbert KM, Burt SA, Klump KL. Advanced paternal age at birth: phenotypic and etiologic associations with eating pathology in offspring. *Psychol Med* 2014;**44**:1029–1041.

Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, Rabinowitz J, Shulman C, Malaspina D, Lubin G *et al*. Advancing paternal age and autism. *Arch Gen Psychiatry* 2006;**63**:1026–1032.

Reichenberg A, Gross R, Sandin S, Susser ES. Advancing paternal and maternal age are both important for autism risk. *Am J Public Health* 2010;**100**:772–773.

Reichman NE, Teitler JO. Paternal age as a risk factor for low birthweight. *Am J Public Health* 2006;**96**:862–866.

Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, Steer C, Sherriff A. Early life risk factors for obesity in childhood: cohort study. *BMJ* 2005;**330**:1357.

Riccardi VM, Dobson ICE, Chakraborty R, Bontke C. The pathophysiology of neurofibromatosis: IX. Paternal age as a factor in the origin of new mutations. *Am J Med Genet* 1984;**18**:169–176.

Roecker GO, Huether CA. An analysis for paternal-age effect in Ohio's Down syndrome births, 1970–1980. *Am J Hum Genet* 1983;**35**:1297–1306.

Roth MP, Stoll C, Taillemite JL, Girard S, Boue A. Paternal age and Down's syndrome diagnosed prenatally: no association in French data. *Prenat Diagn* 1983a;**3**:327–335.

Roth MP, Feingold J, Baumgarten A, Bigel P, Stoll C. Reexamination of paternal age effect in Down's syndrome. *Hum Genet* 1983b;**63**:149–152.

Rudant J, Menegaux F, Leverger G, Baruchel A, Lambilliotte A, Bertrand Y, Patte C, Pacquement H, Verite C, Robert A *et al*. Childhood hematopoietic malignancies and parental use of tobacco and alcohol: the ESCALE study (SFCE). *Cancer Causes Control* 2008;**19**:1277–1290.

Saha S, Barnett AG, Foldi C, Burne TH, Eyles DW, Buka SL, McGrath JJ. Advanced paternal age is associated with impaired neurocognitive outcomes during infancy and childhood. *PLoS Med* 2009;**6**:e40.

Sandin S, Schendel D, Magnusson P, Hultman C, Suren P, Susser E, Gronborg T, Gissler M, Gunnes N, Gross R *et al*. Autism risk associated with parental age and with increasing difference in age between the parents. *Mol Psychiatry* 2016;**21**:693–700.

Sartorius GA, Nieschlag E. Paternal age and reproduction. *Hum Reprod Update* 2010;**16**:65–79.

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.

Savitz DA, Schwingl PJ, Keels MA. Influence of paternal age, smoking, and alcohol consumption on congenital anomalies. *Teratology* 1991;**44**:429–440.

Schuz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol* 1999;**28**:631–639.

Selvin S, Garfinkel J. The relationship between parental age and birth order with the percentage of low birth-weight infants. *Hum Biol* 1972;**44**:501–509.

Sergentanis TN, Thomopoulos TP, Gialamas SP, Karalexi MA, Biniaris-Georgallis SI, Kontogeorgi E, Papathoma P, Tsilimidos G, Skalkidou A, Iliadou AN *et al*. Risk for childhood leukemia associated with maternal and paternal age. *Eur J Epidemiol* 2015;**30**:1229–1261.

Shah PS. Paternal factors and low birthweight, preterm, and small for gestational age births: a systematic review. *Am J Obstet Gynecol* 2010;**202**:103–123.

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.

Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B, Robison LL. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. *J Natl Cancer Inst* 1996;**88**:24–31.

Sinclair KD, Watkins AJ. Parental diet, pregnancy outcomes and offspring health: metabolic determinants in developing oocytes and embryos. *Reprod Fertil Dev* 2013;**26**:99–114.

Sipos A, Rasmussen F, Harrison G, Tynelius P, Lewis G, Leon DA, Gunnell D. Paternal age and schizophrenia: a population based cohort study. *BMJ* 2004;**329**:1070.

Sorahan T, Lancashire RJ, Hulten MA, Peck I, Stewart AM. Childhood cancer and parental use of tobacco: deaths from 1953 to 1955. *Br J Cancer* 1997a;**75**:134–138.

Sorahan T, Prior P, Lancashire RJ, Faux SP, Hulten MA, Peck IM, Stewart AM. Childhood cancer and parental use of tobacco: deaths from 1971 to 1976. *Br J Cancer* 1997b;**76**:1525–1531.

Sorahan T, McKinney PA, Mann JR, Lancashire RJ, Stiller CA, Birch JM, Dodd HE, Cartwright RA. Childhood cancer and parental use of tobacco: findings from the inter-regional epidemiological study of childhood cancer (IRESCC). *Br J Cancer* 2001;**84**:141–146.

Sorahan T, Lancashire RJ. Parental cigarette smoking and childhood risks of hepatoblastoma: OSCC data. *Br J Cancer* 2004;**90**:1016–1018.

Sorensen HJ, Pedersen CB, Nordentoft M, Mortensen PB, Ehrenstein V, Petersen L. Effects of paternal age and offspring cognitive ability in early adulthood on the risk of schizophrenia and related disorders. *Schizophr Res* 2014;**160**:131–135.

Soubry A, Verbeke G, Hoyo C. Do early paternal exposures to lifestyle factors such as smoking increase the risk of chronic diseases in the offspring? *Eur J Hum Genet* 2014;**22**:1341–1342.

Steegers-Theunissen RP, Twigt J, Pestinger V, Sinclair KD. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. *Hum Reprod Update* 2013;**19**:640–655.

Stene J, Fischer G, Stene E, Mikkelsen M, Petersen E. Paternal age effect in Down's syndrome. *Ann Hum Genet* 1977;**40**:299–306.

Stene J, Stene E, Stengel-Rutkowski S, Murken JD. Paternal age and Down's syndrome: data from prenatal diagnoses (DFG). *Hum Genet* 1981;**59**:119–124.

Stene LC, Magnus P, Lie RT, Sovik O, Joner G. Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study. *BMJ* 2001;**323**:369.

Stern JE, Luke B, Hornstein MD, Cabral H, Gopal D, Diop H, Kotelchuck M. The effect of father's age in fertile, subfertile, and assisted reproductive technology pregnancies: a population based cohort study. *J Assist Reprod Genet* 2014;**31**:1437–1444.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. 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.

Su XJ, Yuan W, Huang GY, Olsen J, Li J. Paternal age and offspring congenital heart defects: a national cohort study. *PLoS One* 2015;**10**:e0121030.

Suren P, Gunnes N, Roth C, Bresnahan M, Hornig M, Hirtz D, Lie KK, Lipkin WI, Magnus P, Reichborn-Kjennerud T *et al*. Parental obesity and risk of autism spectrum disorder. *Pediatrics* 2014;**133**:e1128–e1138.

Taal HR, de Jonge LL, van Osch-Gevers L, Steegers EA, Hofman A, Helbing WA, van der Heijden AJ, Jaddoe VW. Parental smoking during pregnancy and cardiovascular structures and function in childhood: the Generation R Study. *Int J Epidemiol* 2013;**42**:1371–1380.

Takano T, Kawashima T, Yamanouchi Y, Kitayama K, Baba T, Ueno K, Hamaguchi H. Genetics of neurofibromatosis 1 in Japan: mutation rate and paternal age effect. *Hum Genet* 1992;**89**:281–286.

Tang ML. Environmental tobacco smoke and child development: a case-control study on Hong Kong Chinese toddlers. *Hong Kong J Paediatr* 2006;**11**; 118–127+160–161.

Tay JS, Yip WC, Joseph R. Parental age and birth order in Chinese children with congenital heart disease. *J Med Genet* 1982;**19**:441–443.

Tellier AL, Lyonnet S, Cormier-Daire V, de Lonlay P, Abadie V, Baumann C, Bonneau D, Labrune P, Lacombe D, Le Merrer M *et al*. Increased paternal age in CHARGE association. *Clin Genet* 1996;**50**:548–550.

Teras LR, Gaudet MM, Blase JL, Gapstur SM. Parental age at birth and risk of hematological malignancies in older adults. *Am J Epidemiol* 2015;**182**:41–48.

Tiesler CM, Chen CM, Sausenthaler S, Herbarth O, Lehmann I, Schaaf B, Kramer U, von Berg A, von Kries R, Wichmann HE *et al*. Passive smoking and behavioural problems in children: results from the LISAplus prospective birth cohort study. *Environ Res* 2011;**111**:1173–1179.

To WW, Cheung W, Kwok JS. Paternal height and weight as determinants of birth weight in a Chinese population. *Am J Perinatol* 1998;**15**:545–548.

Torrey EF, Buka S, Cannon TD, Goldstein JM, Seidman LJ, Liu T, Hadley T, Rosso IM, Bearden C, Yolken RH. Paternal age as a risk factor for schizophrenia: how important is it? *Schizophr Res* 2009;**114**:1–5.

Toschke AM, Ehlin A, Koletzko B, Montgomery SM. Paternal smoking is associated with a decreased prevalence of type 1 diabetes mellitus among offspring in two national British birth cohort studies (NCDS and BCS70). *J Perinat Med* 2007;**35**:43–47.

Tough SC, Faber AJ, Svenson LW, Johnston DW. Is paternal age associated with an increased risk of low birthweight, preterm delivery, and multiple birth? *Can J Public Health* 2003;**94**:88–92.

Tsuchiya KJ, Takagai S, Kawai M, Matsumoto H, Nakamura K, Minabe Y, Mori N, Takei N. Advanced paternal age associated with an elevated risk for schizophrenia in offspring in a Japanese population. *Schizophr Res* 2005;**76**:337–342.

Tsuchiya KJ, Matsumoto K, Miyachi T, Tsujii M, Nakamura K, Takagai S, Kawai M, Yagi A, Iwaki K, Suda S *et al*. Paternal age at birth and high-functioning autistic-spectrum disorder in offspring. *Br J Psychiatry* 2008;**193**:316–321.

Urhoj SK, Jespersen LN, Nissen M, Mortensen LH, Nybo Andersen AM. Advanced paternal age and mortality of offspring under 5 years of age: a register-based cohort study. *Hum Reprod* 2014;**29**:343–350.

Urhoj SK, Mortensen LH, Nybo Andersen AM. Advanced paternal age and risk of musculoskeletal congenital anomalies in offspring. *Birth Defects Res B Dev Reprod Toxicol* 2015;**104**:273–280.

Urhoj SK, Andersen PK, Mortensen LH, Davey Smith G, Nybo Andersen AM. Advanced paternal age and stillbirth rate: a nationwide register-based cohort study of 944,031 pregnancies in Denmark. *Eur J Epidemiol* 2017a;**32**:227–234.

Urhoj SK, Raaschou-Nielsen O, Hansen AV, Mortensen LH, Andersen PK, Nybo Andersen AM. Advanced paternal age and childhood cancer in offspring: A nationwide register-based cohort study. *Int J Cancer* 2017b;**140**:2461–2472.

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.

van Rooij IA, Wijers CH, Rieu PN, Hendriks HS, Brouwers MM, Knoers NV, de Blaauw I, Roeleveld N. Maternal and paternal risk factors for anorectal malformations: a Dutch case-control study. *Birth Defects Res A Clin Mol Teratol* 2010;**88**:152–158.

Vashist M, Neelkamal, Kumar A. Whether paternal age effect exists as a risk factor in trisomy 21. *Biosci Biotechnol Res Asia* 2011;**8**:247–252.

Wang SH, Liu CM, Hwu HG, Hsiao CK, Chen WJ. Association of older paternal age with earlier onset among co-affected schizophrenia sib-pairs. *Psychol Med* 2015;**45**:2205–2213.

Wasserman CR, Shaw GM, O'Malley CD, Tolarova MM, Lammer EJ. Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. *Teratology* 1996;**53**:261–267.

Waye MMY, Cheng HY. Genetics and epigenetics of autism (Review). *Psychiatry Clin Neurosci* 2017.

Wennberg AL, Opdahl S, Bergh C, Aaris Henningsen AK, Gissler M, Romundstad LB, Pinborg A, Tiitinen A, Skjaerven R, Wennerholm UB. Effect of maternal age on maternal and neonatal outcomes after assisted reproductive technology. *Fertil Steril* 2016;**106**:1142–1149.e1114.

Wilcox MA, Newton CS, Johnson IR. Paternal influences on birthweight. *Acta Obstet Gynecol Scand* 1995;**74**:15–18.

Winikoff B, Debrovner CH. Anthropometric determinants of birth weight. *Obstet Gynecol* 1981;**58**:678–684.

Wohl M, Gorwood P. Paternal ages below or above 35 years old are associated with a different risk of schizophrenia in the offspring. *Eur Psychiatry* 2007;**22**:22–26.

Wolf CM. Paternal age effect for cleft lip and palate. *Am J Hum Genet* 1963;**15**:389–393.

Wu Y, Liu X, Luo H, Deng W, Zhao G, Wang Q, Zhang L, Ma X, Liu X, Murray RA *et al*. Advanced paternal age increases the risk of schizophrenia and obsessive-compulsive disorder in a Chinese Han population. *Psychiatry Res* 2012;**198**:353–359.

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. *Acta Psychiatr Scand* 2017;**135**:29–41.

Wunsch G, Gourbin C. Parents' age at birth of their offspring and child survival. *Soc Biol* 2002;**49**:174–184.

Yang Q, Olshan AF, Bondy ML, Shah NR, Pollock BH, Seeger RC, Look AT, Cohn SL. Parental smoking and alcohol consumption and risk of neuroblastoma. *Cancer Epidemiol, Biomarkers Prev* 2000;**9**:967–972.

Yang Q, Wen SW, Leader A, Chen XK, Lipson J, Walker M. Paternal age and birth defects: how strong is the association? *Hum Reprod* 2007;**22**:696–701.

Yeung EH, Sundaram R, Ghassabian A, Xie Y, Buck Louis G. Parental obesity and early childhood development. *Pediatrics* 2017;**139**:1–12.

Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *Int J Epidemiol* 2006;**35**:1495–1503.

Zakar R, Zakar MZ, Aqil N, Nasrullah M. Paternal factors associated with neonatal deaths and births with low weight: evidence from Pakistan Demographic and Health Survey 2006–2007. *Matern Child Health J* 2015;**19**:1634–1642.

Zammit S, Allebeck P, Dalman C, Lundberg I, Hemmingson T, Owen MJ, Lewis G. Paternal age and risk for schizophrenia. *Br J Psychiatry* 2003;**183**:405–408.

Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. *Hum Reprod Update* 2000;**6**:122–131.

Zhan SY, Lian ZH, Zheng DZ, Gao L. Effect of fathers' age and birth order on occurrence of congenital heart disease. *J Epidemiol Community Health* 1991;**45**: 299–301.

Zhang J, Ratcliffe JM. Paternal smoking and birthweight in Shanghai. *Am J Public Health* 1993;**83**:207–210.

Zhang X, Lv CC, Tian J, Miao RJ, Xi W, Hertz-Picciotto I, Qi L. Prenatal and perinatal risk factors for autism in China. *J Autism Dev Disord* 2010;**40**:1311–1321.

Zhu JL, Madsen KM, Vestergaard M, Basso O, Olsen J. Paternal age and preterm birth. *Epidemiol* 2005a;**16**:259–262.

Zhu JL, Madsen KM, Vestergaard M, Olesen AV, Basso O, Olsen J. Paternal age and congenital malformations. *Hum Reprod* 2005b;**20**:3173–3177.

Zhu JL, Vestergaard M, Madsen KM, Olsen J. Paternal age and mortality in children. *Eur J Epidemiol* 2008;**23**:443–447.

Zhu JL, Olsen J, Liew Z, Li J, Niclasen J, Obel C. Parental smoking during pregnancy and ADHD in children: the Danish national birth cohort. *Pediatrics* 2014;**134**: e382–e388.

Zorlu P, Ergor GUL, Tezic T, Duru F, Ertem U. Evaluation of risk factors in children with acute lymphoblastic leukemia. *Turkish J Cancer* 2002;**32**:5–11.