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Asthma and allergies in offspring conceived by ART: a systematic review and meta-analysis

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BACKGROUND: Currently, 1 in 25 children born in Australia are conceived through ARTs such as IVF and ICSI. Worldwide over 8 million children have been born after ART. There is evidence that these children are at an increased risk of congenital malformations, preterm birth, low birth weight and neonatal morbidity. However, studies on long-term health outcomes of offspring conceived after ART are lacking. Atopic disorders, such as asthma, atopic dermatitis and various allergies are increasingly common within society, and concerns have been raised that ART increases the risk of atopy amongst offspring.

OBJECTIVE AND RATIONALE: The aim of this study was to systematically summarise and quantify the risk of atopic disorders in offspring conceived with ART compared to those conceived without ART.

SEARCH METHODS: A systematic review was conducted according to the PRISMA guidelines. Several systematic searches were performed in the following international databases: Medline, Embase, Cinahl, PsychINFO, AMED, Global Health and ISI Web of Science. Search terms utilised were all terms pertaining to ART, IVF, ICSI, asthma, atopic dermatitis and allergies. The search period was 1978–2021. Included observational studies stated a primary outcome of asthma or allergies in offspring conceived after ART, with a comparison group conceived without ART. Individual studies were scored on quality and risk of bias, using the Newcastle-Ottawa scale (NOS).

OUTCOMES: There were 26 studies which met the inclusion criteria; of these, 24 studies investigated asthma in offspring conceived after ART. While 10 studies, including the two largest population-based studies, reported a significantly increased risk of asthma in offspring conceived after ART (adjusted odds ratio (aOR) range: 1.20–2.38), 14 smaller cohort studies found no difference (aOR range 0.70–1.27). In the meta-analysis of the 14 highest-quality studies (NOS $\geq$ 7), a modest yet significantly increased risk of asthma was demonstrated in offspring conceived after ART [risk ratio (RR) 1.28 (1.08–1.51)]. Although heterogeneity in these 14 studies was high (I^2 = 85%), the removal of outliers and high weight studies significantly reduced heterogeneity (I^2 = 0% and I^2 = 34% respectively) while still demonstrating a significantly increased risk [RR 1.19 (1.10–1.28) and RR 1.31 (1.03–1.65), respectively]. The increased asthma risk was also observed in most subgroup and sensitivity analyses. The allergy rates were not increased in offspring conceived after ART in 9 of 12 studies (aOR range 0.60–1.30). In summary, the findings of this systematic review and meta-analysis suggest a trend towards a significantly increased risk of asthma, but not allergies, in offspring conceived after ART. There was no evidence of publication bias in the asthma studies and minimal evidence of publication bias in the allergy studies (both $P > 0.05$).

WIDER IMPLICATIONS: Asthma brings considerable burden to the quality of life of individuals and to society. Hence, it is of great importance to untangle potential causal pathways. Although ART use is common, knowledge about its long-term health effects is required to provide evidence-based advice to couples considering ART, and to be vigilant for any potential adverse health effects on offspring conceived after ART.

Key words: IVF/ICSI outcome / IVF / ICSI / ART / offspring / long-term outcome / asthma / allergy / atopy / atopic disorders

Introduction

With one-in-six couples encountering personal fertility difficulties in their lifetime, and with the widespread availability and success of fertility treatments, the use of ARTs has become commonplace (Calhaz-Jorge *et al.*, 2017). In Australia, 1 in 25 children are currently born after ART, and worldwide it is estimated that over 8 million children have been born after assisted conception (Calhaz-Jorge *et al.*, 2017; Farquhar and Marjoribanks, 2018; Fauser, 2019; Newman *et al.*, 2019). It is well established that ART is associated with various unfavourable short-term health outcomes, such as an increase in preterm birth (PTB), low birth weight (LBW), congenital malformations, imprinting disorders and neonatal morbidity (Schieve *et al.*, 2002; Zhu *et al.*, 2007; Pandey *et al.*, 2012; Wen *et al.*, 2012; Vermeiden and Bernardus, 2013; Declercq *et al.*, 2015; Qin *et al.*, 2015). However, there is a dearth of information on the long-term health consequences of these frequently used health interventions.

Asthma and allergies are among the most common chronic childhood disorders worldwide and the prevalence of both diseases has increased markedly over recent decades (Asher *et al.*, 2006; WHO, 2020). The World Health Organization (WHO) estimated that 339 million people suffered from asthma worldwide in 2016 (Vos *et al.*, 2017; WHO, 2020). The World Allergy Organisation's (WAO) estimates of allergy prevalence range between 10% and 40% depending on country (Pawankar, 2014). Worldwide, 200–250 million people suffer from food allergies, one-tenth of the population suffers from drug allergies, and 400 million people suffer from rhinitis (Pawankar *et al.*, 2013; Pawankar, 2014). Asthma and allergies should be viewed as a major public health problem, because of their high prevalence as well as their societal and healthcare burden. Atopic disorders reduce quality of life and exercise tolerance, and increase hospitalisation and the number of missed schooldays. All of these factors result in increased morbidity and health costs related to asthma and allergies (Duijts, 2012; Pawankar *et al.*, 2013; Mukherjee *et al.*, 2016).

Although the exact aetiology of both asthma and allergies is not entirely understood, important gene–environment interactions appear to be at play (Torgerson *et al.*, 2011; Pawankar *et al.*, 2013; Papi *et al.*, 2018). It has been suggested that ART could induce epigenetic alterations in the embryo around the highly susceptible window of conception (Fleming *et al.*, 2018). Epigenetic alterations have been linked to the development of immunological disorders such as asthma and allergies (Harris *et al.*, 2013; Reese *et al.*, 2019). Therefore, ART conception may increase the risk of atopic disorders in offspring through direct epigenetic effects. Furthermore, pregnancy-related risk factors for asthma, such as PTB, LBW and delivery via caesaran section (CS) (Jaakkola *et al.*, 2006; Mu *et al.*, 2014; Huang *et al.*, 2015), are also common in ART pregnancies (Pandey *et al.*, 2012; Declercq *et al.*, 2015; Qin *et al.*, 2015), and could perhaps explain a potential association between ART conception and subsequent asthma and allergies in the offspring.

There is limited research on the risk of atopic disorders, specifically asthma and various allergies, in children born after ART. Hart and Norman (2013) reviewed the literature in 2013 and concluded that there is likely no increase in asthma and allergies in offspring conceived after ART; however, the authors emphasised that the literature was limited. Kettner *et al.* (2015) summarised the literature on childhood morbidity in children born after ART in 2015, concluding that the results to date on the risk of asthma and allergies are inconsistent. On the other hand, a number of recent population-based studies, as well as a recent systematic review and meta-analysis have found an increased risk of atopy among offspring conceived after ART (Ericson *et al.*, 2002; Kallen *et al.*, 2005; Finnstrom *et al.*, 2011; Källén et al., 2013; Krieger *et al.*, 2018; Magnus *et al.*, 2019; Tsabouri et al., 2021).

Table I Characteristics for asthma studies.

Author, year and country	Study design, N	Study population	Age	Type of ART	Plurality	Adjustment for covariates	Diagnosis	Main findings	NOS
Carson *et al.*, 2013 UK	Prospective cohort Age 5: ART = 104, Controls = 6575 Age 7: ART = 87, Controls = 5837	National sample	5 and 7	IVF, ICSI	Singletons	++	Standardised questionnaire and parental interview	**Overall ↑ asthma** aOR 1.84 (1.03–3.28)	9
Källén *et al.*, 2013 Sweden[a]	Retrospective cohort ART = 31 918 Controls = 2 596 810	Swedish Medical Birth register	2–27	IVF	Any	++	Drug prescription registry	**Overall ↑ asthma** aOR 1.28 (1.23–1.34)	7
Finnstrom *et al.*, 2011 Sweden[a]	Retrospective cohort ART = 15 570 Controls = unknown	Swedish Medical Birth register	4–9	IVF, ICSI	Any	+	Drug prescription registry	**Overall ↑ asthma** aOR 1.28 (1.21–1.35)	6
Kallen *et al.*, 2005 Sweden[a]	Retrospective cohort ART = 16 120 Controls = unknown	Swedish Medical Birth register	1–20 (mean 5.5)	IVF, ICSI	Any	+	Hospital discharge diagnosis	**Overall ↑ asthma** aOR 1.40 (1.25–1.57)	8
Ericson *et al.*, 2002 Sweden[a]	Retrospective cohort ART = 9056 Controls = 1 417 166	Swedish Medical Birth register	1–14	IVF (not specified)	Any	+	Hospital admission diagnosis	**Overall ↑ asthma** aOR 1.37 (1.20–1.56)	7
Magnus *et al.*, 2019 Norway	Retrospective cohort ART = 8368 Controls = 466 034	Medical Birth Registry of Norway	7	IVF, ICSI, other/un-specified	Singletons	+	Drug prescription registry	**Overall ↑ asthma** aRR 1.20 (1.09–1.32)	8
Kuiper *et al.*, 2015 Netherlands[b]	Prospective cohort ART = 81 ART natural cycle = 53 Subfertile controls = 79	University Medical Centre	4	IVF, ICSI	Singletons	++	Non-standardised and non-validated questionnaire	**Overall ↑ asthma** aOR 1.96 (1.00–3.84)	7
Guibas *et al.*, 2013 Greece	Cross-sectional ART = 59 Controls = 1957	Schoolchildren across four different regions	9–13	IVF (not specified)	Any	++	Validated (ISAAC) questionnaire	**Overall ↑ asthma** aOR 2.25 (1.11–4.56)	7
Harju *et al.*, 2013 Finland	Retrospective cohort ART = 437 Controls = 40 477	University Hospital	1–19	IVF, ICSI	Singletons	++	Drug prescription registry	**Overall ←→ asthma**	7
Halliday *et al.*, 2019 Australia[c]	Prospective cohort Questionnaire ART = 193 controls = 86	ART births in state of Victoria, Australia, controls from random dialling in Victoria	22–35	IVF, GIFT, donor sperm/egg	Singletons	–	Non-validated questionnaire	**Overall ↑ self-reported asthma** $P = 0.05$	5
	Prospective cohort Spirometry ART = 165 Controls = 79					+	Spirometry	**Overall ←→ spirometry**	8
Sicignano *et al.*, 2010 USA	Prospective cohort ART = 157 Controls = 5339	Tertiary clinic	18–24	IVF, gamete donation	Any	+	Non-validated questionnaire	**Overall ←→ asthma**	5

Continued

Table I Continued

Author, year and country	Study design, N	Study population	Age	Type of ART	Plurality	Adjustment for covariates	Diagnosis	Main findings	NOS
Fruchter *et al.*, 2017 Israel	Retrospective cohort ART = 253 Controls = 253	One IVF centre, controls general population	16–17	ART (not specified)	Any	+	Medical examination, review of medical records and specialist screening for military service	**Overall ←→ asthma**	8
Bonduelle *et al.*, 2005 Multi-country; Belgium, Sweden, Denmark, Greece, UK	Prospective cohort ICSI = 540 IVF = 437 Controls = 538	Multi-country, multi-clinic study, controls from local schools/nurseries and birth registries	4.5–5.5	IVF, ICSI	Singletons	+	Parental interview and paediatrician review	**Overall ←→ asthma**	7

aOR, adjusted odds ratio; aRR, adjusted risk ratio; ART, offspring conceived with ARTs; Controls, offspring conceived without ART; ISAAC, The International Study of Asthma and Allergies in Childhood; GIFT, Gamete intrafallopian Transfer.-, no adjustment for covariates; +, adjustment for covariates other than gestational age and birthweight; ++, adjustment for ≧1 main covariate (gestational age, birthweight), and other relevant covariates (plurality, mode of delivery, sex of the study participant, parental smoking and parental atopy).
[a, b, c]indicate studies with (partially) overlapping populations (also see Table 3).

Given the recent population studies linking childhood asthma and allergies to ART conception, in combination with the inconsistency in the literature at present, a comprehensive, thorough and complete systematic review is timely and justified. The aim of this study, which is the first such prospectively registered systematic review and meta-analysis, was to comprehensively summarise the current literature regarding the association between ART and the development of asthma and atopy in offspring.

Methods

Study protocol

This review was conducted in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement' (PRISMA) guidelines (Moher *et al.*, 2009). All steps of the review were completed independently by two of the authors (L.A.W. and M.R.F). In case of disagreement, a third author (R.J.H.) mediated to reach a consensus. The study protocol was registered in PROSPERO (CRD42020183502), on 5 July 2020 (accessible at http://www.crd.york.ac.uk/PROSPERO/).

Search strategy and study selection

Several systematic searches were performed from the inception of the review until June 2021 in the following international databases: Medline, Embase, Cinahl, PsychINFO, AMED, Global Health and ISI Web of Science. Additionally, Mednar, LILACS, WorldCat, Trove Library and conference proceedings of Medline and Embase were searched for grey literature. The International Clinical Trials Registry Platform, ClinicalTrials.gov and the Australian New Zealand Trial Registry were searched for ongoing studies. References of identified studies were checked for additional papers to ensure literature saturation on the topic and study authors were contacted if additional information was required.

The initial search was performed in Medline, including the following search terms: assisted reproductive technology/technologies; assisted reproductive techniques; in vitro fertilization/fertilisation; IVF; intracytoplasmic sperm injection; ICSI; embryo transfer; zygote intrafallopian transfer; gamete intrafallopian transfer; infertility; asthma; lung function; airway function; bronchial hyper reactivity; forced expiratory volume; peak expiratory flow rate; hypersensitivity; allergy; atopy; rhino-conjunctivitis; food hypersensitivity; urticaria; angioedema; and anaphylaxis.

This search was then adapted to search the other databases. A detailed search strategy for Medline and other databases, as described above, is included in Supplementary File S1.

The search was performed by two of the authors (L.A.W. and M.R.F.), with assistance from a medical librarian. Screening of titles and abstracts was completed by the reviewers independently. After initial screening, the full texts of potentially eligible studies were read and assessed on eligibility criteria. All identified studies were saved in EndNote Reference Manager.

Inclusion and exclusion criteria

Studies were considered eligible if they reported on the association of ART and asthma or allergies.

Table II Characteristics for allergy studies.

Author, year and country	Study design and N	Study population	Age	Type of ART	Plurality	Adjustment for covariates	Diagnosis	Main findings	NOS
Krieger *et al.*, 2018 Israel	Retrospective cohort ART = 4324 Controls = 237 863	Tertiary hospital	Up to 18	Fertility treatment, not specified	Singletons	++	Hospital diagnosis ICD codes	**Overall ↑ skin eruptions** Allergic skin eruptions $P = 0.024$	8
Leslie *et al.*, 1998 Australia	Prospective cohort ART = 95 Controls = 79	IVF clinic in hospital, controls from same hospital	Up to 12 months	IVF	Singletons, twins	–	Maternal report and review of infant health booklets	**Overall ←→ allergic reactions**	6

ART, offspring conceived with ARTs; Controls: offspring conceived without ART; ICD, international classification of diseases.-, no adjustment for covariates; ++, adjustment for ≥1 main covariate (gestational age, birthweight), and other relevant covariates (plurality, mode of delivery, sex of the study participant, parental smoking and parental atopy).

The inclusion criteria were as follows. The population studied consisted of children, adolescents or adults conceived from ARTs. The exposure was IVF, ICSI, zygote intrafallopian transfer and gamete intrafallopian transfer, including both fresh embryo transfer (ET) and frozen embryo transfer (FET) embryo transfers. The study was controlled, meaning that there was a comparison group of children or adults who were spontaneously conceived without ART or conceived through any type of fertility treatment other than ART (e.g. artificial insemination, ovulation induction (OI) etc.). The primary outcomes were: asthma, atopic eczema/dermatitis, allergic rhino-conjunctivitis, food allergy/hypersensitivity, urticaria, anaphylaxis and angioedema. The secondary outcomes were: objective and subjective measures of disease severity and impact on quality of life including asthma exacerbations, use of medications, hospitalisation and indicators of airway function. The principal summary measures reported by studies were odds ratio (OR) and risk ratio (RR) with 95% CI, and *P*-values. The types of studies were: analytic observational epidemiologic studies (e.g. cohort, case-control and cross-sectional studies). Study types to be excluded were reviews, case studies and animal studies. The years of study publication considered were 1978 (first ART birth) until 2021. There were no language restrictions applied. Full-text accessibility was required. Studies were excluded if they were duplicates.

Data extraction and data items

Data from the included studies were extracted into structured data tables (Table I for asthma studies, Table II for allergy studies and Table III for studies investigating asthma and allergies); these were developed *a priori*. Extracted data included: study author, year and country of publication, study design, study size, study population, control population, type of ART intervention, plurality, adjustment for covariates, assessment of outcomes, age at assessment of outcome and study results/main findings.

Risk of bias in individual studies

To assess quality and risk of bias in the individual studies, the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies was used for cohort and case-control studies (Wells *et al.*, 2000). For cross-sectional studies, a modified version of the NOS was used (Modesti *et al.*, 2016). This quality assessment was completed independently by the two reviewers (L.A.W. and M.R.F.) and mediated by the third reviewer (R.J.H.). Quality was assessed based on representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and outcome, adjustment for covariates and loss to follow up. Studies were not excluded from the systematic review based on quality. Gestational age and birthweight were considered the most important covariates, when evaluating comparability of the study groups. Additional important potential covariates were plurality, mode of delivery, sex of the study participant, parental smoking and parental atopy. As per the NOS, all studies were given a score between 0–9 for cohort and case-control studies and between 0–10 for cross-sectional studies. For this review, a widely used score cut-off of $\geq$7 was used to indicate a high-quality study, as a formal criterion for high-quality has not yet been universally established. NOS scores per study are reported in Table I (asthma studies), Table II (allergy studies) and Table III (studies investigating asthma and allergies).

Table III Characteristics of studies reporting on asthma and allergies.

Author, year and country	Study design and N	Study population	Age	Type of ART	Plurality	Adjustment for covariates	Diagnosis	Main findings	NOS
Kuiper *et al.*, 2019 Netherlands[b]	Prospective cohort ART = 95 ART natural cycle = 48 Controls = 68	University Medical Centre	9	IVF, ICSI	Singletons	+	Validated (ISAAC) questionnaire	**Overall ←→ asthma, rhinitis and hay fever**	7
Halliday *et al.*, 2014 Australia[c]	Prospective cohort ART = 705 Controls = 868	ART births in state of Victoria, Australia, controls from random dialling in Victoria	18–28	IVF, GIFT, donor sperm/egg	Singletons	+	Non-validated interview	**Overall ↑ asthma and atopy** Any: aOR 1.53 (1.16–2.01) Respiratory atopy: aOR 1.62 (1.21–2.16)	7
Koivurova *et al.*, 2003 Finland	Retrospective Cohort ART = 299 Controls = 558	IVF clinics	Up to 3	IVF	Singletons, twins	+	Medical records, ICD codes	**Overall ←→ asthma and atopic eczema**	7
Cetinkaya *et al.*, 2009 Turkey	Prospective cohort ART = 158 Controls = 102	Hospital IVF clinic, controls from hospital day-care centre	ART = 4.60 ± 2.14 Controls = 5.27 ± 2.8	IVF	Singletons, twins	–	ISAAC	**Overall ←→ asthma, allergic rhinitis and atopic dermatitis**	4
Jaderberg *et al.*, 2012 Denmark	Cross-sectional ART = 5119 Controls = 14 629	Danish twin registry	3–20	IVF, IUI, hormone treatment, operation, 'fallopian tube'	Twins	+	Non-validated questionnaire	**Overall ←→ asthma, hay fever and atopic dermatitis**	7
Pinborg, 2003 Denmark	Prospective cohort ART twins = 454 ART singletons = 626 Controls twins = 1118	Danish Medical Birth and Danish IVF registry	3–4	IVF, ICSI	Singletons, twins	–	Questionnaire and cross checking of discharge reports	**Overall ←→ asthma, infantile eczema and ingestion allergy**	6
Klemetti *et al.*, 2006 Finland	Retrospective cohort ART = 4527 Controls = 26 877	Finish Medical Birth Register	Up to 2	IVF	Any plurality	+	Hospital discharge registry, ICD, reimbursement scheme for chronic conditions	**Overall ←→ asthma and allergies (dermatitis, eczema and urticaria)**	7
Knoester *et al.*, 2008 Netherlands	Prospective cohort ICSI = 87 Controls = 85	University Medical Centre	5.1–8.3 (mean 6.1)	ICSI	Singletons	++	WHO airway questionnaire	**Overall ←→ asthma, eczema and allergy**	7
Ludwig *et al.*, 2009 Germany	Prospective cohort ART = 276 Controls = 273	ICSI centres across Germany, controls from same areas	4–6	ICSI	Singletons	+	Non-validated questionnaire, blinded interview with paediatrician, and reference to child health examination booklet	**Overall ←→ asthma and hay fever, ↓ allergies other than hay fever** Asthma $P = 0.178$, hay fever $P = 0.471$, allergy other than hay fever $P =$ **0.028**	7
Wennerholm *et al.*, 1998 Sweden	Retrospective cohort ART = 510 (255 fresh, 255 frozen) Controls = 252	IVF clinics and controls from delivery registers	18 months	IVF, fresh and FET	Any plurality	+	Child health centre data and hospital records	**Overall ←→ asthma and allergies**	6

aOR, adjusted odds ratio; ART, offspring conceived with ARTs; Controls, offspring conceived without ART; ISAAC, The International Study of Asthma and Allergies in Childhood; GIFT, Gamete intrafallopian Transfer; ICD, international classification of diseases; WHO, World Health Organization; FET, frozen embryo transfer.-, no adjustment for covariates; +, adjustment for covariates other than gestational age and birthweight; ++, adjustment for ≧1 main covariate (gestational age, birthweight), and other relevant covariates (plurality, mode of delivery, sex of the study participant, parental smoking and parental atopy).

[b, c]indicate studies with (partially) overlapping populations (also see Table I).

Data synthesis and meta-analysis methods

Meta-analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA).

To assess publication bias, funnel plots for both asthma and allergy studies separately were constructed and Egger's regression tests of likelihood of publication bias were performed. Meta-analyses were performed on asthma studies of high quality (NOS $\geq$ 7). Allergy studies with NOS $\geq$ 7 were low in numbers (n = 7), and highly heterogeneous, reporting on various different types of allergies, therefore, meta-analyses of allergy studies were not attempted.

Random effects meta-analyses of asthma studies were performed to account for the expected variability in subject-level and study-level characteristics within and among individual studies, and to obtain pooled estimates of the ORs of asthma studies of high quality (NOS $\geq$ 7). ORs of individual studies were log transformed and risk ratios (RRs) were calculated for the purpose of reporting (van Rhee and Suurmond, 2015). Meta-analyses were conducted using crude effect measures, as studies adjusted for a wide range of different covariates, which may introduce bias if pooled (Metelli and Chaimani, 2020). For completeness and to test the robustness of the effect, all analyses have also been conducted using adjusted log transformed RRs, that were consistent with the effects found when using unadjusted measures (data not shown).

I^2 (%) were calculated to evaluate heterogeneity. I^2 values of <25% were considered low, scores around 50% were considered moderate and scores >75% were considered high (Borenstein *et al.*, 2009). Low I^2 values indicate that almost all of the observed inconsistencies between studies are due to random error, whereas in case of high I^2 values, additional analyses (such as sensitivity and subgroup analyses) can help explain the observed inconsistencies.

Where several studies reported on overlapping populations, only one study (NOS $\geq$ 7) per population was included in statistical analyses, to avoid giving unreasonable weight to any study population in the meta-analysis. After consultation with the authors of the respective studies, it was attempted to include the study with the most objective method of diagnosing asthma (i.e. the use of a validated/standardised method of diagnosis) and/or the most complete study population (i.e. largest number of ART offspring). If effect measures were not reported by a paper, we calculated ORs and 95% CIs. If more than one OR was available in a study (e.g. crude and adjusted or separate analyses for singletons and multiples), all ORs were extracted for subgroup analyses where relevant. Where studies included several follow-ups on the same participants, the most recent or complete follow-up was used, to avoid including the same individuals multiple times in analyses. Where different asthma outcomes were reported by a study, the most objective and standardised outcome was used.

Influence analysis

Influence analyses were performed to identify possible outliers. Identified outliers were removed from the analysis to explore their contribution to observed heterogeneity. We also explored the relative weights of individual studies and calculated a pooled estimate excluding studies with a high weight (>10%), which allowed us to examine robustness of the effect.

Subgroup analysis

Subgroup analyses were performed to investigate potential sources of heterogeneity through differences in study designs and to explore the risk of asthma in different relevant subgroups. The following subgroups were examined: (1) primary school age (age 3–12) versus adolescents/adults (age 12–35) (studies only including participants <3 years of age were excluded from this subgroup analysis), and (2) subgroup analysis by birthyear (80s-mid 90s, mid-late 90s and >2000).

Sensitivity analysis

To further investigate the data, the following sensitivity analyses were performed: studies with confirmed ART (excluding studies that included IUI, OI and 'other' fertility treatments in their ART group), studies with objective asthma diagnosis either through secure records or through the standardised 'International Study of Asthma and Allergies in Childhood' (ISAAC) questionnaire (excluding non-standardised and non-validated questionnaires, as well as spirometry only), and singleton studies (excluding analyses including multiples). Lastly, a sensitivity analysis of a select sample of singletons of appropriate age (age >3 years), with confirmed ART status and objective diagnosis of asthma was performed. We believe this portrays a 'clean' and objective sample.

Results

Search results

The medical database searches and reference checking resulted in 2673 papers, which were screened by title and abstract for a potential association between ART conception and subsequent asthma and allergies in the offspring. Of these papers, 2644 did not meet eligibility criteria or were duplicates. The full-text of the 29 remaining studies was assessed; three studies did not meet the inclusion criteria (Neri *et al.*, 2008; Beydoun *et al.*, 2010; Pelkonen *et al.*, 2015). Hence, 26 studies were included in the systematic review. Eight of the included studies included partially overlapping study populations, reporting on three different populations (Ericson *et al.*, 2002; Kallen *et al.*, 2005; Finnstrom *et al.*, 2011; Källén et al., 2013; Halliday *et al.*, 2014; Kuiper *et al.*, 2015; Halliday *et al.*, 2019; Kuiper *et al.*, 2019). Only one study per population was included in statistical analyses, following the previously described criteria (i.e. validated/standardised method of diagnosis and/or most complete study population) (Källén et al., 2013; Halliday *et al.*, 2019; Kuiper *et al.*, 2019). Therefore, a further five studies from the 26 studies included in the systematic review, were subsequently excluded from statistical analyses (Ericson *et al.*, 2002; Kallen *et al.*, 2005; Finnstrom *et al.*, 2011; Halliday *et al.*, 2014; Kuiper *et al.*, 2015). The study selection process is displayed in Fig. 1.

Of the included studies, 24 were cohort studies, of which 13 were prospective and 11 retrospective, while two studies were cross-sectional. The studies were published between 1998 and 2019 and reported on ART populations ranging from n = 59 to n = 31 918. The age of the included participants varied from <12 months to 35 years of age. Asthma and allergy diagnosis was made in various ways, ranging from self-report to use of secure records. Study characteristics and results from the individual studies are displayed in Table I (asthma studies), Table II (allergy studies) and Table III (studies investigating

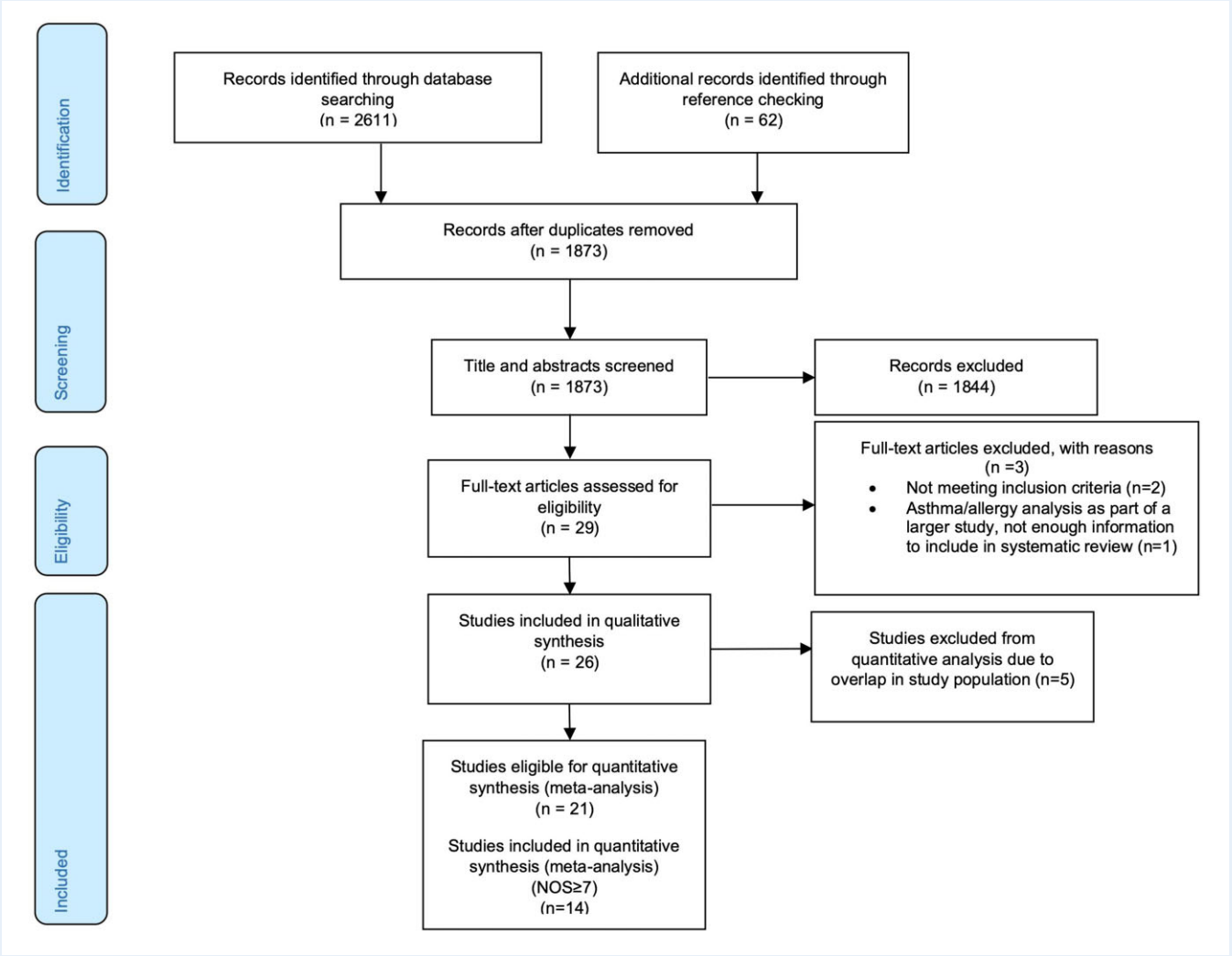

Figure 1. PRISMA flowchart of study selection process. NOS, Newcastle-Ottawa scale.

asthma and allergies). More detailed versions of the study tables can be viewed in Supplemental Tables SI–SIII, respectively.

Assessment of study quality and risk of bias

The average NOS score of all studies in this systematic review was 6.84 (range 4–9). The average NOS score of asthma studies was 6.83 (range 4–9) and the average NOS score of allergy studies was 6.58 (range 4–8).

Assessment of publication bias

The separate funnel plots for 21 (of the 24) asthma studies and for the 12 allergy studies are shown in Supplementary Fig. S1 and S2. The funnel plot for asthma studies (Supplementary Fig. S1) appeared fairly symmetrical, indicating no evidence of small-study effect or publication bias. This was supported by the results of the Egger's regression test for asthma studies ($P > 0.05$). Three of the asthma studies did not disclose raw numbers (only ORs) and we were unable to contact the authors; therefore, these studies could not be included in the funnel plot and Egger's test (Ericson *et al.*, 2002; Kallen *et al.*, 2005; Finnstrom *et al.*, 2011). The funnel plot for allergy studies (Supplementary Fig. S2) indicated some evidence of a combination of publication bias and small-study effect. Results of the Egger's regression test for allergy studies supported this with a *P*-value close to 1 ($P = 0.104$). These results support the decision to not perform a meta-analysis on allergy studies.

Assessment of asthma

Of the 26 included studies, 24 investigated the risk of asthma in offspring born from ART, reporting on approximately 95 500 ART conceived offspring (54 000 when excluding overlapping populations). Ten of these 24 used parental/self-reporting to diagnose asthma, both through the standardised ISAAC questionnaire (n = 4) and through non-standardised (n = 6) questionnaires and interviews (Bonduelle *et al.*, 2005; Knoester *et al.*, 2008; Cetinkaya *et al.*, 2009; Sicignano *et al.*, 2010; Jaderberg *et al.*, 2012; Carson *et al.*, 2013; Guibas *et al.*, 2013; Halliday *et al.*, 2014; Kuiper *et al.*, 2015, 2019). Twelve studies

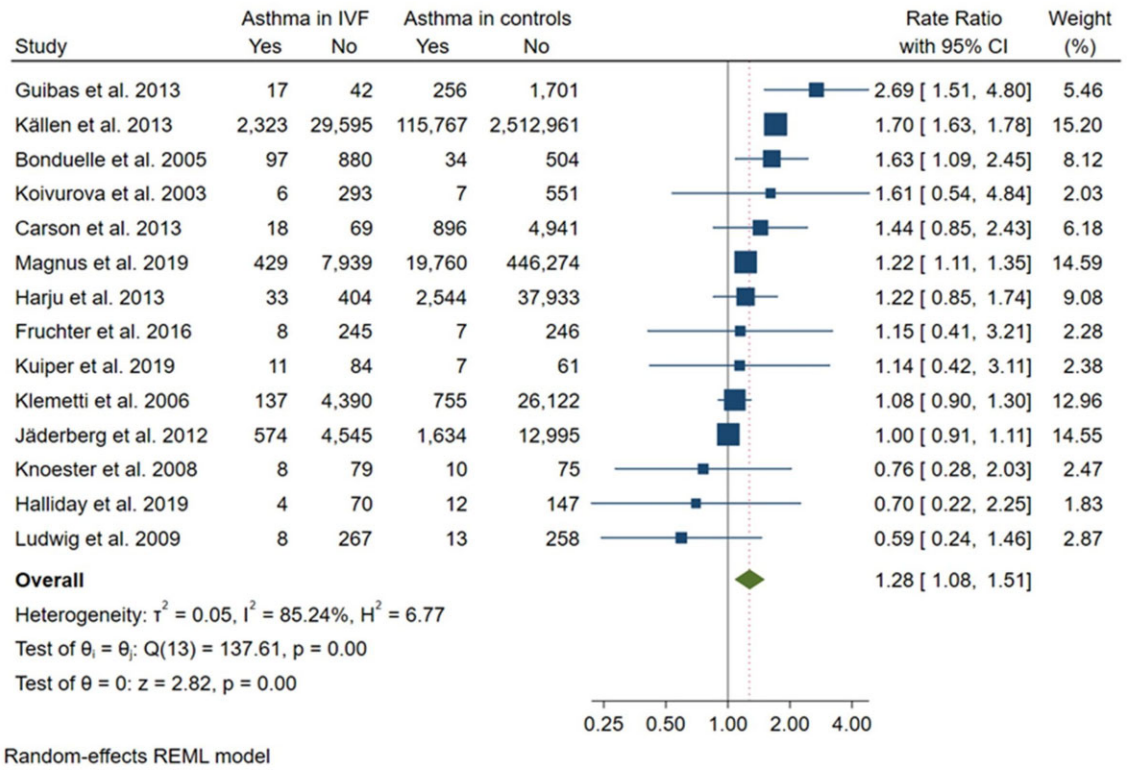

Figure 2. Forest plot of meta-analysis of high-quality asthma studies (NOS ≥ 7) (n = 14). NOS, Newcastle-Ottawa scale.

used secure records (hospital records, drug prescription registries), either alone or in combination with parental/self-reports (ISAAC n = 0, non-standardised = 3) (Wennerholm *et al.*, 1998; Ericson *et al.*, 2002; Koivurova *et al.*, 2003; Pinborg, 2003; Kallen *et al.*, 2005; Klemetti *et al.*, 2006; Ludwig *et al.*, 2009; Finnstrom *et al.*, 2011; Harju *et al.*, 2013; Källén et al., 2013; Fruchter *et al.*, 2017; Magnus *et al.*, 2019). One study used both spirometry (as a surrogate marker for asthma) and self-report (Halliday *et al.*, 2019).

Association between ART and asthma in offspring of various ages

Of the 24 asthma studies, 10 reported a statistically significant increased risk of asthma in offspring conceived after ART compared to those conceived without ART (adjusted OR (aOR) 1.20–2.38) (Ericson *et al.*, 2002; Kallen *et al.*, 2005; Finnstrom *et al.*, 2011; Carson *et al.*, 2013; Guibas *et al.*, 2013; Källén et al., 2013; Halliday *et al.*, 2014; Kuiper *et al.*, 2015; Halliday *et al.*, 2019; Magnus *et al.*, 2019), while 14 studies found no difference (aOR 0.70–1.27) (Wennerholm *et al.*, 1998; Koivurova *et al.*, 2003; Pinborg 2003; Bonduelle *et al.*, 2005; Klemetti *et al.*, 2006; Knoester *et al.*, 2008; Cetinkaya *et al.*, 2009; Ludwig *et al.*, 2009; Sicignano *et al.*, 2010; Jaderberg *et al.*, 2012; Harju *et al.*, 2013; Fruchter *et al.*, 2017; Halliday *et al.*, 2019; Kuiper *et al.*, 2019). The study by Halliday *et al.* (2019) contained two separate analyses on spirometry and self-reported asthma; hence, these have been considered as two separate studies for the purpose of this review (Halliday *et al.*, 2019).

Eight of the asthma studies were considered population studies (national registry studies and studies including all births over a period of several years). Of these eight larger population studies (NOS score between six and eight), five demonstrated a statistically significant increased risk of asthma in offspring conceived after ART when compared with offspring conceived without ART (Ericson *et al.*, 2002; Kallen *et al.*, 2005; Finnstrom *et al.*, 2011; Källén et al., 2013; Magnus *et al.*, 2019), whereas three found no difference in the rate of asthma between groups (Klemetti *et al.*, 2006; Jaderberg *et al.*, 2012; Harju *et al.*, 2013). Notably, four of the five studies that found a statistically significantly increased risk of asthma in ART offspring reported on partially overlapping populations (Ericson *et al.*, 2002; Kallen *et al.*, 2005; Finnstrom *et al.*, 2011; Källén et al., 2013).

Subfertility and the risk of asthma in offspring

In two studies that found a significant association between ART conception and subsequent asthma in the offspring, significance was lost after adjusting for parental subfertility, suggesting that the underlying subfertility might play a role in developing asthma in these offspring, and not just the ART itself (Källén et al., 2013; Magnus *et al.*, 2019). A Finnish study found a significantly increased risk of asthma in offspring born to women who experienced fertility problems in the past [aOR 1.39 (1.19–1.63)], as well as if the index pregnancy was conceived after 'any type of fertility treatment' [aOR 1.50 (1.26–1.79)] compared to offspring born to women without fertility problems. However, when investigating only the ART offspring as a subgroup compared to offspring

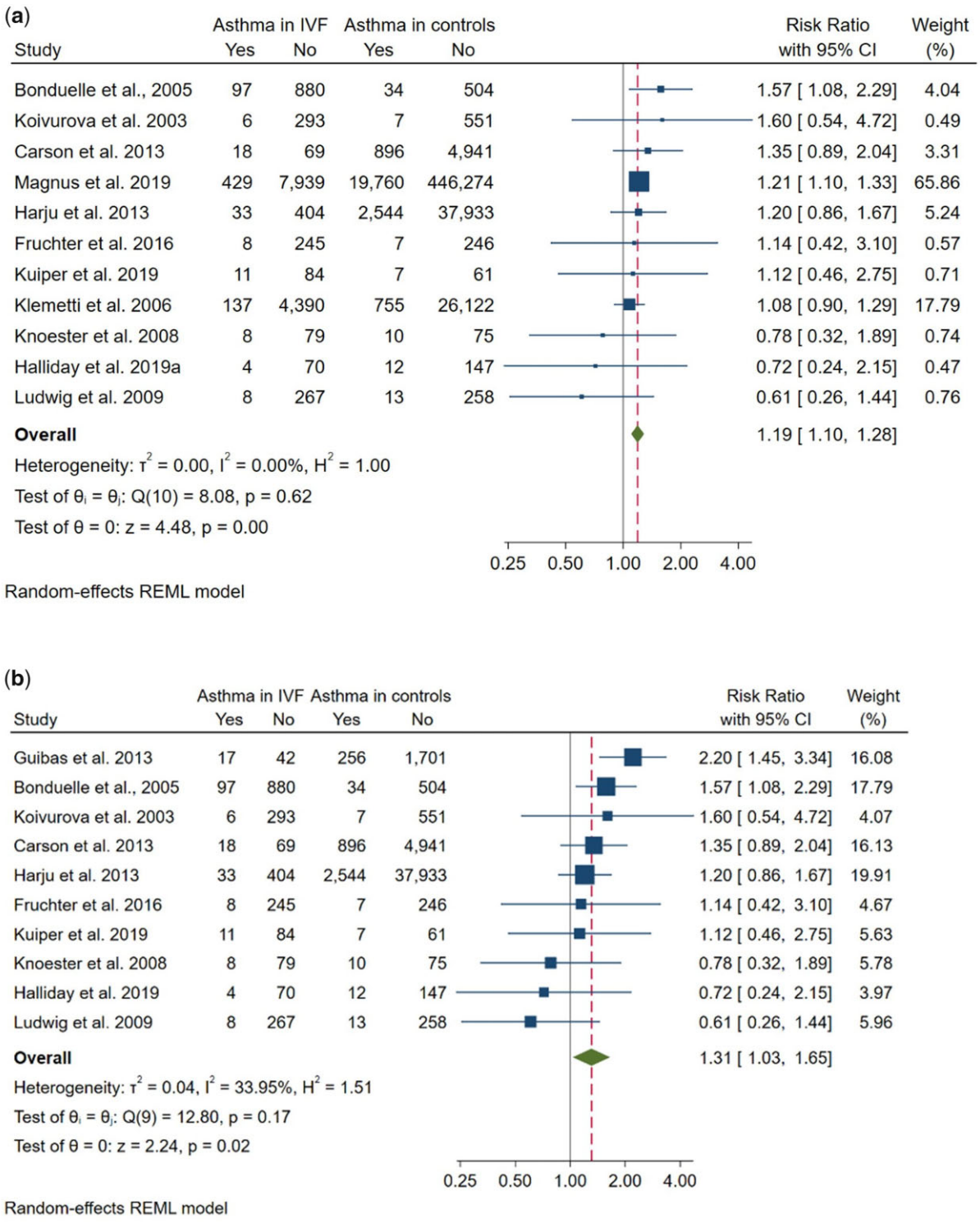

Figure 3. Forest plots of influence analyses of asthma studies. (A) Removal of three obvious outliers (n = 11). (B) Removal of four high weight studies (n = 10).

conceived without fertility treatment, there was no significantly increased risk of asthma [aOR 1.27 (0.89–1.83)] (Harju *et al.*, 2013), again suggesting that the increased risk is largely due to the underlying subfertility of a couple, and not the ART treatment or intervention itself.

Conversely, Carson *et al.* (2013) reported an increased risk of asthma amongst offspring conceived after ART compared to both offspring conceived without ART by fertile couples, as well as compared to offspring conceived without ART born to subfertile parents (Time to Pregnancy

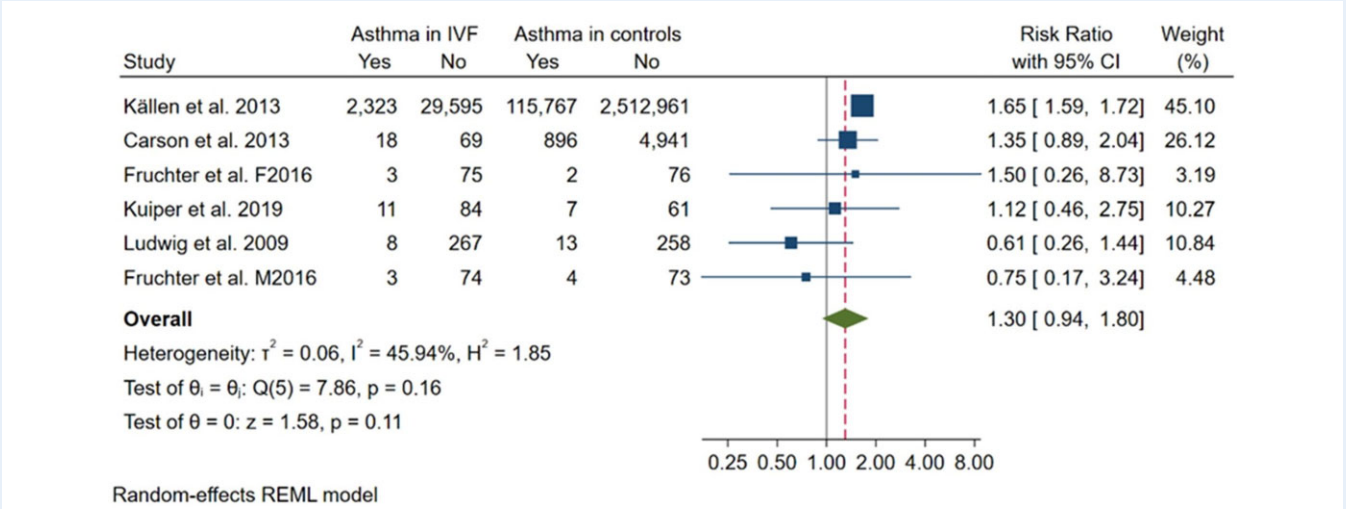

Figure 4. Forest plot of sensitivity analysis of clean and objective sample of asthma studies (i.e. singletons, of appropriate age (excluding age <3), with confirmed ART status and objective diagnosis of asthma) (n = 6).

(TTP) > 12 months) (ART vs. subfertile TTP > 12 months [aOR 1.98 (1.06–3.72)]. A Swedish study investigated asthma as a hospital discharge diagnosis, and demonstrated that the risk of asthma was increased in offspring conceived through IVF, after adjusting for years of unwanted childlessness [aOR 1.40 (1.25–1.57)] (Kallen *et al.*, 2005). However, no effect of ART on the risk of asthma was demonstrated in a Dutch study, as they reported no difference in asthma prevalence when comparing 9-year-olds conceived by subfertile parents without fertility treatment, with natural cycle IVF and with conventional IVF (Kuiper *et al.*, 2019).

Meta-analysis of asthma studies

A meta-analysis was performed after removing the low-quality studies with NOS < 7. Where studies included partially overlapping populations, only one study was included based on the previously described criteria (i.e. validated/standardised method of diagnosis and/or most complete study population). This resulted in a total of 14 studies included in the meta-analysis. The risk of asthma amongst these studies was increased in offspring conceived after ART [RR = 1.28 (1.08–1.51), $I^2 = 85.24$] (Fig. 2).

Influence analyses. To explore the heterogeneity observed in the meta-analysis of the high-quality studies, an influence analysis was performed, and this revealed three obvious outliers (Jaderberg *et al.*, 2012; Guibas *et al.*, 2013; Källén et al., 2013) (Influence analysis graph shown in Supplementary Fig. S3). When these three outliers were excluded from the analysis, the risk of asthma was still increased [RR = 1.19 (1.10–1.28)], while heterogeneity was reduced to $I^2 = 0\%$ (Fig. 3).

When the four studies with the highest relative weight (>10%) were removed from the analysis, the risk of asthma was still increased [RR 1.31 (1.03–1.65), $I^2 = 33.95\%$], indicating that the effect is robust (Fig. 3) (Klemetti *et al.*, 2006; Jaderberg *et al.*, 2012; Källén et al., 2013; Magnus *et al.*, 2019).

Subgroup analyses. The subgroup analysis of different age groups showed an increased risk of asthma in offspring conceived after ART at both primary school age [RR 1.25 (1.01–1.55)] and adolescent/adult age [RR 1.39 (1.21–1.59)] (Supplementary Fig. S4). Subgroup analysis by birth year showed an increased asthma risk in offspring conceived after ART in the 80s-mid 90s subgroup [RR 1.28 (1.06–1.56)] and in the >2000 subgroup [RR 1.26 (1.20–1.31)]. This increased risk lost significance in the mid-late 90s subgroup [RR 1.20 (0.88–1.63)] (Supplementary Fig. S5).

Sensitivity analyses. When running a sensitivity analysis on studies with confirmed ART, the risk of asthma was increased in offspring conceived after ART [RR 1.25 (1.03–1.53)] (Supplementary Fig. S6). When only investigating studies with an objective asthma diagnosis either through secure records or through the standardised ISAAC questionnaire, the increased risk was also observed [RR 1.32 (1.11–1.58)] (Supplementary Fig. S7). Furthermore, when performing a sensitivity analysis of singletons only, the risk of asthma was also increased [RR 1.22 (1.03–1.46)] (Supplementary Fig. S8).

Lastly, we performed a selective sensitivity analysis of a set of 'clean' studies which met the following criteria: singletons of appropriate age for asthma diagnosis (<3 years of age excluded), with confirmed ART status (excluding IUI, OI and 'other' fertility treatments) and objective asthma diagnosis (secure records or ISAAC questionnaire). In this sample, the risk for asthma was again increased, with a similar effect size, although it just lost statistical significance [RR 1.30 (0.94–1.80)] (Fig. 4).

Assessment of allergies

Of the 26 included studies, 12 investigated the risk of allergies in offspring born after ART, reporting on approximately 16 650 ART conceived offspring. Five of these 12 studies used parental/self-reporting to diagnose allergies, both through the standardised ISAAC questionnaire (n = 2) and through non-standardised (n = 3) questionnaires and interviews (Knoester *et al.*, 2008; Cetinkaya *et al.*, 2009; Jaderberg *et al.*, 2012; Halliday *et al.*, 2014; Kuiper *et al.*, 2019). Seven studies

used secure records (hospital records), alone or in combination with parental/self-report (ISAAC n = 0, non-standardised = 3) (Leslie *et al.*, 1998; Wennerholm *et al.*, 1998; Koivurova *et al.*, 2003; Pinborg, 2003; Klemetti *et al.*, 2006; Ludwig *et al.*, 2009; Krieger *et al.*, 2018).

Association between ART and allergies in offspring of various ages

Two of the 12 studies reported an increased risk of allergies (specifically hay fever and allergic skin reactions) (aOR 1.53–1.875) (Halliday *et al.*, 2014; Krieger *et al.*, 2018), whereas nine studies found no significant difference between offspring conceived with and without ART (aOR 0.60–1.30) (Leslie *et al.*, 1998; Wennerholm *et al.*, 1998; Koivurova *et al.*, 2003; Pinborg 2003; Klemetti *et al.*, 2006; Knoester *et al.*, 2008; Cetinkaya *et al.*, 2009; Jaderberg *et al.*, 2012; Kuiper *et al.*, 2019). One study reported no difference for hayfever ($P = 0.471$) and a decreased risk of allergies other than hayfever in ART offspring ($P = 0.028$) (Ludwig *et al.*, 2009).

The three largest population-based studies investigating a link between ART and risk of allergies reported contradictory results. One study reported a statistically significantly increased risk for skin eruptions (Krieger *et al.*, 2018), whereas another study found no difference in the rate of allergies (specifically dermatitis and urticaria) (Klemetti *et al.*, 2006). The third large study reported a statistically significantly decreased risk of hay fever and atopic dermatitis in the ART conceived group. However, after adjusting for sex, age and zygosity, these significant associations disappeared (Jaderberg *et al.*, 2012). These three studies had a NOS score of seven or eight.

Discussion

The present comprehensive systematic review investigated a potential association between assisted conception and subsequent asthma and allergies in the offspring. This is the first prospectively registered systematic review and meta-analysis solely focussing on atopic disorders.

In the current meta-analysis of 14 high-quality studies, a statistically significantly increased risk of asthma in ART offspring was observed [RR 1.28 (1.08–1.51)], although the magnitude of the effect was relatively modest. Although heterogeneity in the 14 studies was high ($I^2 = 85\%$), the removal of outliers and studies with high weight significantly reduced heterogeneity ($I^2 = 0\%$ and $I^2 = 34\%$, respectively), while maintaining a significantly increased risk of asthma [RR 1.19 (1.10–1.28) and RR 1.31 (1.03–1.65), respectively]. Interestingly, this increased risk was seen across almost all subgroups and sensitivity analyses. In two of the sensitivity analyses (confirmed ART and objective asthma diagnosis), the increased risk was even more evident than in the overall meta-analysis, meaning that the excluded studies diminished any effect seen. The increased risk only just lost significance in the analysis of the 'clean' sample (i.e. singletons, of appropriate age (excluding age < 3), with confirmed ART status and objective diagnosis of asthma), as well as in children born between the mid and late 90s [RR 1.30 (0.94–1.80) and RR 1.20 (0.88–1.63), respectively]. As the effect size was preserved, but the variance increased, the former potentially indicates a reduction in combined study size. The latter could potentially be explained by changes in IVF protocols over time, although an increased asthma risk was reported in both the older and the most recent birth years. Additional subgroup analyses did not provide further insight into potential explanations for an increased asthma risk in offspring conceived after ART. Heterogeneity was largely reduced by excluding outliers; however, this was also reduced in some of the subgroups. A clear increased risk of allergies in offspring conceived with ART versus offspring conceived without ART was not detected in this review.

A recent systematic review and meta-analysis reported an increased risk of 'asthma medication use', 'wheezing' and asthma in ART offspring, 'regardless of how the diagnosis was made', but not of 'physician diagnosed asthma' (Tsabouri et al., 2021). It is worth noting that the publication included substantially fewer studies than the current prospectively registered review (13 versus 18 primary study populations investigating asthma), omitting some important high-quality studies and reporting on an overall lower number of offspring. The study did not extensively explore heterogeneity, nor did it report on allergies. Two older reviews, reporting on various different health outcomes, reported no increased risk of asthma in offspring conceived after ART or inconsistent results (Hart and Norman, 2013; Kettner *et al.*, 2015). This current systematic review incorporates a substantial number of new publications on the topic (16 additional studies compared to Kettner *et al.* (2015) and 24 additional studies compared to Hart and Norman (2013)), including a number of large population studies, thereby providing a more up-to-date and robust set of findings and conclusions on the topic.

Potential causal pathways for an association between ART and atopy

There are several different hypotheses that may explain a potential association between conception via ART and risk of atopic disorders in the offspring. It is clear that a combination of genetic, epigenetic, environmental and pregnancy-related mechanisms lead to the development of asthma (Moffatt *et al.*, 2010; Torgerson *et al.*, 2011; Papi *et al.*, 2018), and many of these mechanisms could play a role in a potential association between ART conception and the development of asthma in the offspring.

Epigenetics and ART treatment

ART, by its very nature, perturbs the natural process of conception, requiring ovarian stimulation, manipulation of the oocyte and sperm, IVF or ICSI and culture of the embryo in the laboratory setting. Hence, these significant environmental influences around the time of conception have been associated with inducing epigenetic alterations in the embryo (Fleming *et al.*, 2018). These epigenetic alterations can affect perinatal outcomes and developmental trajectories, and thereby increase risks of later pathophysiologic processes (Jiang *et al.*, 2017; Fleming *et al.*, 2018; Roseboom, 2018). The hypothesis that perturbation of early gametes or embryos could induce epigenetic alterations in the peri-conception period and lead to potential adverse effects on long-term health has been summarised elsewhere (Fleming *et al.*, 2018; Penova-Veselinovic *et al.*, 2021). Several studies have reported epigenetic alterations in genes linked to childhood asthma (Harris *et al.*, 2013; Reese *et al.*, 2019). Furthermore, epigenetic changes leading to an increased risk of asthma have already been demonstrated with prenatal exposure to smoke and air pollution; hence, it is plausible that epigenetic changes from ART could increase risk of asthma in offspring (Hsu *et al.*, 2015; Miller and Lawrence 2018).

Subfertility and genetics

Couples seeking ART treatments may differ from those who conceive naturally; hence, genetic predisposition to asthma may be contributed to by the genetic risk of parental subfertility rather than the direct effect of ART treatments. Three of the studies in the current review that controlled for parental subfertility found that the association of asthma with ART conception was not significant after controlling for parental subfertility (Harju *et al.*, 2013; Källén et al., 2013; Magnus *et al.*, 2019). On the other hand, two studies demonstrated an increased risk of asthma in ART offspring even after controlling for subfertility, indicating that the increased risk of asthma could be a direct effect of the ART treatment (Kallen *et al.*, 2005; Carson *et al.*, 2013).

Additionally, it remains unclear whether or not couples with asthma are more likely to be subfertile. A recent systematic review summarised the literature on female asthma and atopy and the impact on fertility. Outcomes of interest were number of offspring, TTP and the need for fertility treatment. Although the results are conflicting, there appears to be a trend towards an increase in subfertility in asthmatic women, particularly an increased TTP and the need for fertility treatment. The eventual number of offspring appears to not differ (Blafoss *et al.*, 2019). One registry-based study reported a relation between severity of asthma and infertility, as well as between use of medication (controlled asthma) and infertility (Gade *et al.*, 2014). With respect to a link with male infertility, there is a paucity of data relating asthma and allergy to male causes of infertility. Parental asthma is a known risk factor for the development of asthma in children (Castro-Rodriguez *et al.*, 2016). If parents needing fertility treatment are indeed more often atopic, this could be another explanation for a potential increase in atopic disorders in their offspring, through direct genetic effects. In the current review, five asthma studies adjusted for maternal or parental asthma. Two of these studies report an increased risk of asthma in both unadjusted as well as adjusted analyses (Carson *et al.*, 2013; Magnus *et al.*, 2019), one study reported an increased risk only after adjusting (Kuiper *et al.*, 2015), and two studies report no significant differences between offspring conceived with and without ART (Harju *et al.*, 2013; Kuiper *et al.*, 2019).

Furthermore, pregnancy risk factors for asthma are also more commonly experienced in pregnancies conceived through ART, including PTB, LBW, neonatal morbidity and delivery by CS, which could possibly mediate an association between ART conception and subsequent asthma in the offspring (Pandey *et al.*, 2012; Declercq *et al.*, 2015; Qin *et al.*, 2015). However, it is important to note that maternal asthma is also known to increase the risk of PTB and LBW in offspring (Kemppainen *et al.*, 2018; Rejnö *et al.*, 2018). Furthermore, various studies have demonstrated that subfertility itself, without the use of ART, leads to an increased risk of PTB and LBW (Basso and Baird, 2003; Thomson *et al.*, 2005; Jaques *et al.*, 2010). Interestingly, a Norwegian study, using the sibship approach, and therewith keeping maternal characteristics stable, demonstrated no significant difference in PTB and LBW when comparing offspring conceived naturally and their siblings conceived after ART. This indicates, that the underlying parental subfertility rather than the ART treatment itself could be explaining the increase in perinatal risk factors (Romundstad *et al.*, 2008).

Another possible explanation for an association between ART and asthma risk could be an increased healthcare seeking behaviour from parents of children conceived after ART, who are perhaps more health literate or overprotective (Hahn and DiPietro, 2001). Parents being overprotective can also lead to a 'clean' lifestyle with less exposure to various micro-organisms early in life. Children conceived by ART are also less likely to have a sibling and more likely to be the first born in a family. These factors could in turn lead to higher rates of atopic disorders.

It remains unknown whether the increased risk of asthma in ART offspring demonstrated here is due to a direct effect of ART or mediated by other factors such as the underlying subfertility, an increase in parental atopy, or an increase in perinatal risk factors such as LBW, PTB, CS delivery and other environmental factors. With many Western countries having moved to single embryo transfer policies, a reduction in LBW and PTB is also expected in more recent ART populations (Henningsen *et al.*, 2015; Newman *et al.*, 2019). In this review, we reported that the increased risk of asthma was also evident in the most recent cohorts. This could indicate that the effect seen may be at least partly explained by epigenetic alterations following ART in general and not restricted only to the older/historic protocols; however, further research is needed to clarify the mechanism(s). To further explore the role of the underlying infertility in the development of asthma, future studies could compare offspring conceived without ART to fertile parents, with offspring conceived without ART to subfertile parents, and offspring conceived after ART. To keep parental factors stable and account for the underlying subfertility, large registry studies using the sibship and/or an intersibling approach, as used previously for short-term health outcomes in offspring conceived after ART, may be useful for long-term health outcomes such as asthma and allergies (Seggers *et al.*, 2016). It would also be valuable if studies could combine ART registers with health registers containing parental health information, to account for parental atopy. Furthermore, future studies could investigate the effect of perinatal risk factors by comparing fresh ET with FET, as FET has been associated with a decreased risk of PTB and LBW (Maheshwari *et al.*, 2016; Zhao *et al.*, 2016).

Strengths and limitations

This systematic review utilised a very comprehensive search strategy to thoroughly interrogate databases from the inception of ART until most recent publications, without language restrictions. Furthermore, the search strategy identified studies that investigated the risk of asthma and/or allergies in offspring conceived after ART, as a substudy of a larger study, and studies that did not report on asthma/allergy in the abstract as well as studies that reported non-significant results. Therefore, selective reporting bias is reduced. Selective reporting bias is further reduced by the use of a pre-specified protocol, identifying asthma and allergy as primary outcomes.

Another strength of this systematic review was inclusion of all studies irrespective of quality and subsequent critical analysis of the quality of included studies against standardised and validated criteria using the NOS. Furthermore, through extensive additional analyses, we were able to deal with encountered heterogeneity appropriately.

This systematic review also has various limitations. Studies were largely conducted in Europe (84%), specifically North/Western Europe (68%), and the remaining studies were from the USA and Australia. This potentially decreases the applicability of the findings to other populations and ethnicities. Many of the studies were retrospective register studies, which limited the ability to adjust for covariates by the availability of information. Furthermore, several of the larger studies were

multi-outcome studies. Therefore, the choice of adjustment for covariates in included studies was not always optimal for investigating asthma and allergies. Additionally, asthma manifests across the first few years of life and a limitation of many studies was the young age of the participants, often under age 3.

The study designs varied significantly between included studies, for example, length of follow up, age at diagnosis and assessment of outcome. Variation in follow-up periods, in combination with the diverse expression of the disease during different periods of life, may also possibly account for the contradicting results in literature to date and lead to bias when pooling results. Assessment of outcomes varied significantly from self-reported non-standardised questionnaires to hospital discharge diagnosis or drug registries for anti-asthmatic and allergy drugs. Only one study used spirometry (as a surrogate marker for asthma) and none used skin-prick tests to confirm allergies. Partly, it was difficult to ascertain the type of ART utilised in treatment groups, with some studies stating as little as 'fertility treatments'. If the 'ART group' in those studies included children conceived through OI or IUI, any overall effect seen due to IVF/ICSI conception on increased risk of asthma could be weakened. However, this was tested by running a sensitivity analysis of 'confirmed ART', which showed a similar effect size and variance as the overall meta-analysis.

As described above, the clinical and methodological heterogeneity among the included studies in the meta-analysis of high-quality asthma studies was high ($I^2 = 85\%$), which reduced the level of reliability of a meta-analysis. However, as additional influence, subgroup and sensitivity analyses partly reduced heterogeneity, while still demonstrating an increased risk; we believe the findings are robust and valid. To some extent, heterogeneity was expected, as ART is an emerging technology that has undergone dramatic changes and advancements over the past 40 years; in addition, treatment is very centre based. Nonetheless, residual bias due to pooling of data cannot be entirely ruled out and these results need to be interpreted with caution.

Of the 26 included studies, eight studies (reporting on three different populations) had a partial overlap in study population, meaning that individual patients are potentially included several times in the current review, which can compromise the evidence behind the results of the systematic review. In particular, four of the studies with overlap in study populations were large population studies, which reported a significantly increased risk of asthma in children conceived after ART. The overlap was either due to multiple studies reporting on the same population at different ages or with the diagnosis made in a different way or by registry studies including additional participants. To avoid compromising statistical analyses in this systematic review, only one study per population was included in quantitative analyses.

Lastly, there does not appear to be evidence of data being skewed due to publication bias in asthma studies, although this cannot be entirely ruled out. In the allergy studies there appeared to be some evidence of minimal publication bias and small study effect. Therefore, it is possible that there is a small amount of evidence that we are not reporting on. Despite a recent increase in studies investigating the topic, it is still questionable whether there is enough homogeneous evidence to draw strong conclusions.

Conclusion

This systematic review and meta-analysis demonstrated an increased risk of childhood asthma in the offspring conceived after ART [RR = 1.28 (1.08–1.51)]. There did not appear to be a link between ART and other atopic disorders.

It is still unclear, whether the reported increased risk of asthma in ART conceived offspring is a direct effect of ART treatment, or mediated by the underlying subfertility and/or perinatal risk factors in ART pregnancies. Furthermore, the magnitude of the increased asthma risk was relatively modest, and it cannot be excluded that it is a result of residual confounding and bias. However, since ART is an increasingly common practice in the developed world, it is important to further investigate this potential increased risk, both to be vigilant for high-risk disorders in these offspring, as well as to give future parents considering ART evidence-based advice.

Additional well-designed large studies are needed to provide confirmation of the findings and greater clarity and confidence with regards to the risks for different types of ART (i.e. ICSI and IVF) in different populations with differing underlying risk factors (i.e. causes of subfertility). Large registry studies could potentially consider conducting individual patient meta-analysis for more homogeneous results.

Supplementary data

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

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

The authors' contributions were as follows. L.A.W. contributed to the study hypothesis and study design, reviewed the literature, collected the data, provided interpretation of the results, assisted in statistical analyses and drafted and edited the manuscript. M.R.F. contributed to the study design, reviewed the literature, collected the data, provided interpretation of the results and assisted in drafting and editing the manuscript. R.J.H. contributed to the study hypothesis and study design, settled disagreements between the first two authors, provided interpretation of the results and assisted in editing the manuscript. D.A.D. contributed to the study hypothesis and study design, provided

interpretation of the results, conducted the statistical analyses and assisted in editing the manuscript. J.A.K. contributed to the study hypothesis and study design, provided interpretation of the results and assisted in editing the manuscript. All authors assisted in critical discussion and approval of the final manuscript.

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Conflict of interest

R.J.H. is the medical director of Fertility Specialists of Western Australia; he has equity interests in Western IVF and has received educational grants from Merck and Ferring Pharmaceuticals and has received honoraria from Merck. No other conflicts of interest are reported.

References

Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–743.

Basso O, Baird DD. Infertility and preterm delivery, birthweight, and Caesarean section: a study within the Danish National Birth Cohort. *Hum Reprod* 2003;**18**:2478–2484.

Beydoun HA, Sicignano N, Beydoun MA, Matson DO, Bocca S, Stadtmauer L, Oehninger S. A cross-sectional evaluation of the first cohort of young adults conceived by in vitro fertilization in the United States. *Fertil Steril* 2010;**94**:2043–2049.

Blafoss J, Hansen AV, Malchau Lauesgaard SS, Ali Z, Ulrik CS. Female asthma and atopy—impact on fertility: a systematic review. *J Asthma Allergy* 2019;**12**:205–211.

Bonduelle M, Wennerholm UB, Loft A, Tarlatzis BC, Peters C, Henriet S, Mau C, Victorin-Cederquist A, Van Steirteghem A, Balaska A *et al*. A multi-centre cohort study of the physical health of 5-year-old children conceived after intracytoplasmic sperm injection, in vitro fertilization and natural conception. *Hum Reprod* 2005;**20**:413–419.

Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis*. United Kingdom: John Wiley & Sons Ltd, 2009.

Calhaz-Jorge C, De Geyter C, Kupka MS, de Mouzon J, Erb K, Mocanu E, Motrenko T, Scaravelli G, Wyns C, Goossens V; European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. *Hum Reprod* 2017;**32**:1957–1973.

Carson C, Sacker A, Kelly Y, Redshaw M, Kurinczuk JJ, Quigley MA. Asthma in children born after infertility treatment: findings from the UK Millennium Cohort Study. *Hum Reprod* 2013;**28**:471–479.

Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, Celedon JC. Risk and protective factors for childhood asthma: what is the evidence? *J Allergy Clin Immunol Pract* 2016;**4**:1111–1122.

Cetinkaya F, Gelen SA, Kervancioglu E, Oral E. Prevalence of asthma and other allergic diseases in children born after in vitro fertilisation. *Allergol Immunopathol (Madr)* 2009;**37**:11–13.

Declercq E, Luke B, Belanoff C, Cabral H, Diop H, Gopal D, Hoang L, Kotelchuck M, Stern JE, Hornstein MD. Perinatal outcomes associated with assisted reproductive technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). *Fertil Steril* 2015;**103**:888–895.

Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol* 2012;**27**:5–14.

Ericson A, Nygren K, Otterblad Olausson P, Kallen B. Hospital care utilization of infants born after IVF. *Hum Reprod* 2002;**17**:929–932.

Farquhar C, Marjoribanks J. Assisted reproductive technology: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2018;**8**:CD010537–146.

Fauser BC. Towards the global coverage of a unified registry of IVF outcomes. *Reprod Biomed Online* 2019;**38**:133–137.

Finnstrom O, Kallen B, Lindam A, Nilsson E, Nygren KG, Olausson PO. Maternal and child outcome after in vitro fertilization—a review of 25 years of population-based data from Sweden. *Acta Obstet Gynecol Scand* 2011;**90**:494–500.

Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, Barker M, Saffery R, Yajnik CS, Eckert JJ *et al*. Origins of lifetime health around the time of conception: causes and consequences. *Lancet* 2018;**391**:1842–1852.

Fruchter E, Beck-Fruchter R, Hourvitz A, Weiser M, Goldberg S, Fenchel D, Lerner-Geva L. Health and functioning of adolescents conceived by assisted reproductive technology. *Fertil Steril* 2017;**107**:774–780.

Gade EJ, Thomsen SF, Lindenberg S, Kyvik KO, Lieberoth S, Backer V. Asthma affects time to pregnancy and fertility: a register-based twin study. *Eur Respir J* 2014;**43**:1077–1085.

Guibas GV, Moschonis G, Xepapadaki P, Roumpedaki E, Androutsos O, Manios Y, Papadopoulos NG. Conception via in vitro fertilization and delivery by Caesarean section are associated with paediatric asthma incidence. *Clin Exp Allergy* 2013;**43**:1058–1066.

Hahn C, DiPietro JA. In vitro fertilization and the family: quality of parenting, family functioning, and child psychosocial adjustment. *Dev Psychol* 2001;**37**:37–48.

Halliday J, Lewis S, Kennedy J, Burgner DP, Juonala M, Hammarberg K, Amor DJ, Doyle LW, Saffery R, Ranganathan S *et al*. Health of adults aged 22 to 35 years conceived by assisted reproductive technology. *Fertil Steril* 2019;**112**:130–139.

Halliday J, Wilson C, Hammarberg K, Doyle LW, Bruinsma F, McLachlan R, McBain J, Berg T, Fisher JR, Amor D. Comparing indicators of health and development of singleton young adults conceived with and without assisted reproductive technology. *Fertil Steril* 2014;**101**:1055–1063.

Harju M, Keski-Nisula L, Raatikainen K, Pekkanen J, Heinonen S. Maternal fecundity and asthma among offspring-is the risk

programmed preconceptionally? Retrospective observational study. *Fertil Steril* 2013;**99**:761–767.

Harris RA, Nagy-Szakal D, Kellermayer R. Human metastable epiallele candidates link to common disorders. *Epigenetics* 2013;**8**:157–163.

Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment: Part I—general health outcomes. *Hum Reprod Update* 2013;**19**:232–243.

Henningsen AA, Gissler M, Skjaerven R, Bergh C, Tiitinen A, Romundstad LB, Wennerholm UB, Lidegaard O, Nyboe Andersen A, Forman JL *et al*.. Trends in perinatal health after assisted reproduction: a Nordic study from the CoNARTaS group. Hum Reprod 2015;**30**:710–716. 10.1093/humrep/deu345 25605701

Hsu HH, Chiu YH, Coull BA, Kloog I, Schwartz J, Lee A, Wright RO, Wright RJ. Prenatal particulate air pollution and asthma onset in urban children. Identifying sensitive windows and sex differences. *Am J Respir Crit Care Med* 2015;**192**:1052–1059.

Huang L, Chen Q, Zhao Y, Wang W, Fang F, Bao Y. Is elective cesarean section associated with a higher risk of asthma? A meta-analysis. *J Asthma* 2015;**52**:16–25.

Jaakkola JJ, Ahmed P, Ieromnimon A, Goepfert P, Laiou E, Quansah R, Jaakkola MS. Preterm delivery and asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2006;**118**:823–830.

Jaderberg I, Thomsen SF, Kyvik KO, Skytthe A, Backer V. Atopic diseases in twins born after assisted reproduction. *Paediatr Perinat Epidemiol* 2012;**26**:140–145.

Jaques AMPD, Amor D, Baker H, Healy DLPD, Ukoumunne OCPD, Breheny SBS, Garrett CPD, Halliday JLPD. Adverse obstetric and perinatal outcomes in subfertile women conceiving without assisted reproductive technologies. *Fertil Steril* 2010;**94**:2674–2679.

Jiang Z, Wang Y, Lin J, Xu J, Ding G, Huang H. Genetic and epigenetic risks of assisted reproduction. *Best Pract Res Clin Obstet Gynaecol* 2017;**44**:90–104.

Kallen B, Finnstrom O, Nygren KG, Olausson PO. In vitro fertilization in Sweden: child morbidity including cancer risk. *Fertil Steril* 2005;**84**:605–610.

Källén B, Finnström O, Nygren K-G, Otterblad Olausson P. Asthma in Swedish children conceived by in vitro fertilisation. *Arch Dis Child* 2013;**98**:92–96.

Kemppainen M, Lahesmaa-Korpinen A-M, Kauppi P, Virtanen M, Virtanen SM, Karikoski R, Gissler M, Kirjavainen T. Maternal asthma is associated with increased risk of perinatal mortality. *PLoS One* 2018;**13**:e0197593.

Kettner LO, Henriksen TB, Bay B, Ramlau-Hansen CH, Kesmodel US. Assisted reproductive technology and somatic morbidity in childhood: a systematic review. *Fertil Steril* 2015;**103**:707–719.

Klemetti R, Sevon T, Gissler M, Hemminki E. Health of children born as a result of in vitro fertilization. *Pediatrics* 2006;**118**:1819–1827.

Knoester M, Helmerhorst FM, Vandenbroucke JP, van der Westerlaken LA, Walther FJ, Veen S; Leiden Artificial Reproductive Techniques Follow-up Project (L-art-FUP). Perinatal outcome, health, growth, and medical care utilization of 5- to 8-year-old intracytoplasmic sperm injection singletons. *Fertil Steril* 2008;**89**:1133–1146.

Koivurova S, Hartikainen AL, Sovio U, Gissler M, Hemminki E, Jarvelin MR. Growth, psychomotor development and morbidity up to 3 years of age in children born after IVF. *Hum Reprod* 2003;**18**:2328–2336.

Krieger Y, Wainstock T, Sheiner E, Harlev A, Landau D, Horev A, Bogdanov-Berezovsky A, Walfisch A. Long-term pediatric skin eruption-related hospitalizations in offspring conceived via fertility treatment. *Int J Dermatol* 2018;**57**:317–323.

Kuiper DB, Koppelman GH, la Bastide-van Gemert S, Seggers J, Haadsma ML, Roseboom TJ, Hoek A, Heineman MJ, Hadders-Algra M. Asthma in 9-year-old children of subfertile couples is not associated with in vitro fertilization procedures. *Eur J Pediatr* 2019;**178**:1493–1499.

Kuiper DB, Seggers J, Schendelaar P, Haadsma ML, Roseboom TJ, Heineman MJ, Hadders-Algra M. Asthma and asthma medication use among 4-year-old offspring of subfertile couples—association with IVF? *Reprod Biomed Online* 2015;**31**:711–714.

Leslie GI, Gibson FL, McMahon C, Tennant C, Saunders DM. Infants conceived using in-vitro fertilization do not overutilize health care resources after the neonatal period. *Hum Reprod* 1998;**13**:2055–2059.

Ludwig AK, Katalinic A, Thyen U, Sutcliffe AG, Diedrich K, Ludwig M. Physical health at 5.5 years of age of term-born singletons after intracytoplasmic sperm injection: results of a prospective, controlled, single-blinded study. *Fertil Steril* 2009;**91**:115–124.

Magnus MC, Karlstad O, Parr CL, Page CM, Nafstad P, Magnus P, London SJ, Wilcox AJ, Nystad W, Haberg SE. Maternal history of miscarriages and measures of fertility in relation to childhood asthma. *Thorax* 2019;**74**:106–113.

Maheshwari A, Raja EA, Bhattacharya S. Obstetric and perinatal outcomes after either fresh or thawed frozen embryo transfer: an analysis of 112,432 singleton pregnancies recorded in the Human Fertilisation and Embryology Authority anonymized dataset. *Fertil Steril* 2016;**106**:1703–1708.

Metelli S, Chaimani A. Challenges in meta-analyses with observational studies. *Evid Based Ment Health* 2020;**23**:83–87.

Miller RL, Lawrence J. Understanding root causes of asthma. Perinatal environmental exposures and epigenetic regulation. *Ann Am Thorac Soc* 2018;**15**:S103–S108.

Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, Perruolo E, Parati G; ESH Working Group on CV Risk in Low Resource Settings. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. *PLoS One* 2016;**11**:e0147601.

Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, von Mutius E, Farrall M, Lathrop M, Cookson WOCM; GABRIEL Consortium. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010;**363**:1211–1221.

Moher D, Liberati A, Tetzlaff J, Altman DG, Group P; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.

Mu M, Ye S, Bai MJ, Liu GL, Tong Y, Wang SF, Sheng J. Birth weight and subsequent risk of asthma: a systematic review and meta-analysis. *Heart Lung Circ* 2014;**23**:511–519.

Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, Fitzsimmons D, Bandyopadhyay A, Aftab C, Simpson CR *et al*. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016;**14**:113.

Neri QV, Takeuchi T, Palermo GD. An update of assisted reproductive technologies results in the United States. *Ann N Y Acad Sci* 2008;**1127**:41–48.

Newman JE, Fitzgerald O, Paul RC, Chambers GM. Assisted Reproductive Technology in Australia and New Zealand 2017. In: National Perinatal Epidemiology and Statistics Unit. *Sydney: The University of New South Wales*. 2019.

Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update* 2012;**18**:485–503.

Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018; **391**:783–800.

Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J* 2014;**7**:1–3.

Pawankar R, Canonica GW, Holgate ST, Lockey RG, Blaiss M. *The WAO White Book on Allergy*. Wisconsin, USA: World Allergy Organ. 2013.

Pelkonen S, Gissler M, Koivurova S, Lehtinen S, Martikainen H, Hartikainen AL, Tiitinen A. Physical health of singleton children born after frozen embryo transfer using slow freezing: a 3-year follow-up study. *Hum Reprod* 2015;**30**:2411–2418.

Penova-Veselinovic B, Melton PE, Huang RC, Yovich JL, Burton P, Wijs LA, Hart RJ. DNA methylation patterns within whole blood of adolescents born from assisted reproductive technology are not different from adolescents born from natural conception. *Hum Reprod* 2021;**36**:2035–2049.

Pinborg A. Morbidity in a Danish National cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: health-related and social implications for the children and their families. *Hum Reprod* 2003;**18**:1234–1243.

Qin J, Sheng X, Wang H, Liang D, Tan H, Xia J. Assisted reproductive technology and risk of congenital malformations: a meta-analysis based on cohort studies. *Arch Gynecol Obstet* 2015;**292**: 777–798.

Reese SE, Xu C-J, den Dekker HT, Lee MK, Sikdar S, Ruiz-Arenas C, Merid SK, Rezwan FI, Page CM, Ullemar V *et al*. Epigenome-wide meta-analysis of DNA methylation and childhood asthma. *J Allergy Clin Immunol* 2019;**143**:2062–2074.

Rejnö G, Lundholm C, Larsson K, Larsson H, Lichtenstein P, D'Onofrio BM, Saltvedt S, Almqvist C. Adverse pregnancy outcomes in asthmatic women: a population-based family design study. *J Allergy Clin Immunol Pract* 2018;**6**:916–922.e6.

Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjærven R, Gunnell D, Vatten LJ. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. *Lancet* 2008;**372**:737–743.

Roseboom TJ. Developmental plasticity and its relevance to assisted human reproduction. *Hum Reprod* 2018;**33**:546–552.

Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. *N Engl J Med* 2002;**346**:731–737.

Seggers J, Pontesilli M, Ravelli ACJ, Painter RC, Hadders-Algra M, Heineman MJ, Repping S, Mol BWJ, Roseboom TJ, Ensing S. Effects of in vitro fertilization and maternal characteristics on perinatal outcomes: a population-based study using siblings. *Fertil Steril* 2016; **105**:590–598.e2.

Sicignano N, Beydoun HA, Russell H, Jones H Jr, Oehninger S. A descriptive study of asthma in young adults conceived by IVF. *Reprod Biomed Online* 2010;**21**:812–818.

Thomson F, Shanbhag S, Templeton A, Bhattacharya S. Obstetric outcome in women with subfertility. *BJOG* 2005;**112**:632–637.

Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, Himes BE, Levin AM, Mathias RA, Hancock DB *et al.*; Genetic Research on Asthma in African Diaspora (GRAAD) Study. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat Genet* 2011; **43**:887–892.

Tsabouri S, Lavasidis G, Efstathiadou A, Papasavva M, Bellou V, Bergantini H, Priftis K, Ntzani EE. Association between childhood asthma and history of assisted reproduction techniques: a systematic review and meta-analysis. *Eur J Pediatr* 2021;**180**:2007–2017.

van Rhee H, Suurmond R. Meta-analyze dichotomous data: do the calculations with log odds ratios and report risk ratios or risk differences. 2015. Available at SSRN: https://ssrn.com/abstract=3241369 (25 March, 2021, date last accessed).

Vermeiden JP, Bernardus RE. Are imprinting disorders more prevalent after human in vitro fertilization or intracytoplasmic sperm injection? *Fertil Steril* 2013;**99**:642–651.

Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abdulkader RS, Abdulle AM, Abebo TA, Abera SF *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;**390**:1211–1259.

Wells GA, Shea B, O'Connel D, Peterson J, Welch V, Losos M, Tugwell P. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Canada: University of Ottawa, 2000. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Wen J, Jiang J, Ding C, Dai J, Liu Y, Xia Y, Liu J, Hu Z. Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis. *Fertil Steril* 2012;**97**: 1331–1337.

Wennerholm U-B, Albertsson-Wikland K, Bergh C, Hamberger L, Niklasson A, Nilsson L, Thiringer K, Wennergren M, Wikland M, Borres MP. Postnatal growth and health in children born after cryopreservation as embryos. *Lancet* 1998;**351**:1085–1090.

WHO. Asthma Fact Sheet. World Health Organization. https://www.who.int/en/news-room/fact-sheets/detail/asthma (2 March, 2021, date last accessed). 2020.

Zhao J, Xu B, Zhang Q, Li YP. Which one has a better obstetric and perinatal outcome in singleton pregnancy, IVF/ICSI or FET?: a systematic review and meta-analysis. *Reprod Biol Endocrinol* 2016;**14**:51.

Zhu JL, Obel C, Hammer Bech B, Olsen J, Basso O. Infertility, infertility treatment and fetal growth restriction. *Obstet Gynecol* 2007; **110**:1326–1334.