ABSTRACT

Background. Reduced birth weight is associated with many maternal environmental exposures during pregnancy, but the gestational age at onset of this association is unknown. We have previously reported associations between maternal smoking and fetal size.

Objective. To report on our systematic review of the literature describing associations between antenatal size and growth and maternal exposures during pregnancy.

Data sources. Electronic databases (OVID and EMBASE) and web sites for cohort studies were searched.

Study eligibility. Studies were eligible if they examined associations between maternal environmental exposures (including ambient air exposure, diet and alcohol) and antenatal fetal ultrasound measurements.

Study appraisal. The Navigation Guide was used to assess the strength of evidence.

Results. There were 451 abstracts identified and 36~~5~~ papers were included of which maternal diet was the exposure of interest in 15, maternal ambient air exposure in 10, maternal alcohol in 3 and other exposures in 8~~7~~. The first paper was published in 2006. Associations were present between exposures in 18~~9~~% of comparisons with second trimester measurements and in 46~~4~~% of comparisons with third trimester measurements. In the third trimester, when an association was present, reduced head size was most commonly (58~~60~~%) associated with current or previous maternal exposure, with reduced length being least commonly (32~~27~~%) associated and reduced weight being intermediate (52~~46~~%). In the third trimester, increased maternal nitrogen dioxide exposure was associated with reduced head size was associated with in all seven studies identified and reduced fetal weight in five out of six studies.

Conclusion. There is sufficient evidence of toxicity in the context of maternal exposure to nitrogen dioxide and reduced third trimester fetal head size. There is insufficient evidence of toxicity with regard to maternal exposures to dietary factors, alcohol and environmental chemicals and reduced fetal size.

Key words. Air pollution; Benzene; Diet; Ethanol; Fetus; Mother; Phthalic acids

ABBREVIATIONS

HC=head circumference

AC=abdominal circumference

BPD=biparietal diameter

BTEX= aromatic hydrocarbons (benzene, toluene, ethylbenzene, m/p-xylene, and o-xylene)

CO=carbon monoxide

4,4’DDE=4,4’dichlorodiphenlychloroethylene

EFW=estimated fetal weight.

HCB= hexacholorbenzene

MAD=mean abdominal circumference

NCD=non-communicable diseases

NO_2= nitrogen dioxide

O_3=ozone

PAH=polyaromatic hydrocarbons

PCB=polychlorinated biphenyls

PM_{10}=particulates with diameter less than 10 microns

PUFA=poly unsaturated fatty acids

SO_2=sulphur dioxide

INTRODUCTION

Being small for gestational age (SGA) at birth is associated with increased risk for conditions that include coronary artery disease(Barker 1995a), type II diabetes(Hales CN and Barker DJ 1992) and asthma(Shaheen SO et al. 1999). The fetal origins hypothesis(Barker 1995a) and more recently, concepts including developmental plasticity(Bateson et al. 2004) and predictive adaptive responses(Gluckman et al. 2005), suggest that some antenatal exposures (or cues) predispose an unborn individual to non-communicable diseases (NCD) in later life by a mechanism which involves reduced fetal size and growth. A recent systematic review linking reduced fetal size, as evidenced by fetal ultrasound scan, to NCD in children supports the principle of the developmental origins of disease(Alkandari et al. 2015).

The mechanism(s) where antenatal cues reduce fetal size and pre-dispose to NCD are not fully understood, but are thought to include epigenetic modification in fetal cells following maternal exposure during pregnancy(Gluckman et al. 2011). Maternal exposures linked to SGA at birth include maternal smoking(Pereira et al. 2017), exposures to poor quality ambient air(Maisonet et al. 2004; Shah PS. Balkhair T. Knowledge Synthesis Group on Determinants of Preterm/LBW births 2011), dietary factors(Gresham E et al. 2014) and exposure to chemicals such as bisphenol A(Perera F and Herbstman J 2011). Knowledge of which exposures are associated with reduced antenatal size and the gestation at which these exposures may be acting would be important to our understanding of “fetal origins” and for public health educational messages and interventions, but the literature describing associations between these exposures and fetal size has not been systematically reviewed. Our group has recently undertaken a systematic review of the literature linking antenatal size and growth to maternal smoking and found that maternal smoking is consistently associated with fetal growth failure after the second trimester(Abraham et al. 2017). Here, we undertake a systematic review designed to answer the population exposure, comparator and outcome (PECO) question: Are fetuses who are exposed to maternal environmental exposures other than smoking small for gestational age compared to unexposed fetuses?

The Navigation Guide methodology is ideally suited for determining the strength of evidence between exposures and fetal size (Johnson et al. 2014) and was used in our study.

METHODS

Search methodology

A database search was carried out September 2017 using OVID MEDLINE and Embase databases and updated in May 2018. Search terms were developed initially using those used in previous systematic reviews(Abraham et al. 2017; Alkandari et al. 2015) and modified after identifying relevant publications not identified using these previous search terms (Aguilera I et al. 2010; Slama R et al. 2009). The online supplement shows the search terms used. Additional papers were identified from bibliographies and from the web sites of the following cohorts known to have collected ultrasound measurements of fetal size: the Raine cohort (http://www.rainestudy.org.au/), the EDEN cohort (https://eden.vjf.inserm.fr), Southampton Women Study (SWS, http://www.leu.soton.ac.uk/sws/), Generation R (http://www.erasmusmc.nl/epi/research/Generation-R/), and INMA Mother and Child Cohort Study(Guxens M et al. 2012). The supplement describes these cohorts in greater detail. Two researchers (MA and ST or IH and ST) independently reviewed abstracts identified by the database search and full papers considered potentially eligible were obtained. Eligible papers had to report fetal ultrasound anthropometric measurements (i.e. crown rump length, biparietal diameter, head circumference, femur length, abdominal circumference or estimated fetal weight) and relate these to a current or previous maternal environmental exposures. From background reading, the following exposures were sought: ambient air pollution, maternal alcohol ingestion, maternal diet, maternal drug use, occupational exposures, or pesticide exposure. Papers where fetal size was related to obstetric complications, maternal smoking (as the primary exposure) and maternal drug treatment were excluded. The outcome measures were fetal size and fetal growth.

Fetal measurements. First trimester (i.e. ≤13 weeks gestation) measurements were: crown rump length (CRL), biparietal diameter (BPD), head circumference (HC) abdominal circumference (AC) and mean abdominal diameter (MAD). Second trimester (i.e. >13 to <28 weeks gestation) and third trimester (i.e. ≥28 weeks) measurements were femur length (FL), HC, BPD, MAD, AC and estimated fetal weight (EFW) (the latter was derived from BPD, AC and FL measurements(Hadlock et al. 1984)).

Quality assessment of data

The Navigation Guide methodology was used to assess the risk of bias and the quality and strength of evidence(Johnson et al. 2014). We developed a protocol to assess risk of bias, quality of evidence and strength of evidence and which was based on the study of Johnson *et al* (Johnson et al. 2014) and which is described in the supplement. Risk of bias was rated for each paper and then across each of four exposure groups (i.e. maternal dietary exposures, air pollution exposures, alcohol exposure and other exposures) to inform the rating of quality of the evidence. The quality of the evidence was then used as part of the assessment of the strength of evidence. Two researchers (DM and PC) independently assessed each paper and then consensus was reached during discussion with three researchers (DM, PC and ST).

Meta-Analysis of data

We sought to identify results which might be suitable for meta-analysis. To do this we identified exposures where the same units of exposure were used in studies using comparable methodologies and reporting the same fetal measurement outcome.

RESULTS

Papers identified

The search identified 451 abstracts and 36~~5~~ papers were ultimately included in this review, (figure 1). Fifteen papers considered maternal dietary factors(Bergen et al. 2016; Bouwland-Both MI et al. 2013; Carlsen K et al. 2013; Drouillet P et al. 2009; Drouillet-Pinard P et al. 2010; Heppe DH et al. 2011a; Heppe DH et al. 2011b; Ioannou C et al. 2012; Karateke et al.

2015; Mahon P et al. 2010; Steenweg-de Graaff et al. 2017; Timmermans S et al. 2009; Timmermans S et al. 2012; Turner SW et al. 2010; Young BE et al. 2012), ten ambient air exposures(Aguilera I et al. 2010; Carvalho M.A. et al. 2016; Clemens et al. 2017; Hansen CA et al. 2008; Iniguez C et al. 2012; Iniguez et al. 2016; Malmqvist et al. 2017; Ritz B et al. 2014; Slama R et al. 2009; van den Hooven EH et al. 2012), three maternal alcohol consumption(Bakker R et al. 2010; Handmaker NS et al. 2006; Kfir M et al. 2009) and eight~~seven~~ considered other exposures(Botton et al. 2016; Casas et al. 2016; Harari et al. 2015; Lopez-Espinosa et al. 2015; Philippat et al. 2014; Snijder CA et al. 2012b; Snijder CA et al. 2013; Lopez-Espinosa et al. 2016). Studies which related environmental exposures to fetal anomalies (e.g. kidney cysts) and one relating physical demands of work(Snijder CA et al. 2012a) to fetal size were excluded. All studies were observational and the first was published in 2006. Three publications were from the USA, one each from Australia, Argentina, Brazil, Pakistan and Ukraine and the remaining 28~~7~~ from European populations. Twenty one publications were from one of three birth cohorts (including ten from the Generation R cohort, six~~five~~ from INMA and five from EDEN).

Risk of bias

There was generally a low risk of overall bias across the studies, with the exception of recruitment bias and to a lesser extent, exposure assessment, confounding and incomplete outcome data. Recruitment bias was low in three studies, probably low in 29~~8~~ studies and high in another four, figure two. Risk of bias in exposure assessment was low in 17~~6~~ studies, probably low in 8 and probably high in 11, figure two. Bias due to confounding was low risk in 30, probably low risk in one~~two~~, probably high risk in a further four~~two~~ and high risk in one study. Incomplete outcome data was at low risk for bias in 18, probably low risk in ten, probably high risk in seven and high risk in one study. Risk for bias from selective reporting was low in 33~~2~~ studies, probably low in two more and probably high in one. Supplemental table one explains reasons why a study was not rated at low risk of bias for the eight domains considered. The quality and strength of evidence are described later for each separate category of exposure.

Overview of findings

Table 1 describes the exposure, the trimester where an association was sought and the direction of any association between exposures and fetal measurement. Regarding consistency of findings for second trimester measurements, an association was present between a maternal exposure in 16 of 88~~4~~ (18~~9~~%) comparisons made, and these associations were distributed evenly across all fetal measurements and all the exposures measured (table 1 and supplemental table 2). Third trimester measurements were associated with maternal exposures in 443~~1~~ of the 96~~3~~ comparisons made (46~~4~~%) and were present for 15 of 26~~5~~ (58~~60~~%) analyses where BPD or HC were considered, 9~~7~~ of 28~~6~~ (32~~27~~%) where FL was considered, 8 of 19~~8~~ (42~~4~~%) where AC was considered and 12~~1~~ of 23~~2~~ (52~~0~~%) where EFW was considered (table 1 and supplemental table 2). Meta-analysis was not possible for maternal exposures to dietary factors, alcohol and other chemicals since either only one exposure was reported in the literature or if more than one study reported the same outcome, it was not valid or possible to pool the data. Meta-analysis was therefore only considered for ambient air exposures since comparable data seemed available (but not for other exposure categories), however the studies identified used a variety of methods to measure and report exposure (including units) meaning that meta analysis was not possible (table 2).

Maternal dietary exposures

Maternal plasma nutrient concentrations and fetal measurements

Vitamin D. FL was linked to maternal plasma 25(OH)D hydroxyl vitamin D in one study of 171 mothers aged <18 years(Young BE et al. 2012) and reduced exposure (i.e. ≤ 50 nmol/L) was associated with reduced FL (mean 0.15 z score) and humerus length (mean 0.18 z score) compared to higher exposure (i.e.>50 nmol/L). The associated reduction was limited to those whose mothers had both reduced plasma 25(OH)D and reduced dietary calcium intake (i.e. <1050 mg/d)(Young BE et al. 2012); this study was at high risk for recruitment bias and probably low risk for bias in two other domains of bias. Two studies from the SWS(Mahon P et al. 2010; Ioannou C et al. 2012), one with probably low risk for bias in confounding and probably high risk for bias due to incomplete outcome(Mahon P et al. 2010), used 3-D ultrasound technology to explore associations between maternal plasma vitamin D status at 34 weeks gestation and fetal femur dimensions. There was no association between maternal vitamin D and FL but there were associations with characteristics of the femur. One study, which included data from 424 fetuses, found an association between reduced maternal 25(OH)D (i.e. <25 nmol/L) and greater splaying of the distal femur at 19 and 34 weeks(Mahon P et al. 2010). The second study(Ioannou C et al. 2012) reported a weak positive association between maternal 25 (OH)D and proximal metaphyseal diameter (r=0.18), but not estimated femur volume at 34 weeks gestation in 357 fetuses.

Vitamin E. Maternal plasma α-tocopherol (vitamin E) was positively linked to CRL at ten weeks gestation in 766 mother-fetus pairs: the mean CRL was 42mm and 46 mm for the lowest and highest quartiles, respectively(Turner SW et al. 2010). Maternal exposure was not linked to fetal size later in gestation. The study was at probably low risk for bias in incomplete outcome.

Fatty Acids. A Danish study related maternal whole blood fatty acid composition at 24 weeks gestation to fetal measurements made at 20 weeks gestation in 583 fetuses(Carlsen K et al. 2013), and found a weak relationship between increasing n-3 PUFA and reducing FL (but not HC or AC), the regression coefficient was -0.15 p=0.02.

Folate, vitamin B12 and homocysteine. A study from the Generation R cohort related maternal and cord plasma concentrations of folate and vitamin B12, and also homocysteine (associated with reduced birth weight and antioxidant properties) at 13 weeks gestation to fetal weight gain and size at birth(Bergen et al. 2016). The main finding was that lower folate and higher homocysteine in maternal and cord plasma were associated with a slowing of fetal growth as pregnancy progressed (equivalent to 0.3 z score reduction in birth weight between the upper and lower quartile groups). Unexpectedly, the highest quintile of maternal and cord plasma vitamin B12 was associated with lower birth weight compared to the lowest quintile (mean different 43g for maternal plasma and 258g for cord plasma). A second Generation R study(Timmermans S et al. 2009) related timing of folate supplementation to EFW in 6365 fetuses and, consistent with the previously mentioned study(Bergen et al. 2016), found increased second trimester AC, third trimester AC and HC and EFW growth for those whose mothers started folic acid before or at the time of conception relative to no folic acid (mean EFW difference 0.10 z scores [0.02, 0.19]); individuals whose mothers who started folate supplementation in the first eight weeks had greater EFW growth in the second and third trimester (but no other fetal measurements) compared to no folic acid. A third Generation R study linked plasma folate concentration to fetal head growth and identified a small positive association equivalent to 3mm at birth per standard deviation increase in folate concentrations (Steenweg-de Graaff et al. 2017).

Maternal dietary intake and fetal measurements

Energy rich diet. A study from the Generation R cohort (Bouwland-Both MI et al. 2013) reported that an energy rich diet (i.e. rich in bread, nuts and margarine and therefore vitamins D and E), was associated with increased size in first trimester in 847 fetuses (mean increase in CRL 1.6mm relative to low energy rich diet); there was no association between diet and fetal measurements in later pregnancy. An observational study from Pakistan recruited 240 pregnant women (80 in each trimester, half of whom who fasted and half who did not fast during the month of Ramadan) and although mothers who fasted were 1kg lighter in the second and third trimester, there was no difference in growth in FL, BPD or EFW in any of the trimesters(Karateke et al. 2015); this study was at probably high risk for bias for confounding since socioeconomic status was not considered.

Mediterranean diet. A study from the Generation R cohort (Timmermans S et al. 2012) linked maternal Mediterranean diet to fetal measurements (n=3207), and individuals whose mothers were in the tertile with highest adherence to a “Mediterranean diet” (characterised by higher intake of fruit, vegetables, fish, pasta and rice) had higher EFW at 20 and 30 weeks and increased AC at 30 20 weeks compared to those in the lowest adherence tertile (mean difference in z scores 0.11 for both measurements). The study was at probably high risk for bias in exposure assessment and probably low risk from incomplete data.

<u>Milk</u>. A further Generation R cohort paper described associations between maternal milk intake, as reported by food frequency questionnaire at 13 weeks gestation, and fetal measurements at 21 and 30 weeks gestation in 3405 mother-fetus pairs(Heppe DH et al. 2011b). There were associations between higher intakes and increased second trimester EFW and third trimester HC; with reference to ≤1 glass/day, 1-2 glasses/day was associated with 0.8mm increased HC and a 6g increased EFW. The study was at probably high risk for bias in exposure assessment and incomplete data.

<u>Fish and seafood.</u> A further Generation R study found no association between maternal fish and seafood consumption to fetal measurements at 21 and 30 weeks(Heppe DH et al. 2011a). A report from the EDEN mother–child cohort also found no association between maternal seafood intake and fetal measurements (Drouillet P et al. 2009). A second report from this cohort found no consistent evidence for mercury contamination of seafood to be associated with reduced second or third trimester fetal size in 691 mother-child pairs where maternal hair mercury was assessed (Drouillet-Pinard P et al. 2010). Both reports from the EDEN study were scored probably low risk for incomplete outcome since they reported significant associations between exposure and outcome for the subset whose mothers were overweight; this analysis was not pre-specified and the findings may be false positives.

Quality and strength of evidence

Collectively the quality of evidence linking maternal dietary exposures to fetal measurements was low since there was low risk of bias in population recruitment in all but one population, and often further risk from (questionnaire-based) exposure assessment and from incomplete outcomes. The strength of evidence was inadequate to relate exposure to fetal size and growth due to lack of replication for most exposures and differences in methodology between studies which did consider the same dietary exposure.

Ambient air pollution

Ten studies described associations between maternal air pollution exposure and fetal ultrasound scan measurement. Three studies were from the INMA cohort. Air pollutant exposures were: nitrogen dioxide (NO_2), particulate matter <10 microns (PM_{10}), benzene, sulphur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3). Table 2 provides further details of the methodology used and magnitude of any association.

Nitrogen dioxide. Nine studies described the relationship between maternal NO_2 exposure and fetal measurement. Seven studies described associations between higher NO_2 exposures and reduced fetal size and/or growth(Aguilera I et al. 2010; Clemens et al. 2017; Iniguez C et al. 2012; Iniguez et al. 2016; Malmqvist et al. 2017; Ritz B et al. 2014; van den Hooven EH et al. 2012) and two studies reported no association(Carvalho M.A. et al. 2016; Hansen CA et al. 2008). The first of three studies from the INMA cohort, limited to 562 mothers in one of the recruitment centres (Sabadell), found increased NO_2 exposure was associated with a restriction in HC growth at weeks 12-20 and a reduction in BPD, intAC and EFW restriction at weeks 20-32 but only among mothers who spent <2 hours outdoors in non-residential areas per day(Aguilera I et al. 2010). The second report from the INMA cohort(Iniguez C et al. 2012) extended their previous results(Aguilera I et al. 2010) by relating cumulative NO_2 exposure during pregnancy to fetal size in a larger proportion of the cohort (785 mother). Here, the authors demonstrated an association for all mothers between increased maternal NO_2 exposure (i.e. 38 $\mu g/m^3$) and a reduction in growth for BPD, AC and EFW between 20 and 34 weeks gestation; the authors concluded that NO_2 exposure before 20 weeks gestation was critical to the associations described. The third paper from the INMA cohort extended the previous findings(Iniguez C et al. 2012) to 2478 mothers(Iniguez et al. 2016) and the latter found evidence of faltering growth in the second (as well as the third) trimester associated with increasing NO_2 exposure. Two papers observed associations between increasing maternal NO_2 exposure and reduced fetal head size, but no other fetal measurement(Clemens et al. 2017; Ritz B et al. 2014). One study reported increased maternal NO_2 exposure was associated with both reduced fetal head size and FL(van den Hooven EH et al. 2012) and another with both reduced FL and AC but not HC or BPD at 32-33 weeks gestation(Malmqvist et al. 2017). A small study of 366 mothers where NO_2 exposure was measured using personal passive samplers in each trimester found no association between exposure and third trimester EFW(Carvalho M.A. et al. 2016).

Fine particulates (PM_{10}). Three of the four papers which related maternal PM_{10} exposure to fetal measurements found a link between increasing exposure and smaller measurements(Clemens et al. 2017; Hansen CA et al. 2008; van den Hooven EH et al. 2012). Where associations were present, they were found with reduced head size. The association with reduced head size was present only in the second trimester in one study(Hansen CA et al. 2008) and only after the second trimester in the other two studies(Clemens et al. 2017; van den Hooven EH et al. 2012). The study by Clemens *et al*(Clemens et al. 2017) found the association with PM_{10} was also present for smaller particulates ($PM_{2.5}$) and also that the association was restricted to fetuses of non-smoking mothers. One study found an association between PM_{10} exposure and reduced FL(Hansen CA et al. 2008) and a fourth found no association with any fetal measurement(Ritz B et al. 2014). The study by Hansen *et al* (Hansen CA et al. 2008) did not include socioeconomic status was rated probably high risk for bias in confounding.

Benzene. Two studies described an association between increased maternal benzene exposure and reduced head size(Aguilera I et al. 2010; Slama R et al. 2009). One study which was restricted to non-smoking mothers reported reduced second and third trimester fetal head size associated with increasing benzene exposure (equivalent to 2mm difference by 35 weeks gestation)(Slama R et al. 2009). The second study found no association between benzene and other fetal measurements including FL, AC and EFW, but found reduced BPD growth between weeks 20-32 associated with benzene exposure among a subset of mothers who did not spend ≥15 hours at home per day(Aguilera I et al. 2010).

Other exposures. One study found an association between maternal ozone exposure in the first trimester and AC(Hansen CA et al. 2008) but two other studies found no association between ozone exposure and any fetal measurement(Carvalho M.A. et al. 2016; Ritz B et al. 2014). Only one study related SO_2 exposure to fetal measurements and reported associations between increased first trimester exposure and reduced BPD and AC(Hansen CA et al. 2008). One study explored the relationship between CO and fetal measurements and found no associations(Ritz B et al. 2014).

Quality and strength of evidence

Collectively the ten well-designed well-conducted studies provided a high quality of evidence linking maternal exposure to NO_2 and $PM_{2.5}$ to reduced third trimester fetal measurements (especially head size). The "default" for human studies having moderate quality of evidence was upgraded on account of evidence of dose response between NO_2 and $PM_{2.5}$ exposures and reduced fetal head size. Many studies were at probably low risk for bias in recruitment and exposure assessment. There was sufficient evidence to link NO_2 and $PM_{2.5}$ to reduced fetal head size since findings were consistent across a number of studies, reporting different concentrations of exposures, using different design and in different countries. The evidence linking other air pollution exposures to fetal measurements was of high quality but there was inadequate evidence of an association due to inconsistent findings between studies (e.g. benzene) and not all exposures were measured in all studies, e.g. ozone, carbon monoxide.

Maternal alcohol intake

One paper from the Generation R cohort assessed maternal alcohol intake in the first, second and third trimesters for 7333 mother-fetal pairs(Bakker R et al. 2010). In the longitudinal analysis, the fetuses of mothers who continued to consume alcohol (typically <1 drink a week) had a small increase in EFW growth (0.6g per week). In cross-sectional analyses, there was no association between second and third trimester intake and fetal HC, AC, FL or EFW. There was no evidence of a dose-response effect of alcohol on fetal measurements. A second publication which excluded mothers who smoked obtained routinely collected ultrasound measurements between 18 and 41 weeks gestation and reported reduced HC:AC during the pregnancy for fetuses whose mothers who continued to drink compared to those who quit (magnitude not described)(Handmaker NS et al. 2006). There was reduced cerebellar growth, but no difference in HC, AC and FL, among fetuses exposed to persistent maternal alcohol intake compared to those whose mothers who quit drinking during pregnancy. In this cohort(Handmaker NS et al. 2006), 40% of mothers were marijuana users and 20% used amphetamines with the latter being associated with increased HC:AC growth. A third study (a pilot study) screened 6745 Ukrainian mothers in early pregnancy and identified 84 moderate-to-heavy drinkers and 82 abstinent mothers(Kfir M et al. 2009); moderate-to-heavy drinking was a reported average of 30mls ethanol (or three UK “units”) daily at conception and 4mls daily after knowingly being pregnant (including binges with an average of 66mls ethanol/day). FL was reduced in the second trimester among alcohol exposed fetuses (mean 53rd centile versus 65th centile for controls) but not in the third trimester. Third trimester BPD was reduced in exposed fetuses when compared to controls (54th centile versus 70th centile, respectively).

Collectively these studies were of low quality due to bias in recruitment, use of reported alcohol intake and incomplete follow up and within this limited literature there was inadequate evidence identified to link maternal alcohol intake to fetal measurements.

Other exposures

Occupational exposures. A study of occupational exposures (by questionnaire) in 4680 pregnant mothers related FL, HC and EFW to exposures including phthalates, pesticides, polyaromatic hydrocarbons and alkylphenolic compounds(Snijder CA et al. 2012b). There were associations of small magnitude seen between some exposures and some fetal measurements, most consistently for phthalates whose exposure was associated with reduced EFW and fetal length (approximately 1% of a z score per week).

Bisphenol A. A second Generation R study measured maternal urinary Bisphenol A (BPA) in the first, second and third trimesters and related these to fetal growth in 419 pregnancies (Snijder CA et al. 2013). In 80 mothers (i.e. 19% of the study population) urine samples were obtained in each trimester there was reduced growth EFW and HC per unit increase in BPA (typically 2% reduction per week per unit increase in BPA exposure), but this finding was not replicated in models which included mothers where exposure data were not complete nor in a report from the INMA cohorts where there was no association between maternal first and third trimester BPA and fetal measurements (488 mothers)(Casas et al. 2016).

Phenols. A study from the EDEN cohort related maternal exposure to nine phenol-based chemicals to fetal size and growth throughout pregnancy and found evidence that one (triclosan) was linked to minor reductions in fetal size in the third trimester but at no other time(Philippat et al. 2014).

Phthalates. Two studies related maternal phthalate exposure to fetal size and growth and report apparently contrasting findings. The first study, again restricted to male offspring in the EDEN cohort, measured 11 phthalate molecules in maternal urine and found a negative relationship between phthalate metabolites and EFW (10-15g per quartile increase in phthalate exposure) but also a positive association between one molecule (monocarboxyisononyl) and FL in the second and third trimesters(Botton et al. 2016) (which is consistent with the previously mentioned study(Casas et al. 2016)). A study from the INMA cohorts found association of small magnitude between increased concentrations of two of eight phthalate molecules in maternal urine and reduced growth HC in the first, and FL second half of pregnancy(Casas et al. 2016). Both cohorts only measured one common phthalate molecule (monoethyl phthalate) so the results are not necessarily inconsistent.

Polybrominated diphenyl ethers (PBDEs). A further evaluation of the INMA cohorts measured PBDEs in maternal and cord concentrations and related these to fetal measurements in 670 mothers(Lopez-Espinosa et al. 2015); a doubling of PBDE exposure was associated with <5% reduced growth in AC, EFW and BPD (but not FL) between 20-34 weeks (but not 12-20 weeks), although associations were not always present for both maternal and cord blood concentrations.

Organochlorine compounds. The final study identified from 2369 the INMA cohorts related maternal organochlorine compounds in maternal plasma at 12 weeks gestation and cord blood to fetal growth in early, mid and late pregnancy (Lopez-Espinosa et al. 2016); a doubling of exposures to polychlorinated biphenyls (PCB) -138, -153 and -180 were associated with a 2-4% reduction in femur length growth and a doubling of PCB-138 was associated with a 2% reduction in EFW growth between gestational weeks 20-34. There were inverse associations between cord Hexachlorobenzene and reduced AC growth between 0 and 20 weeks. Five of 120 associations in this analysis achieved significance.

Lithium in drinking water. The northern Argentinian Andes has variable concentrations of lithium in its drinking water and a study of 194 mothers observed no significant relationships between maternal plasma and urinary lithium and second and third trimester BPD, HC, AC, FL and EFW(Harari et al. 2015).

Collectively the quality of evidence for these studies was low since although objective measurements of exposure were made in all but one study, multiple comparisons were made within studies increasing the chance of false positive findings, findings (when replicated) were not consistent and risk of bias from incomplete follow up was probably high or high in four studies. Additionally, data were limited only to male offspring in two studies (Botton et al. 2016; Philippat et al. 2014). In conclusion, there was inadequate strength of evidence linking chemicals to fetal size since the quality of evidence was low, many different chemicals were studies and where associations with fetal size were present, these were not replicated elsewhere.

DISCUSSION

This systematic review was designed to describe the literature associating maternal exposures to fetal size being small for gestational age. The papers identified were all published since 2006, indicating that this is a relatively new literature. The first major finding was that maternal exposures to increased ambient air NO_2 and $PM_{2.5}$ were consistently associated with reduced third trimester fetal head size and we judge that the literature presents sufficient evidence of toxicity in this context. The second major finding was that the strength of evidence was inadequate for all the other exposures considered. The third notable finding was that, where associations were present, they were more commonly seen in the third compared to the second trimester and that reduced third trimester head size was more commonly associated with potentially adverse maternal exposures compared to other fetal measurements. Together these findings suggest that public health measures are urgently required to minimise pregnant mother's exposure to NO_2 and $PM_{2.5}$, and more high-quality research is required to better understand the relationship between other (modifiable) maternal exposures and fetal measurements.

The fetus has traditionally been thought to have a privileged position, where it was protected from the adverse effects of environmental exposures by the maternal-placental "unit", but associations between reduced birth weight and many maternal exposures argue against this paradigm. The fetal origins hypothesis(Barker 1995a) speculated that maternal exposures in mid pregnancy were relevant to birth weight and risk for subsequent increased risk for non-communicable diseases. Since we find evidence of reduced second trimester fetal size and some maternal exposures, and our findings suggest that maternal exposures in early pregnancy are also relevant.

There were some associations between exposure and fetal size which were mostly consistent across different populations, whilst other associations were less consistently seen, or were even counterintuitive. An example of consistency was the inverse association between NO_2 exposure and third trimester fetal size, which was seen in all seven studies which explored this link (two studies measured NO_2 but not third trimester head size Carvalho M.A. et al. 2016; Hansen CA et al. 2008). In contrast, there were some instances where an apparently harmful exposure was associated with increased fetal size (e.g. current PM_{10} exposure and first trimester length and second trimester weight(van den Hooven EH et al. 2012), one phthalate molecule and increased third trimester fetal length(Botton et al. 2016), increased maternal and cord plasma vitamin B12 concentrations and reduced birth weight(Bergen et al. 2016), maternal alcohol intake and increased third trimester EFW(Bakker R et al. 2010)); although these associations may challenge the paradigm that "harmful" exposures invariably cause reduced fetal growth, these may be false positive findings.

A further example of inconsistency comes from the ambient air exposure literature where two studies found that the magnitude of association between NO_2 and fetal size was only present(Ritz B et al. 2014), or was greater(Iniguez et al. 2016), among mothers who smoked whereas a second study only found an association between NO_2 and fetal head size among non-smokers(Clemens et al. 2017). Our review also identified many associations of borderline significance and instances of multiple testing, and these increase the risk of false positive results. Given that the body of literature reviewed is relatively young, it is not unexpected that there is a spectrum of consistency/inconsistency between maternal exposure and fetal size and further research activity is required to replicate some of the apparently inconsistent associations.

There are consistencies and inconsistencies in the literature describing associations between maternal exposures and birth weight and these exposures and fetal size. Maternal exposures to poor quality ambient air is associated with reduced birth weight (Maisonet et al. 2004; Shah PS. Balkhair T. Knowledge Synthesis Group on Determinants of Preterm/LBW births 2011) and we confirm this association is already present in fetal life. In contrast, many maternal dietary exposures are associated with reduced birth weight (Gresham E et al.

2014) but there were no consistent associations between maternal dietary exposures and fetal size in the literature we reviewed. Similarly, maternal exposure to chemicals such as bisphenol A(Perera F and Herbstman J 2011) is associated with reduced birth weight but bisphenol A was associated with reduced fetal size in one study (Casas et al. 2016) but not a second (Snijder CA et al. 2013). The inconsistent findings between size before and after birth in the context of maternal exposures may reflect a smaller literature describing antenatal size, the challenges of accurately measuring fetal size or theoretically may be due to associations only becoming detectable towards the very end of pregnancy.

Maternal alcohol ingestion during pregnancy is an established risk factors for reduced birth weight(Henderson J et al. 2007), but the literature was not adequate to determine when the relationship between alcohol ingestion and fetal growth failure begins. The studies identified were at high risk of bias and collectively provided inadequate evidence of toxicity This absence of evidence does not mean that any change is required to current guidelines which recommend that pregnant mothers should abstain from drinking alcohol.

A weakness of the present literature is that all the evidence comes from observational studies where, in addition to the risk of false positive findings previously discussed, some of the results may be influenced by confounding factors and also the results are based on populations who are not necessarily representative of the general population. Drop out from cohort studies also may contribute bias, for example a study which related fetal size to risk for later asthma found a relationship of greater magnitude when using questionnaire reported asthma outcome (available in 39% of the cohort) compared to using routinely acquired asthma outcome (available in 88%) (Turner et al. 2018).

One further limitation of the literature is that whilst there are some maternal exposures linked to fetal size in three or more studies, for example smoking (Abraham et al. 2017) and air pollution (the present review), many exposures are linked to fetal size in only one or two studies (for example chemicals and dietary nutrients) and this leaves insufficient evidence upon which to form an opinion. A second potential limitation to the literature is that fetal measurements and exposures were made at different gestational age, although this limitation applies to the different studies in the literature linking post natal exposures and post natal outcomes. Fetal size is driven by gestational age, and fetal size was determined over a range of gestations within and between different studies. Gestational age was included as a covariate in all but one study (Karateke et al. 2015) and this minimises the potential for differences in gestational age at assessment confounding associations with maternal exposure. Differences between studies in the gestational age when fetal size and maternal exposure are likely to weaken and not strengthen the associations (where present) between maternal exposure and fetal size.

A~~One~~ further limitation to the literature was that different methods were used to measure exposures, even where the same exposure (NO_2 for example) was measured in several studies. This meant that meta-analysis was not possible for single exposures. ~~A second limitation of the literature is that many of the exposures studied, especially maternal diet and plasma nutrients, there was only one study which linked that exposure to fetal size and the findings require replication.~~ Another limitation to the literature is that there are some areas where the evidence is of a poor quality, e.g. maternal alcohol exposure, which is an increasing public health concern due to increasing awareness of fetal alcohol syndrome(Popova et al. 2017). Finally, there are several maternal exposures including recreational drug use (Behnke M et al. 2013), pesticides(Sathyanarayana et al. 2010), proximity to land fill sites(Elliott et al. 2001) and electromagnetic fields (de Vocht F and Lee B 2014) which are linked to reduced birth weight but where there are no studies associating such exposures to fetal measurements.

Pregnant mothers are constantly exposed to multiple environmental exposures and identifying which single exposure may be important to fetal size is a challenge, for example increased maternal alcohol intake may be associated with smoking, use of illicit drugs and poor diet. Furthermore, any reduction in fetal size associated with tobacco and alcohol consumption may be modified by increased size associated with amphetamine intake (Handmaker NS et al. 2006). Only intervention studies are able to infer causality, but these are practically and ethically challenging to do in the context of potentially harmful maternal exposures during pregnancy and the evidence base may remain dependent on observational studies.

The mechanism(s) where environmental exposures may cause fetal growth failure (or acceleration) are not well understood but likely to be multiple. The mechanism for maternal diet influencing fetal size assumes that macro and micro nutrients cross the placenta, and maternal dietary fat intake during the third trimester has been associated with cord blood lipid concentrations (Elias SL and Innis SM 2001) but the fetus is not necessarily exposed to all maternal plasma nutrients, for example triglycerides do not cross the placenta(Herrera 2002). The mechanism for ambient air exposures leading to fetal growth failure is not understood but ultrafine particles (which correlate with PM_{10} and NO_2 concentrations) are able to directly enter the maternal circulation via the alveoli (Geiser M et al. 2005) and placenta (Wick P et al. 2010), and thus theoretically enter the fetal circulation where they may be pathogenic by causing vascular inflammation(Gojova A et al. 2007).

In summary, there is an emerging literature which suggests that some maternal exposures during early pregnancy are associated with changes in fetal size which are apparent by the second and third trimester. Evidence from randomised controlled trials where maternal exposures are modified are unlikely due to practical and ethical issues, and the evidence base is likely to arise from observational studies. The literature is mostly based on Western populations and is dominated by three cohort studies and replication in other populations of the associations described is required.

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FIGURE LEGENDS

Figure 1. CONSORT style diagram showing how the papers included in the review were identified.

Figure two. Bar chart summarising the risk of bias for each of the eight domains considered across the 36~~5~~ papers included in this systematic review.

Figure three. This figure shows the risk of bias in each of eight domains considered for each of the 36~~5~~ studies included in this systematic review.

ABSTRACT

Background. Reduced birth weight is associated with many maternal environmental exposures during pregnancy, but the gestational age at onset of this association is unknown. We have previously reported associations between maternal smoking and fetal size.

Objective. To report on our systematic review of the literature describing associations between antenatal size and growth and maternal exposures during pregnancy.

Data sources. Electronic databases (OVID and EMBASE) and web sites for cohort studies were searched.

Study eligibility. Studies were eligible if they examined associations between maternal environmental exposures (including ambient air exposure, diet and alcohol) and antenatal fetal ultrasound measurements.

Study appraisal. The Navigation Guide was used to assess the strength of evidence.

Results. There were 451 abstracts identified and 36 papers were included of which maternal diet was the exposure of interest in 15, maternal ambient air exposure in 10, maternal alcohol in 3 and other exposures in 8. The first paper was published in 2006. Associations were present between exposures in 18% of comparisons with second trimester measurements and in 46% of comparisons with third trimester measurements. In the third trimester, when an association was present, reduced head size was most commonly (58%) associated with current or previous maternal exposure, with reduced length being least commonly (32%) associated and reduced weight being intermediate (52%). In the third trimester, increased maternal nitrogen dioxide exposure was associated with reduced head size was associated with in all seven studies identified and reduced fetal weight in five out of six studies.

Conclusion. There is sufficient evidence of toxicity in the context of maternal exposure to nitrogen dioxide and reduced third trimester fetal head size. There is insufficient evidence of toxicity with regard to maternal exposures to dietary factors, alcohol and environmental chemicals and reduced fetal size.

Key words. Air pollution; Benzene; Diet; Ethanol; Fetus; Mother; Phthalic acids

ABBREVIATIONS

HC=head circumference

AC=abdominal circumference

BPD=biparietal diameter

BTEX= aromatic hydrocarbons (benzene, toluene, ethylbenzene, m/p-xylene, and o-xylene)

CO=carbon monoxide

4,4’DDE=4,4’dichlorodiphenlychloroethylene

EFW=estimated fetal weight.

HCB= hexacholorbenzene

MAD=mean abdominal circumference

NCD=non-communicable diseases

NO_2= nitrogen dioxide

O_3=ozone

PAH=polyaromatic hydrocarbons

PCB=polychlorinated biphenyls

PM_{10}=particulates with diameter less than 10 microns

PUFA=poly unsaturated fatty acids

SO_2=sulphur dioxide

INTRODUCTION

Being small for gestational age (SGA) at birth is associated with increased risk for conditions that include coronary artery disease(Barker 1995a), type II diabetes(Hales CN and Barker DJ 1992) and asthma(Shaheen SO et al. 1999). The fetal origins hypothesis(Barker 1995a) and more recently, concepts including developmental plasticity(Bateson et al. 2004) and predictive adaptive responses(Gluckman et al. 2005), suggest that some antenatal exposures (or cues) predispose an unborn individual to non-communicable diseases (NCD) in later life by a mechanism which involves reduced fetal size and growth. A recent systematic review linking reduced fetal size, as evidenced by fetal ultrasound scan, to NCD in children supports the principle of the developmental origins of disease(Alkandari et al. 2015).

The mechanism(s) where antenatal cues reduce fetal size and pre-dispose to NCD are not fully understood, but are thought to include epigenetic modification in fetal cells following maternal exposure during pregnancy(Gluckman et al. 2011). Maternal exposures linked to SGA at birth include maternal smoking(Pereira et al. 2017), exposures to poor quality ambient air(Maisonet et al. 2004; Shah PS. Balkhair T. Knowledge Synthesis Group on Determinants of Preterm/LBW births 2011), dietary factors(Gresham E et al. 2014) and exposure to chemicals such as bisphenol A(Perera F and Herbstman J 2011). Knowledge of which exposures are associated with reduced antenatal size and the gestation at which these exposures may be acting would be important to our understanding of “fetal origins” and for public health educational messages and interventions, but the literature describing associations between these exposures and fetal size has not been systematically reviewed. Our group has recently undertaken a systematic review of the literature linking antenatal size and growth to maternal smoking and found that maternal smoking is consistently associated with fetal growth failure after the second trimester(Abraham et al. 2017). Here, we undertake a systematic review designed to answer the population exposure, comparator and outcome (PECO) question: Are fetuses who are exposed to maternal environmental exposures other than smoking small for gestational age compared to unexposed fetuses?

The Navigation Guide methodology is ideally suited for determining the strength of evidence between exposures and fetal size (Johnson et al. 2014) and was used in our study.

METHODS

Search methodology

A database search was carried out September 2017 using OVID MEDLINE and Embase databases and updated in May 2018. Search terms were developed initially using those used in previous systematic reviews(Abraham et al. 2017; Alkandari et al. 2015) and modified after identifying relevant publications not identified using these previous search terms (Aguilera I et al. 2010; Slama R et al. 2009). The online supplement shows the search terms used. Additional papers were identified from bibliographies and from the web sites of the following cohorts known to have collected ultrasound measurements of fetal size: the Raine cohort (http://www.rainestudy.org.au/), the EDEN cohort (https://eden.vjf.inserm.fr), Southampton Women Study (SWS, http://www.leu.soton.ac.uk/sws/), Generation R (http://www.erasmusmc.nl/epi/research/Generation-R/), and INMA Mother and Child Cohort Study(Guxens M et al. 2012). The supplement describes these cohorts in greater detail. Two researchers (MA and ST or IH and ST) independently reviewed abstracts identified by the database search and full papers considered potentially eligible were obtained. Eligible papers had to report fetal ultrasound anthropometric measurements (i.e. crown rump length, biparietal diameter, head circumference, femur length, abdominal circumference or estimated fetal weight) and relate these to a current or previous maternal environmental exposures. From background reading, the following exposures were sought: ambient air pollution, maternal alcohol ingestion, maternal diet, maternal drug use, occupational exposures, or pesticide exposure. Papers where fetal size was related to obstetric complications, maternal smoking (as the primary exposure) and maternal drug treatment were excluded. The outcome measures were fetal size and fetal growth.

Fetal measurements. First trimester (i.e. ≤13 weeks gestation) measurements were: crown rump length (CRL), biparietal diameter (BPD), head circumference (HC) abdominal circumference (AC) and mean abdominal diameter (MAD). Second trimester (i.e. >13 to <28 weeks gestation) and third trimester (i.e. ≥28 weeks) measurements were femur length (FL), HC, BPD, MAD, AC and estimated fetal weight (EFW) (the latter was derived from BPD, AC and FL measurements(Hadlock et al. 1984)).

Quality assessment of data

The Navigation Guide methodology was used to assess the risk of bias and the quality and strength of evidence(Johnson et al. 2014). We developed a protocol to assess risk of bias, quality of evidence and strength of evidence and which was based on the study of Johnson *et al* (Johnson et al. 2014) and which is described in the supplement. Risk of bias was rated for each paper and then across each of four exposure groups (i.e. maternal dietary exposures, air pollution exposures, alcohol exposure and other exposures) to inform the rating of quality of the evidence. The quality of the evidence was then used as part of the assessment of the strength of evidence. Two researchers (DM and PC) independently assessed each paper and then consensus was reached during discussion with three researchers (DM, PC and ST).

Meta-Analysis of data

We sought to identify results which might be suitable for meta-analysis. To do this we identified exposures where the same units of exposure were used in studies using comparable methodologies and reporting the same fetal measurement outcome.

RESULTS

Papers identified

The search identified 451 abstracts and 36 papers were ultimately included in this review, (figure 1). Fifteen papers considered maternal dietary factors(Bergen et al. 2016; Bouwland-Both MI et al. 2013; Carlsen K et al. 2013; Drouillet P et al. 2009; Drouillet-Pinard P et al. 2010; Heppe DH et al. 2011a; Heppe DH et al. 2011b; Ioannou C et al. 2012; Karateke et al.

2015; Mahon P et al. 2010; Steenweg-de Graaff et al. 2017; Timmermans S et al. 2009; Timmermans S et al. 2012; Turner SW et al. 2010; Young BE et al. 2012), ten ambient air exposures(Aguilera I et al. 2010; Carvalho M.A. et al. 2016; Clemens et al. 2017; Hansen CA et al. 2008; Iniguez C et al. 2012; Iniguez et al. 2016; Malmqvist et al. 2017; Ritz B et al. 2014; Slama R et al. 2009; van den Hooven EH et al. 2012), three maternal alcohol consumption(Bakker R et al. 2010; Handmaker NS et al. 2006; Kfir M et al. 2009) and eight considered other exposures(Botton et al. 2016; Casas et al. 2016; Harari et al. 2015; Lopez-Espinosa et al. 2015; Philippat et al. 2014; Snijder CA et al. 2012b; Snijder CA et al. 2013; Lopez-Espinosa et al. 2016). Studies which related environmental exposures to fetal anomalies (e.g. kidney cysts) and one relating physical demands of work(Snijder CA et al. 2012a) to fetal size were excluded. All studies were observational and the first was published in 2006. Three publications were from the USA, one each from Australia, Argentina, Brazil, Pakistan and Ukraine and the remaining 28 from European populations. Twenty one publications were from one of three birth cohorts (including ten from the Generation R cohort, six from INMA and five from EDEN).

Risk of bias

There was generally a low risk of overall bias across the studies, with the exception of recruitment bias and to a lesser extent, exposure assessment, confounding and incomplete outcome data. Recruitment bias was low in three studies, probably low in 29 studies and high in another four, figure two. Risk of bias in exposure assessment was low in 17 studies, probably low in 8 and probably high in 11, figure two. Bias due to confounding was low risk in 30, probably low risk in one, probably high risk in a further four and high risk in one study. Incomplete outcome data was at low risk for bias in 18, probably low risk in ten, probably high risk in seven and high risk in one study. Risk for bias from selective reporting was low in 33 studies, probably low in two more and probably high in one. Supplemental table one explains reasons why a study was not rated at low risk of bias for the eight domains considered. The quality and strength of evidence are described later for each separate category of exposure.

Overview of findings

Table 1 describes the exposure, the trimester where an association was sought and the direction of any association between exposures and fetal measurement. Regarding consistency of findings for second trimester measurements, an association was present between a maternal exposure in 16 of 88 (18%) comparisons made, and these associations were distributed evenly across all fetal measurements and all the exposures measured (table 1 and supplemental table 2). Third trimester measurements were associated with maternal exposures in 443 of the 96 comparisons made (46%) and were present for 15 of 26 (58%) analyses where BPD or HC were considered, 9 of 28 (32%) where FL was considered, 8 of 19 (42%) where AC was considered and 12 of 23 (52%) where EFW was considered (table 1 and supplemental table 2). Meta-analysis was not possible for maternal exposures to dietary factors, alcohol and other chemicals since either only one exposure was reported in the literature or if more than one study reported the same outcome, it was not valid or possible to pool the data. Meta-analysis was therefore only considered for ambient air exposures since comparable data seemed available (but not for other exposure categories), however the studies identified used a variety of methods to measure and report exposure (including units) meaning that meta analysis was not possible (table 2).

Maternal dietary exposures

Maternal plasma nutrient concentrations and fetal measurements

Vitamin D. FL was linked to maternal plasma 25(OH)D hydroxyl vitamin D in one study of 171 mothers aged <18 years(Young BE et al. 2012) and reduced exposure (i.e. ≤ 50 nmol/L) was associated with reduced FL (mean 0.15 z score) and humerus length (mean 0.18 z score) compared to higher exposure (i.e.>50 nmol/L). The associated reduction was limited to those whose mothers had both reduced plasma 25(OH)D and reduced dietary calcium intake (i.e. <1050 mg/d)(Young BE et al. 2012); this study was at high risk for recruitment bias and probably low risk for bias in two other domains of bias. Two studies from the SWS(Mahon P et al. 2010; Ioannou C et al. 2012), one with probably low risk for bias in confounding and probably high risk for bias due to incomplete outcome(Mahon P et al. 2010), used 3-D ultrasound technology to explore associations between maternal plasma vitamin D status at 34 weeks gestation and fetal femur dimensions. There was no association between maternal vitamin D and FL but there were associations with characteristics of the femur. One study, which included data from 424 fetuses, found an association between reduced maternal 25(OH)D (i.e. <25 nmol/L) and greater splaying of the distal femur at 19 and 34 weeks(Mahon P et al. 2010). The second study(Ioannou C et al. 2012) reported a weak positive association between maternal 25 (OH)D and proximal metaphyseal diameter (r=0.18), but not estimated femur volume at 34 weeks gestation in 357 fetuses.

Vitamin E. Maternal plasma α-tocopherol (vitamin E) was positively linked to CRL at ten weeks gestation in 766 mother-fetus pairs: the mean CRL was 42mm and 46 mm for the lowest and highest quartiles, respectively(Turner SW et al. 2010). Maternal exposure was not linked to fetal size later in gestation. The study was at probably low risk for bias in incomplete outcome.

Fatty Acids. A Danish study related maternal whole blood fatty acid composition at 24 weeks gestation to fetal measurements made at 20 weeks gestation in 583 fetuses(Carlsen K et al. 2013), and found a weak relationship between increasing n-3 PUFA and reducing FL (but not HC or AC), the regression coefficient was -0.15 p=0.02.

Folate, vitamin B12 and homocysteine. A study from the Generation R cohort related maternal and cord plasma concentrations of folate and vitamin B12, and also homocysteine (associated with reduced birth weight and antioxidant properties) at 13 weeks gestation to fetal weight gain and size at birth(Bergen et al. 2016). The main finding was that lower folate and higher homocysteine in maternal and cord plasma were associated with a slowing of fetal growth as pregnancy progressed (equivalent to 0.3 z score reduction in birth weight between the upper and lower quartile groups). Unexpectedly, the highest quintile of maternal and cord plasma vitamin B12 was associated with lower birth weight compared to the lowest quintile (mean different 43g for maternal plasma and 258g for cord plasma). A second Generation R study(Timmermans S et al. 2009) related timing of folate supplementation to EFW in 6365 fetuses and, consistent with the previously mentioned study(Bergen et al. 2016), found increased second trimester AC, third trimester AC and HC and EFW growth for those whose mothers started folic acid before or at the time of conception relative to no folic acid (mean EFW difference 0.10 z scores [0.02, 0.19]); individuals whose mothers who started folate supplementation in the first eight weeks had greater EFW growth in the second and third trimester (but no other fetal measurements) compared to no folic acid. A third Generation R study linked plasma folate concentration to fetal head growth and identified a small positive association equivalent to 3mm at birth per standard deviation increase in folate concentrations (Steenweg-de Graaff et al. 2017).

Maternal dietary intake and fetal measurements

Energy rich diet. A study from the Generation R cohort (Bouwland-Both MI et al. 2013) reported that an energy rich diet (i.e. rich in bread, nuts and margarine and therefore vitamins D and E), was associated with increased size in first trimester in 847 fetuses (mean increase in CRL 1.6mm relative to low energy rich diet); there was no association between diet and fetal measurements in later pregnancy. An observational study from Pakistan recruited 240 pregnant women (80 in each trimester, half of whom who fasted and half who did not fast during the month of Ramadan) and although mothers who fasted were 1kg lighter in the second and third trimester, there was no difference in growth in FL, BPD or EFW in any of the trimesters(Karateke et al. 2015); this study was at probably high risk for bias for confounding since socioeconomic status was not considered.

Mediterranean diet. A study from the Generation R cohort (Timmermans S et al. 2012) linked maternal Mediterranean diet to fetal measurements (n=3207), and individuals whose mothers were in the tertile with highest adherence to a “Mediterranean diet” (characterised by higher intake of fruit, vegetables, fish, pasta and rice) had higher EFW at 20 and 30 weeks and increased AC at 30 20 weeks compared to those in the lowest adherence tertile (mean difference in z scores 0.11 for both measurements). The study was at probably high risk for bias in exposure assessment and probably low risk from incomplete data.

Milk. A further Generation R cohort paper described associations between maternal milk intake, as reported by food frequency questionnaire at 13 weeks gestation, and fetal measurements at 21 and 30 weeks gestation in 3405 mother-fetus pairs(Heppe DH et al. 2011b). There were associations between higher intakes and increased second trimester EFW and third trimester HC; with reference to ≤1 glass/day, 1-2 glasses/day was associated with 0.8mm increased HC and a 6g increased EFW. The study was at probably high risk for bias in exposure assessment and incomplete data.

Fish and seafood. A further Generation R study found no association between maternal fish and seafood consumption to fetal measurements at 21 and 30 weeks(Heppe DH et al. 2011a). A report from the EDEN mother–child cohort also found no association between maternal seafood intake and fetal measurements (Drouillet P et al. 2009). A second report from this cohort found no consistent evidence for mercury contamination of seafood to be associated with reduced second or third trimester fetal size in 691 mother-child pairs where maternal hair mercury was assessed (Drouillet-Pinard P et al. 2010). Both reports from the EDEN study were scored probably low risk for incomplete outcome since they reported significant associations between exposure and outcome for the subset whose mothers were overweight; this analysis was not pre-specified and the findings may be false positives.

Quality and strength of evidence

Collectively the quality of evidence linking maternal dietary exposures to fetal measurements was low since there was low risk of bias in population recruitment in all but one population, and often further risk from (questionnaire-based) exposure assessment and from incomplete outcomes. The strength of evidence was inadequate to relate exposure to fetal size and growth due to lack of replication for most exposures and differences in methodology between studies which did consider the same dietary exposure.

Ambient air pollution

Ten studies described associations between maternal air pollution exposure and fetal ultrasound scan measurement. Three studies were from the INMA cohort. Air pollutant exposures were: nitrogen dioxide (NO_2), particulate matter <10 microns (PM_{10}), benzene, sulphur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3). Table 2 provides further details of the methodology used and magnitude of any association.

Nitrogen dioxide. Nine studies described the relationship between maternal NO_2 exposure and fetal measurement. Seven studies described associations between higher NO_2 exposures and reduced fetal size and/or growth(Aguilera I et al. 2010; Clemens et al. 2017; Iniguez C et al. 2012; Iniguez et al. 2016; Malmqvist et al. 2017; Ritz B et al. 2014; van den Hooven EH et al. 2012) and two studies reported no association(Carvalho M.A. et al. 2016; Hansen CA et al. 2008). The first of three studies from the INMA cohort, limited to 562 mothers in one of the recruitment centres (Sabadell), found increased NO_2 exposure was associated with a restriction in HC growth at weeks 12-20 and a reduction in BPD, intAC and EFW restriction at weeks 20-32 but only among mothers who spent <2 hours outdoors in non-residential areas per day(Aguilera I et al. 2010). The second report from the INMA cohort(Iniguez C et al. 2012) extended their previous results(Aguilera I et al. 2010) by relating cumulative NO_2 exposure during pregnancy to fetal size in a larger proportion of the cohort (785 mother). Here, the authors demonstrated an association for all mothers between increased maternal NO_2 exposure (i.e. 38 $\mu g/m^3$) and a reduction in growth for BPD, AC and EFW between 20 and 34 weeks gestation; the authors concluded that NO_2 exposure before 20 weeks gestation was critical to the associations described. The third paper from the INMA cohort extended the previous findings(Iniguez C et al. 2012) to 2478 mothers(Iniguez et al. 2016) and the latter found evidence of faltering growth in the second (as well as the third) trimester associated with increasing NO_2 exposure. Two papers observed associations between increasing maternal NO_2 exposure and reduced fetal head size, but no other fetal measurement(Clemens et al. 2017; Ritz B et al. 2014). One study reported increased maternal NO_2 exposure was associated with both reduced fetal head size and FL(van den Hooven EH et al. 2012) and another with both reduced FL and AC but not HC or BPD at 32-33 weeks gestation(Malmqvist et al. 2017). A small study of 366 mothers where NO_2 exposure was measured using personal passive samplers in each trimester found no association between exposure and third trimester EFW(Carvalho M.A. et al. 2016).

Fine particulates (PM_{10}). Three of the four papers which related maternal PM_{10} exposure to fetal measurements found a link between increasing exposure and smaller measurements(Clemens et al. 2017; Hansen CA et al. 2008; van den Hooven EH et al. 2012). Where associations were present, they were found with reduced head size. The association with reduced head size was present only in the second trimester in one study(Hansen CA et al. 2008) and only after the second trimester in the other two studies(Clemens et al. 2017; van den Hooven EH et al. 2012). The study by Clemens *et al*(Clemens et al. 2017) found the association with PM_{10} was also present for smaller particulates ($PM_{2.5}$) and also that the association was restricted to fetuses of non-smoking mothers. One study found an association between PM_{10} exposure and reduced FL(Hansen CA et al. 2008) and a fourth found no association with any fetal measurement(Ritz B et al. 2014). The study by Hansen *et al* (Hansen CA et al. 2008) did not include socioeconomic status was rated probably high risk for bias in confounding.

Benzene. Two studies described an association between increased maternal benzene exposure and reduced head size(Aguilera I et al. 2010; Slama R et al. 2009). One study which was restricted to non-smoking mothers reported reduced second and third trimester fetal head size associated with increasing benzene exposure (equivalent to 2mm difference by 35 weeks gestation)(Slama R et al. 2009). The second study found no association between benzene and other fetal measurements including FL, AC and EFW, but found reduced BPD growth between weeks 20-32 associated with benzene exposure among a subset of mothers who did not spend ≥15 hours at home per day(Aguilera I et al. 2010).

Other exposures. One study found an association between maternal ozone exposure in the first trimester and AC(Hansen CA et al. 2008) but two other studies found no association between ozone exposure and any fetal measurement(Carvalho M.A. et al. 2016; Ritz B et al. 2014). Only one study related SO_2 exposure to fetal measurements and reported associations between increased first trimester exposure and reduced BPD and AC(Hansen CA et al. 2008). One study explored the relationship between CO and fetal measurements and found no associations(Ritz B et al. 2014).

Quality and strength of evidence

Collectively the ten well-designed well-conducted studies provided a high quality of evidence linking maternal exposure to NO_2 and $PM_{2.5}$ to reduced third trimester fetal measurements (especially head size). The “default” for human studies having moderate quality of evidence was upgraded on account of evidence of dose response between NO_2 and $PM_{2.5}$ exposures and reduced fetal head size. Many studies were at probably low risk for bias in recruitment and exposure assessment. There was sufficient evidence to link NO_2 and $PM_{2.5}$ to reduced fetal head size since findings were consistent across a number of studies, reporting different concentrations of exposures, using different design and in different countries. The evidence linking other air pollution exposures to fetal measurements was of high quality but there was inadequate evidence of an association due to inconsistent findings between studies (e.g. benzene) and not all exposures were measured in all studies, e.g. ozone, carbon monoxide.

Maternal alcohol intake

One paper from the Generation R cohort assessed maternal alcohol intake in the first, second and third trimesters for 7333 mother-fetal pairs(Bakker R et al. 2010). In the longitudinal analysis, the fetuses of mothers who continued to consume alcohol (typically <1 drink a week) had a small increase in EFW growth (0.6g per week). In cross-sectional analyses, there was no association between second and third trimester intake and fetal HC, AC, FL or EFW. There was no evidence of a dose-response effect of alcohol on fetal measurements. A second publication which excluded mothers who smoked obtained routinely collected ultrasound measurements between 18 and 41 weeks gestation and reported reduced HC:AC during the pregnancy for fetuses whose mothers who continued to drink compared to those who quit (magnitude not described)(Handmaker NS et al. 2006). There was reduced cerebellar growth, but no difference in HC, AC and FL, among fetuses exposed to persistent maternal alcohol intake compared to those whose mothers who quit drinking during pregnancy. In this cohort(Handmaker NS et al. 2006), 40% of mothers were marijuana users and 20% used amphetamines with the latter being associated with increased HC:AC growth. A third study (a pilot study) screened 6745 Ukrainian mothers in early pregnancy and identified 84 moderate-to-heavy drinkers and 82 abstinent mothers(Kfir M et al. 2009); moderate-to-heavy drinking was a reported average of 30mls ethanol (or three UK "units") daily at conception and 4mls daily after knowingly being pregnant (including binges with an average of 66mls ethanol/day). FL was reduced in the second trimester among alcohol exposed fetuses (mean 53rd centile versus 65th centile for controls) but not in the third trimester. Third trimester BPD was reduced in exposed fetuses when compared to controls (54th centile versus 70th centile, respectively).

Collectively these studies were of low quality due to bias in recruitment, use of reported alcohol intake and incomplete follow up and within this limited literature there was inadequate evidence identified to link maternal alcohol intake to fetal measurements.

Other exposures

Occupational exposures. A study of occupational exposures (by questionnaire) in 4680 pregnant mothers related FL, HC and EFW to exposures including phthalates, pesticides, polyaromatic hydrocarbons and alkylphenolic compounds(Snijder CA et al. 2012b). There were associations of small magnitude seen between some exposures and some fetal measurements, most consistently for phthalates whose exposure was associated with reduced EFW and fetal length (approximately 1% of a z score per week).

Bisphenol A. A second Generation R study measured maternal urinary Bisphenol A (BPA) in the first, second and third trimesters and related these to fetal growth in 419 pregnancies (Snijder CA et al. 2013). In 80 mothers (i.e. 19% of the study population) urine samples were obtained in each trimester there was reduced growth EFW and HC per unit increase in BPA (typically 2% reduction per week per unit increase in BPA exposure), but this finding was not replicated in models which included mothers where exposure data were not complete nor in a report from the INMA cohorts where there was no association between maternal first and third trimester BPA and fetal measurements (488 mothers)(Casas et al. 2016).

Phenols. A study from the EDEN cohort related maternal exposure to nine phenol-based chemicals to fetal size and growth throughout pregnancy and found evidence that one (triclosan) was linked to minor reductions in fetal size in the third trimester but at no other time(Philippat et al. 2014).

Phthalates. Two studies related maternal phthalate exposure to fetal size and growth and report apparently contrasting findings. The first study, again restricted to male offspring in the EDEN cohort, measured 11 phthalate molecules in maternal urine and found a negative relationship between phthalate metabolites and EFW (10-15g per quartile increase in phthalate exposure) but also a positive association between one molecule (monocarboxyisononyl) and FL in the second and third trimesters(Botton et al. 2016) (which is consistent with the previously mentioned study(Casas et al. 2016)). A study from the INMA cohorts found association of small magnitude between increased concentrations of two of eight phthalate molecules in maternal urine and reduced growth HC in the first, and FL second half of pregnancy(Casas et al. 2016). Both cohorts only measured one common phthalate molecule (monoethyl phthalate) so the results are not necessarily inconsistent.

Polybrominated diphenyl ethers (PBDEs). A further evaluation of the INMA cohorts measured PBDEs in maternal and cord concentrations and related these to fetal measurements in 670 mothers(Lopez-Espinosa et al. 2015); a doubling of PBDE exposure was associated with <5% reduced growth in AC, EFW and BPD (but not FL) between 20-34 weeks (but not 12-20 weeks), although associations were not always present for both maternal and cord blood concentrations.

Organochlorine compounds. The final study identified from 2369 the INMA cohorts related maternal organochlorine compounds in maternal plasma at 12 weeks gestation and cord blood to fetal growth in early, mid and late pregnancy (Lopez-Espinosa et al. 2016); a doubling of exposures to polychlorinated biphenyls (PCB) -138, -153 and -180 were associated with a 2-4% reduction in femur length growth and a doubling of PCB-138 was associated with a 2% reduction in EFW growth between gestational weeks 20-34. There were inverse associations between cord Hexachlorobenzene and reduced AC growth between 0 and 20 weeks. Five of 120 associations in this analysis achieved significance.

Lithium in drinking water. The northern Argentinian Andes has variable concentrations of lithium in its drinking water and a study of 194 mothers observed no significant relationships between maternal plasma and urinary lithium and second and third trimester BPD, HC, AC, FL and EFW(Harari et al. 2015).

Collectively the quality of evidence for these studies was low since although objective measurements of exposure were made in all but one study, multiple comparisons were made within studies increasing the chance of false positive findings, findings (when replicated) were not consistent and risk of bias from incomplete follow up was probably high or high in four studies. Additionally, data were limited only to male offspring in two studies (Botton et al. 2016; Philippat et al. 2014). In conclusion, there was inadequate strength of evidence linking chemicals to fetal size since the quality of evidence was low, many different chemicals were studies and where associations with fetal size were present, these were not replicated elsewhere.

DISCUSSION

This systematic review was designed to describe the literature associating maternal exposures to fetal size being small for gestational age. The papers identified were all published since 2006, indicating that this is a relatively new literature. The first major finding was that maternal exposures to increased ambient air NO_2 and $PM_{2.5}$ were consistently associated with reduced third trimester fetal head size and we judge that the literature presents sufficient evidence of toxicity in this context. The second major finding was that the strength of evidence was inadequate for all the other exposures considered. The third notable finding was that, where associations were present, they were more commonly seen in the third compared to the second trimester and that reduced third trimester head size was more commonly associated with potentially adverse maternal exposures compared to other fetal measurements. Together these findings suggest that public health measures are urgently required to minimise pregnant mother's exposure to NO_2 and $PM_{2.5}$, and more high-quality research is required to better understand the relationship between other (modifiable) maternal exposures and fetal measurements.

The fetus has traditionally been thought to have a privileged position, where it was protected from the adverse effects of environmental exposures by the maternal-placental "unit", but associations between reduced birth weight and many maternal exposures argue against this paradigm. The fetal origins hypothesis(Barker 1995a) speculated that maternal exposures in mid pregnancy were relevant to birth weight and risk for subsequent increased risk for non-communicable diseases. Since we find evidence of reduced second trimester fetal size and some maternal exposures, and our findings suggest that maternal exposures in early pregnancy are also relevant.

There were some associations between exposure and fetal size which were mostly consistent across different populations, whilst other associations were less consistently seen, or were even counterintuitive. An example of consistency was the inverse association between NO_2 exposure and third trimester fetal size, which was seen in all seven studies which explored this link (two studies measured NO_2 but not third trimester head size Carvalho M.A. et al. 2016; Hansen CA et al. 2008). In contrast, there were some instances where an apparently harmful exposure was associated with increased fetal size (e.g. current PM_{10} exposure and first trimester length and second trimester weight(van den Hooven EH et al. 2012), one phthalate molecule and increased third trimester fetal length(Botton et al. 2016), increased maternal and cord plasma vitamin B12 concentrations and reduced birth weight(Bergen et al. 2016), maternal alcohol intake and increased third trimester EFW(Bakker R et al. 2010)); although these associations may challenge the paradigm that "harmful" exposures invariably cause reduced fetal growth, these may be false positive findings.

A further example of inconsistency comes from the ambient air exposure literature where two studies found that the magnitude of association between NO_2 and fetal size was only present(Ritz B et al. 2014), or was greater(Iniguez et al. 2016), among mothers who smoked whereas a second study only found an association between NO_2 and fetal head size among non-smokers(Clemens et al. 2017). Our review also identified many associations of borderline significance and instances of multiple testing, and these increase the risk of false positive results. Given that the body of literature reviewed is relatively young, it is not unexpected that there is a spectrum of consistency/inconsistency between maternal exposure and fetal size and further research activity is required to replicate some of the apparently inconsistent associations.

There are consistencies and inconsistencies in the literature describing associations between maternal exposures and birth weight and these exposures and fetal size. Maternal exposures to poor quality ambient air is associated with reduced birth weight (Maisonet et al. 2004; Shah PS. Balkhair T. Knowledge Synthesis Group on Determinants of Preterm/LBW births 2011) and we confirm this association is already present in fetal life. In contrast, many maternal dietary exposures are associated with reduced birth weight (Gresham E et al.

2014) but there were no consistent associations between maternal dietary exposures and fetal size in the literature we reviewed. Similarly, maternal exposure to chemicals such as bisphenol A(Perera F and Herbstman J 2011) is associated with reduced birth weight but bisphenol A was associated with reduced fetal size in one study (Casas et al. 2016) but not a second (Snijder CA et al. 2013). The inconsistent findings between size before and after birth in the context of maternal exposures may reflect a smaller literature describing antenatal size, the challenges of accurately measuring fetal size or theoretically may be due to associations only becoming detectable towards the very end of pregnancy.

Maternal alcohol ingestion during pregnancy is an established risk factors for reduced birth weight(Henderson J et al. 2007), but the literature was not adequate to determine when the relationship between alcohol ingestion and fetal growth failure begins. The studies identified were at high risk of bias and collectively provided inadequate evidence of toxicity This absence of evidence does not mean that any change is required to current guidelines which recommend that pregnant mothers should abstain from drinking alcohol.

A weakness of the present literature is that all the evidence comes from observational studies where, in addition to the risk of false positive findings previously discussed, some of the results may be influenced by confounding factors and also the results are based on populations who are not necessarily representative of the general population. Drop out from cohort studies also may contribute bias, for example a study which related fetal size to risk for later asthma found a relationship of greater magnitude when using questionnaire reported asthma outcome (available in 39% of the cohort) compared to using routinely acquired asthma outcome (available in 88%) (Turner et al. 2018).

One further limitation of the literature is that whilst there are some maternal exposures linked to fetal size in three or more studies, for example smoking (Abraham et al. 2017) and air pollution (the present review), many exposures are linked to fetal size in only one or two studies (for example chemicals and dietary nutrients) and this leaves insufficient evidence upon which to form an opinion. A second potential limitation to the literature is that fetal measurements and exposures were made at different gestational age, although this limitation applies to the different studies in the literature linking post natal exposures and post natal outcomes. Fetal size is driven by gestational age, and fetal size was determined over a range of gestations within and between different studies. Gestational age was included as a covariate in all but one study (Karateke et al. 2015) and this minimises the potential for differences in gestational age at assessment confounding associations with maternal exposure. Differences between studies in the gestational age when fetal size and maternal exposure are likely to weaken and not strengthen the associations (where present) between maternal exposure and fetal size.

A further limitation to the literature was that different methods were used to measure exposures, even where the same exposure (NO_2 for example) was measured in several studies. This meant that meta-analysis was not possible for single exposures. Another limitation to the literature is that there are some areas where the evidence is of a poor quality, e.g. maternal alcohol exposure, which is an increasing public health concern due to increasing awareness of fetal alcohol syndrome(Popova et al. 2017). Finally, there are several maternal exposures including recreational drug use (Behnke M et al. 2013), pesticides(Sathyanarayana et al. 2010), proximity to land fill sites(Elliott et al. 2001) and electromagnetic fields (de Vocht F and Lee B 2014) which are linked to reduced birth weight but where there are no studies associating such exposures to fetal measurements.

Pregnant mothers are constantly exposed to multiple environmental exposures and identifying which single exposure may be important to fetal size is a challenge, for example increased maternal alcohol intake may be associated with smoking, use of illicit drugs and poor diet. Furthermore, any reduction in fetal size associated with tobacco and alcohol consumption may be modified by increased size associated with amphetamine intake (Handmaker NS et al. 2006). Only intervention studies are able to infer causality, but these are practically and ethically challenging to do in the context of potentially harmful maternal exposures during pregnancy and the evidence base may remain dependent on observational studies.

The mechanism(s) where environmental exposures may cause fetal growth failure (or acceleration) are not well understood but likely to be multiple. The mechanism for maternal diet influencing fetal size assumes that macro and micro nutrients cross the placenta, and maternal dietary fat intake during the third trimester has been associated with cord blood lipid concentrations (Elias SL and Innis SM 2001) but the fetus is not necessarily exposed to all maternal plasma nutrients, for example triglycerides do not cross the placenta(Herrera 2002). The mechanism for ambient air exposures leading to fetal growth failure is not understood but ultrafine particles (which correlate with PM_{10} and NO_2 concentrations) are able to directly enter the maternal circulation via the alveoli (Geiser M et al. 2005) and placenta (Wick P et al. 2010), and thus theoretically enter the fetal circulation where they may be pathogenic by causing vascular inflammation(Gojova A et al. 2007).

In summary, there is an emerging literature which suggests that some maternal exposures during early pregnancy are associated with changes in fetal size which are apparent by the second and third trimester. Evidence from randomised controlled trials where maternal exposures are modified are unlikely due to practical and ethical issues, and the evidence base is likely to arise from observational studies. The literature is mostly based on Western populations and is dominated by three cohort studies and replication in other populations of the associations described is required.

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FIGURE LEGENDS

Figure 1. CONSORT style diagram showing how the papers included in the review were identified.

Figure two. Bar chart summarising the risk of bias for each of the eight domains considered across the 36 papers included in this systematic review.

Figure three. This figure shows the risk of bias in each of eight domains considered for each of the 36 studies included in this systematic review.

Table one

Table 1. Summary of results from the papers identified in the systematic review. HC=head circumference, BPD=biparietal diameter, AC=abdominal circumference, MAD=mean abdominal circumference, EFW=estimated fetal weight. X=no association present, ↑exposure associated with increased fetal measurement, ↓ exposure associated with reduced fetal measurement. NO_2= nitrogen dioxide, CO=carbon monoxide, PM_{10}=particulates with diameter less than 10 microns, BTEX= aromatic hydrocarbons benzene, toluene, ethylbenzene, m/p-xylene, and o-xylene, SO_2=sulphur dioxide, O_3=ozone, PUFA=poly unsaturated fatty acids, PAH=polyaromatic hydrocarbons.

	Exposure	Trimester when exposure was measured*	Second trimester				Third trimester			
			HC/BPD	FL	AC/MAD	EFW	HC/BPD	FL	AC/MAD	EFW
Drouillet (Drouillet P et al. 2009) (seafood)	Diet	P and 3	x	x	x		x	x	x	
Timmermans (Timmermans S et al. 2009)(Folic acid supplementation)		P and 1	x	x	↑	x	↑†	x	↑†	↑
Mahon(Mahon P et al. 2010) (Vit D)		3 (week 34)		x				x		
Turner(Turner SW et al. 2010) (Vit E)		1 (week 12)	x	x						
Drouillet-Pinard(Drouillet-Pinard P et al. 2010)(mercury)		P and 3	x	x	x		x	x	x	
Heppe(Heppe DH et al. 2011b)(milk)		1 (week 15)	x	x		↑	↑	x		x
Heppe(Heppe DH et al. 2011a) (fish)		1 (week 15)	x	x	x	x	x	x	x	x
Ioannou(Ioannou C et al. 2012)(Vit D)		3 (week 34)						↑§		
Young(Young BE et al. 2012) (Vit D and calcium)		3						↑		
Timmermans(Timmermans S et al. 2012)(Mediterranean diet)		1 (week 15)	x	x	x	↑	x	x	↑	↑
Carlsen(Carlsen K et al. 2013)(PUFA)		2 (week 24)	x	↓	x	x				
Bouwland-Both(Bouwland-Both MI et al. 2013) (energy rich diet)		1 (week 15)								x
Karateke(Karateke et al. 2015) (fasting)		1, 2 and 3	x‡	x‡		x‡	x‡	x‡		x‡
Bergen(Bergen et al. 2016) (Homocysteine)		1 (week 13)	x	x		x	↓	↓		↓

Steenweg(Steenweg-de Graaff et al. 2017) (folic acid)		1 (week 13)					↑ δ			
Hansen (Hansen CA et al. 2008)	Ambient air pollution¥	1 (first 120 days)	↓	↓	↓					
Slama (Slama R et al. 2009)		2 (week 27)	↓				↓			
Aguilera(Aguilera I et al. 2010)		1 (weeks 1-12) 2 (weeks 12-20) 3 (weeks 20-32)	↓ψ	x	x	x	↓ψ	x	↓ψ	↓ψ
Iniguez (Iniguez C et al. 2012)		1 (weeks 1-12) 2 (weeks 12-20) 3 (weeks 20-32, 32-term)	x	x	x	x	↓ψ	x	↓ψ	↓ψ
van den Hooven(van den Hooven EH et al. 2012)		1, 2 and 3	x	↓		↑	↓	↓		↓
Ritz (Ritz B et al. 2014)		1 (weeks 0-19) 2 (weeks 19-29) 3 (weeks 29-37)					↓	x	x	
Iniguez(Iniguez et al. 2016)		1 (weeks 1-12) 2 (weeks 12-20) 3 (weeks 20-34 and 34-term)	x	x	↓ψ	↓ψ	↓ψ	x	↓ψ	↓ψ
Carvalho(Carvalho M.A. et al. 2016)		1 (week 12) 2 (week 22) 3 (week 32)								x
Malmqvist(Malmqvist et al. 2017)		1, 2 and 3					x	↓	↓	↓
Clemens(Clemens et al. 2017)		Average across all trimesters	x	x	x		↓	x	x	
Handmaker (Handmaker NS et al. 2006)	Maternal alcohol	2 (<28 weeks)					↓	x	x	
Kfir (Kfir M et al. 2009)		2 (18 weeks)	x	↓	x	x	↓	x	x	x
Bakker (Bakker R et al.		1 (<18 weeks)	x	x	x	x	x	x	x	↑

2010)		2(18-25 weeks) 3 (>25 weeks)								
Snijder(Snijder CA et al. 2012b)(Occupational chemicals)	Other exposures	2 (“mid pregnancy”)					↓	↓		↓
Snijder(Snijder CA et al. 2013)(Bisphenol A)		1, 2 and 3	x			x	x			x
Philippat(Philippat et al. 2014)			x	x	x	x	x	x	x	↓ψ
Harari(Harari et al. 2015)(Maternal plasma lithium)		1 or 2 or 3	x	x	x	x	x	x	x	x
Lopez-Espinosa(Lopez-Espinosa et al. 2015)(Flame retardants)		1 (weeks 10-13)	x	x	x	x	↓ψ	x	↓ψ	↓ψ
Botton(Botton et al. 2016)(Phthalates)		2 (week 26)		↓		x		↓		x
Casas(Casas et al. 2016)(Bisphenol A and Phthalates)		1 (12 weeks) 3 (32 weeks)	↓ψ**	x	x	x	x	↓ψ**	x	x
Lopez-Espinosa (Lopez_Espinosa et al. 2016) (organochlorine compounds)		1 (12 weeks)	x	x	x	x	x	↓ψ	x	↓ψ

* P=periconception, 1=first trimester, 2=second trimester, 3=third trimester. †limited to those whose mothers started folate supplementation before conception. §femur diameter and not femur length. ‡growth and not size reported. δ analysis limited to head circumference growth between the second and third trimester. ¥ see table 2 for more details of associations between individual exposures and fetal measurements. Ψ second trimester details are growth between weeks 12-20 and third trimester details are for growth between weeks 20-34. **reduction in association with phthalates and not bisphenol A

Table two

Table 2. Details of studies where maternal ambient air exposures were linked to fetal ultrasound measurements. HC=head circumference, BPD=biparietal diameter, AC=abdominal circumference, EFW=estimated fetal weight. NO_2= nitrogen dioxide, CO=carbon monoxide, PM_{10}=particulates with diameter less than 10 microns, SO_2=sulphur dioxide.

	Number of mothers	Methodology for measuring ambient air exposure	Exposures measured and at what gestation	Units for comparing exposure	Association with fetal size/growth
Hansen (Hansen CA et al. 2008)	14,734	Monthly average of daily exposure from closest monitoring station	PM_{10}, Ozone, NO_2 and SO_2 over first four months	5 microg/m^3 for PM_{10} 5ppb for NO_2 8ppb for ozone 0.8ppb for SO_2	1mm reduction in T2 BPD and SO_2 during month 1 0.2mm reduction in T2 FL and PM_{10} during months 1 and 4 1mm reduction in T2 AC and ozone and PM_{10} during month 2 2mm reduction in T2 AC and SO_2 during month 3 1mm reduction in T2 HC and PM_{10} during month 4
Slama (Slama R et al. 2009)	271	Non-smoking mothers carried diffusive air sampler	Benzene exposure at 27 weeks gestation	log transformed benzene exposure (microg/m^3)	1.5 mm reduction in T2 HC 2mm reduction in T3 HC
Aguilera(Aguilera I et al. 2010)	562	Land-use regression modelling using ambient measurements	NO_2 and aromatic hydrocarbons (BTEX, including benzene, toluene) between weeks 1 and 32	microg/m^3	For all pregnancies 5% reduction in BPD growth between weeks 20-32 and BTEX weeks 1-12 For mothers who spent<2 hours a day out of the home, 6% reduction in HC growth between weeks 12-20 and 5% reduction in AC and EFW growth weeks 20-32 and NO_2 weeks 1-12
Iniguez (Iniguez C et al. 2012)	818	Land-use regression modelling	NO_2 between week 0 and delivery	microg/m^3	2-3% reduction in BPD growth weeks 20-32 and NO_2 weeks 0-20 2% reduction in AC and EFW growth weeks 20-32 and NO_2 weeks 12-20
van den Hooven(van den Hooven EH et al. 2012)	7772	Dispersion modelling	PM_{10} and NO_2 throughout pregnancy	Quartiles and microg/m^3	0.1mm increase in CRL and current PM_{10} 0.2 mm reduction in third trimester HC and current PM_{10} 0.3g increase in second trimester EFW and current PM_{10} 0.1-0.2 mm reduction in second trimester FL and in third trimester FL and HC and current NO_2

Ritz (Ritz B et al. 2014)	500	Closest monitor methods for CO; NO_2; O_3; PM_{10}. Dispersion modelling and land-use regression for NO_x	Mean daily NO_2, nitrogen oxides (NOx), CO, ozone, PM_{10} between weeks 0-19, 19-29 and 29-37.	Quartiles of exposure	0.2-1 reduction in HC at 37 weeks per quartile increase in PM_{10} between weeks 27-29. ~1mm reduction in HC at 37 weeks per quartile increase in NO_2 between weeks 27-39
Iniguez(Iniguez et al. 2016)	2478	Land-use regression modelling	NO_2 for weeks 0-12, 12-20, 20-34 and 34-delivery	10 microg/m^3	2-3% reduced BPD and AC growth weeks 20-34 and exposure <20 weeks (not FL growth)
Carvalho(Carvalho M.A. et al. 2016)	366	Passive personal samplers	NO_2 and Ozone for 7-18 days before first, second and third trimester ultrasound scan	Log transformed microg/m^3	No association with EFW in third trimester. Ozone exposure was associated with umbilical artery characteristics
Malmqvist(Malmqvist et al. 2017)	48,000	Dispersion modelling 500m or 100m grid cells	Nitrogen oxides for each trimester	10 microg/m^3	0.1mm reduction T2 AD and FL (not T2 BPD) 0.16 z score reduction T2 EFW 0.5 mm reduction head circumference 0.7 z score change in growth during T3
Clemens(Clemens et al. 2017)	13,755	Dispersion modelling 1km cells	Average NO_2, PM_{10}, $PM_{2.5}$ throughout pregnancy	Quartiles of exposure	0.3 z score reduction in T3 BPD in highest versus lowest PM_{10} exposure quartile

Figure one

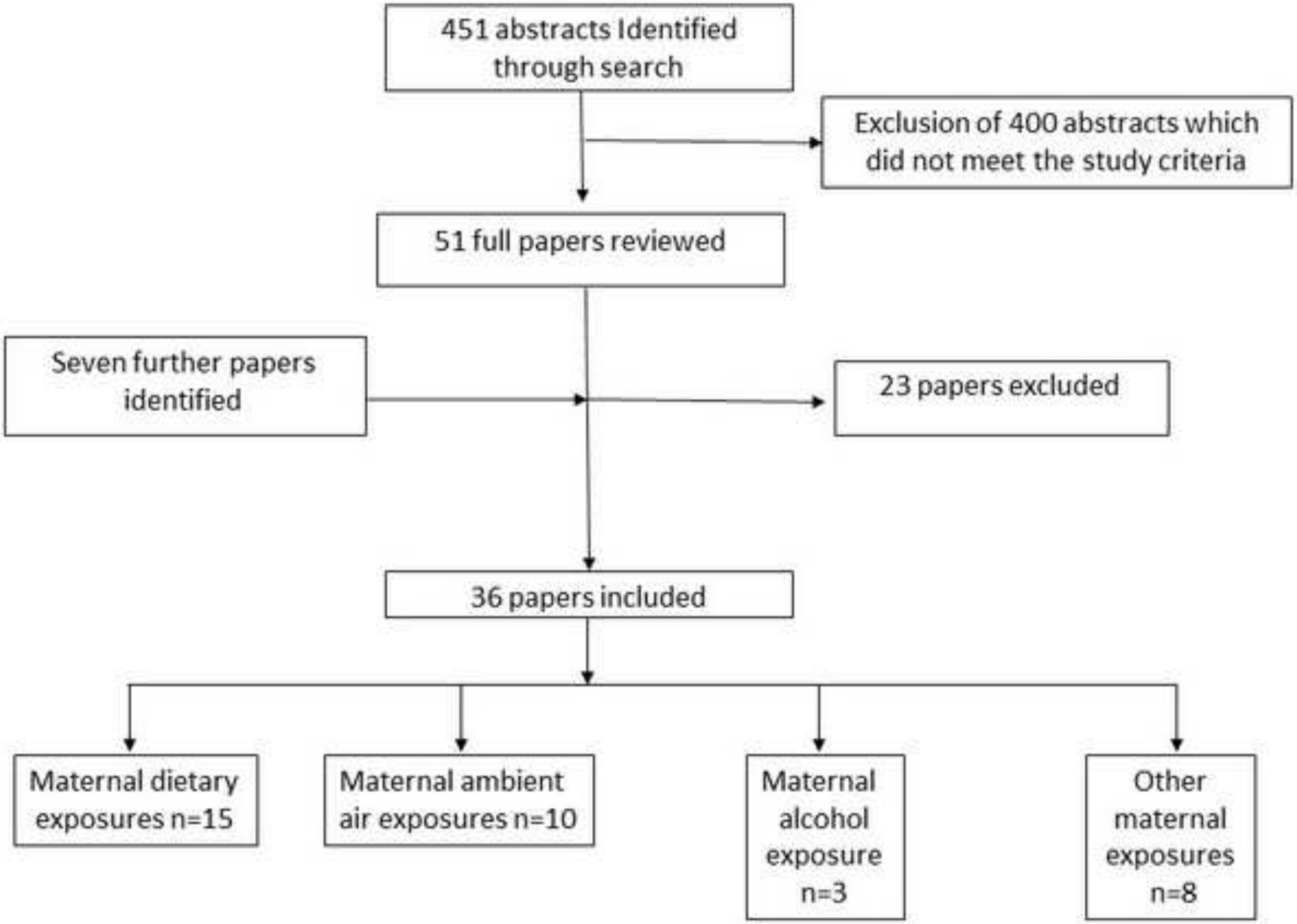
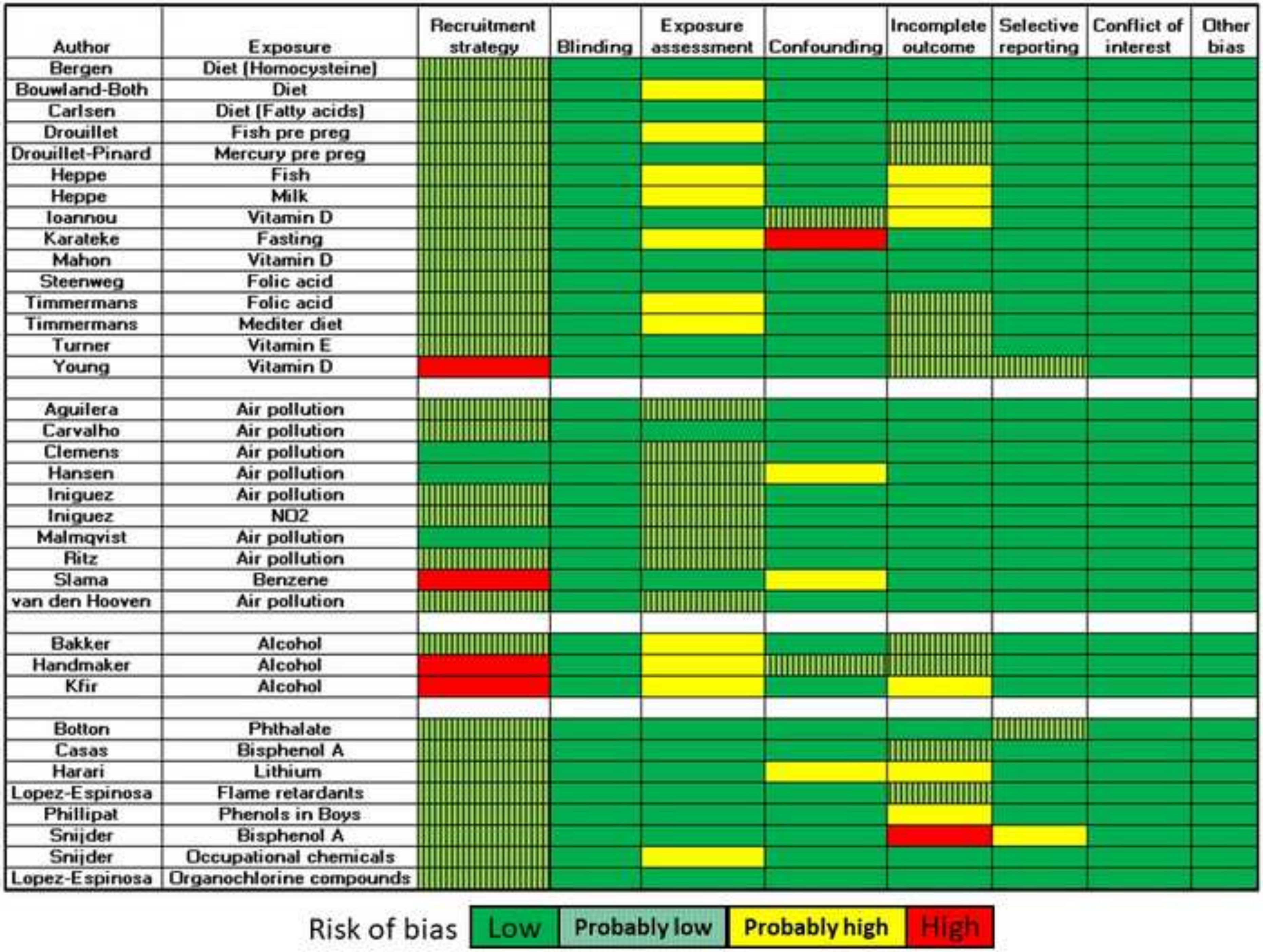

451 abstracts Identified through search
Exclusion of 400 abstracts which did not meet the study criteria
51 full papers reviewed
Seven further papers identified
23 papers excluded
36 papers included
Maternal dietary exposures n=15
Maternal ambient air exposures n=10
Maternal alcohol exposure n=3
Other maternal exposures n=8

Figure two

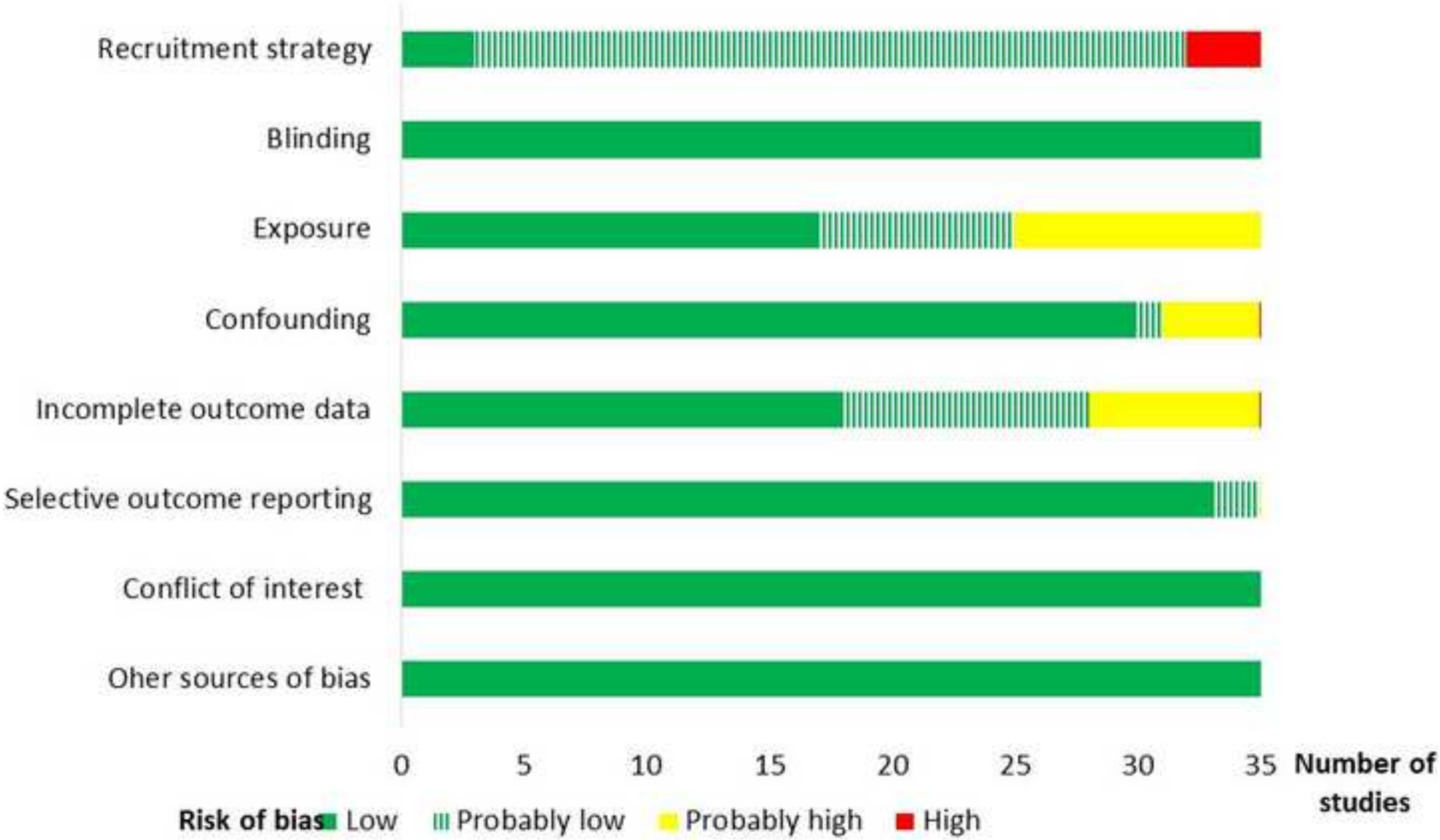
Click here to download high resolution image



Author	Exposure	Recruitment strategy	Blinding	Exposure assessment	Confounding	Incomplete outcome	Selective reporting	Conflict of interest	Other bias
Bergen	Diet (Homocysteine)	▥	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Bouwland-Both	Diet	▥	🟩	🟨	🟩	🟩	🟩	🟩	🟩
Carlsen	Diet (Fatty acids)	▥	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Drouillet	Fish pre preg	▥	🟩	🟨	🟩	▥	🟩	🟩	🟩
Drouillet-Pinard	Mercury pre preg	▥	🟩	🟩	🟩	▥	🟩	🟩	🟩
Heppe	Fish	▥	🟩	🟨	🟩	🟨	🟩	🟩	🟩
Heppe	Milk	▥	🟩	🟨	🟩	🟨	🟩	🟩	🟩
Ioannou	Vitamin D	▥	🟩	🟩	▥	🟨	🟩	🟩	🟩
Karateke	Fasting	▥	🟩	🟨	🟥	🟩	🟩	🟩	🟩
Mahon	Vitamin D	▥	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Steenweg	Folic acid	▥	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Timmermans	Folic acid	▥	🟩	🟨	🟩	▥	🟩	🟩	🟩
Timmermans	Mediter diet	▥	🟩	🟨	🟩	▥	🟩	🟩	🟩
Turner	Vitamin E	▥	🟩	🟩	🟩	▥	🟩	🟩	🟩
Young	Vitamin D	🟥	🟩	🟩	🟩	▥	▥	🟩	🟩
Aguilera	Air pollution	▥	🟩	▥	🟩	🟩	🟩	🟩	🟩
Carvalho	Air pollution	▥	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Clemens	Air pollution	🟩	🟩	▥	🟩	🟩	🟩	🟩	🟩
Hansen	Air pollution	🟩	🟩	▥	🟨	🟩	🟩	🟩	🟩
Iniguez	Air pollution	▥	🟩	▥	🟩	🟩	🟩	🟩	🟩
Iniguez	NO2	▥	🟩	▥	🟩	🟩	🟩	🟩	🟩
Malmqvist	Air pollution	🟩	🟩	▥	🟩	🟩	🟩	🟩	🟩
Ritz	Air pollution	▥	🟩	▥	🟩	🟩	🟩	🟩	🟩
Slama	Benzene	🟥	🟩	🟩	🟨	🟩	🟩	🟩	🟩
van den Hooven	Air pollution	▥	🟩	▥	🟩	🟩	🟩	🟩	🟩
Bakker	Alcohol	▥	🟩	🟨	🟩	▥	🟩	🟩	🟩
Handmaker	Alcohol	🟥	🟩	🟨	▥	▥	🟩	🟩	🟩
Kfir	Alcohol	🟥	🟩	🟨	🟩	🟨	🟩	🟩	🟩
Botton	Phthalate	▥	🟩	🟩	🟩	🟩	▥	🟩	🟩
Casas	Bisphenol A	▥	🟩	🟩	🟩	▥	🟩	🟩	🟩
Harari	Lithium	▥	🟩	🟩	🟨	🟨	🟩	🟩	🟩
Lopez-Espinosa	Flame retardants	▥	🟩	🟩	🟩	▥	🟩	🟩	🟩
Phillipat	Phenols in Boys	▥	🟩	🟩	🟩	🟨	🟩	🟩	🟩
Snijder	Bisphenol A	▥	🟩	🟩	🟩	🟥	🟨	🟩	🟩
Snijder	Occupational chemicals	▥	🟩	🟨	🟩	🟩	🟩	🟩	🟩
Lopez-Espinosa	Organochlorine compounds	▥	🟩	🟩	🟩	🟩	🟩	🟩	🟩

Risk of bias	🟩 Low	▥ Probably low	🟨 Probably high	🟥 High

Figure three



Title page

A systematic review of associations between maternal exposures during pregnancy other than smoking and antenatal fetal measurements

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