Supplementary Materials

Contents

Table S1 Eligibility criteria details

Aspect	Criteria for eligibility
Participants	Women who were pregnant or in the periconceptional period and their offspring (fetuses, infants, or children) were eligible, regardless of health or health treatment status, in any country or hospital setting. Offspring were eligible, regardless of gestational age at birth, or other congenital abnormality status. Live born and stillborn infants as well as miscarriages and terminated pregnancies were eligible. Neonatal deaths were eligible.
Maternal factors (i.e. exposures)	1. Advanced age: all ≥ 35-year categories, or as reported 2. Obesity, defined using BMI (≥ 30 kg/m^2) or other weight measures (e.g., kg), overall and various categories 3. Diabetes mellitus: pre-existing including Type 1 or 2; and gestational; regardless of whether treated, untreated or treatment not specified 4. Hypertension: pre-existing; gestational (pregnancy induced); any (pre-existing or gestational); regardless of treatment 5. Tobacco smoking (e.g., cigarette or cigar), any intake, and different quantified levels or patterns as reported 6. Alcohol consumption (e.g., wine, spirits, or any other types), any intake, and different quantified levels or patterns, as reported.
Comparators	All types of comparator(s) assessed, as defined by the review authors (we anticipated diversity across the included systematic reviews in the definition and composition of comparator groups, and addressed this in the analysis). Reviews in which we were unable to determine the comparator (referent) were excluded.
Outcomes and measures	Outcome: CHDs overall (any types included), however expressed (e.g., as "any congenital heart defect" or "overall congenital heart defects," "cardiovascular defects" or "cardiovascular system defects"). Measures: Odds Ratios (ORs) or/and Risk Ratios (RRs) with 95% confidence intervals, summary or single study, regardless of whether crude or adjusted, single study or summary (i.e., from pooled analysis).
Study design	Systematic review, defined as a literature review with: i) clearly stated review objective(s)/questions addressing association between one or more of the overview risk factors and CHDs; ii) well defined eligibility criteria; iii) a systematic literature search;
Publication date and type	Whilst we searched for relevant reviews from database inception to 27 May 2022, we restricted earliest date of publication to 1990, as it became evidence that this would not lead to exclusion of relevant data. Non-peer reviewed and non-English systematic review publications were excluded. Abstracts with no data for our outcome were excluded.

Notes: 1) Reviews reporting associations between a broader range of factors and CHDs or one or more of the review eligible factors and CHDs in addition to other birth anomalies were eligible, provided we were able to extract associations between a review eligible factor(s) and CHDs.

Abbreviations: CHD - congenital heart defects, GDM - gestational diabetes mellitus, DM - diabetes mellitus

S1 Database search strategies for identification of reviews reporting eligible associations

PubMed (customised version for the University of Adelaide)

Searched on 14 April 2021, from database inception to current, on 27 May 2022 from 2021 to current, and on 28 April 2023 from 2022 to current

("Congenital Abnormalities"[Mesh] OR "birth defect*"[tw] OR "Premature Birth"[Mesh] OR "Heart Defects, Congenital"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Congenital Heart Defect"[tw] OR "Congenital Heart Defects"[tw] OR heart Abnormalit*[tw] OR aortic Coarctation*[tw] OR "Coarctation of the Aorta"[tw] OR "Coarctation of Aorta"[tw] OR "ARVD-C"[tw] OR "Arrhythmogenic Right Ventricular Cardiomyopathy"[tw] OR "Arrhythmogenic Right Ventricular Dysplasia-Cardiomyopathy"[tw] OR "Barth Syndrome"[tw] OR "Cor Triatriatum"[tw] OR "Subdivided Left Atrium"[tw] OR triatrial Heart*[tw] OR "Cor Triatriatum Sinistrum"[tw] OR "Coronary Vessel Anomalies"[tw] OR "Coronary Vessel Anomaly"[tw] OR crisscross Heart*[tw] OR "Criss cross Heart"[tw] OR "Criss cross Hearts"[tw] OR Dextrocardia*[tw] OR "Patent Ductus Arteriosus"[tw] OR "Patency of the Ductus Arteriosus"[tw] OR epstein Anomal*[tw] OR ebstein's Malformation*[tw] OR epstein Malformation*[tw] OR ebstein s Malformation*[tw] OR ebstein's Anomal*[tw] OR ebstein s Anomal*[tw] OR "Ectopia Cordis"[tw] OR "Eisenmenger's Complex"[tw] OR "Eisenmenger Complex"[tw] OR eisenmenger's Syndrome*[tw] OR eisenmenger Syndrome*[tw] OR eisenmenger Syndrome*[tw] OR "Heart Septal Defect"[tw] OR "Heart Septal Defects"[tw] OR atrial Isomerism*[tw] OR "Hypoplastic Left Heart Syndrome"[tw] OR "Isolated Noncompaction of the Ventricular Myocardium"[tw] OR leopard Syndrome*[tw] OR "Cardio Cutaneous Syndrome"[tw] OR lentigines Syndrome*[tw] OR "Levocardia"[tw] OR marfan Syndrome*[tw] OR marfan's Syndrome*[tw] OR noonan Syndme*[tw] OR "Tetralogy of Fallot"[tw] OR "Fallot's Tetralogy"[tw] OR "Fallot Tetralogy"[tw] OR "Fallots Tetralogy"[tw] OR "Transposition of Great Vessels"[tw] OR "Great Vessels Transposition"[tw] OR "Transposition of Great Arteries"[tw] OR "Great Arteries Transposition"[tw] OR "Dextro-Looped Transposition of the Great Arteries"[tw] OR "Dextro Looped Transposition of the Great Arteries"[tw] OR "Double-Outlet Right Ventricle"[tw] OR "Taussig-Bing Anomaly"[tw] OR tricuspid Atresia*[tw] OR "Tricuspid Valve Atresia"[tw] OR "Tricuspid Valve Atresias"[tw] OR "Absent Right Atrioventricular Connection"[tw] OR "Trilogy of Fallot"[tw] OR "Fallot Trilogy"[tw] OR "Fallot's Trilogy"[tw] OR turner Syndrome*[tw] OR turner's Syndrome*[tw] OR turners Syndrome*[tw] OR "Bonnevie Ullrich"[tw] OR "Congenital Heart Disease"[tw] OR "Congenital Heart Diseases"[tw] OR "Congenital Cardiac Defect"[tw] OR "Congenital Cardiac Defects"[tw] OR naxos disease*[tw] OR "Holt Oram syndrome"[tw] OR "heart hand syndrome"[tw] OR "congenital heart block"[tw]) AND ("Smoking"[Mesh] OR Smok*[tw] OR "Cigarette Smoking"[Mesh] OR Cigarette Smok*[tw] OR "Smoking Reduction"[Mesh] OR "Smoking Reduc*"[tw] OR "Smoking Cessation"[tw] OR "Tobacco Use"[Mesh] OR "tobacco use"[tw] OR "alcohols"[Mesh] OR alcohol*[tw] OR "ethanol"[Mesh] OR "Fetal Alcohol Spectrum Disorders"[Mesh] OR "fetal alcohol spectrum disord*"[tw] OR "alcohol"[tw] OR "Alcohol Drinking"[Mesh] OR drink*[tw] OR "Binge Drinking"[Mesh] OR "binge drinking"[tw] OR "Overweight"[Mesh] OR overweight[tw] OR "Obesity, Maternal"[Mesh] OR "Obesity"[Mesh] OR obesity[tw] OR "Thinness"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "diabetes"[tw] OR "Diabetes, Gestational"[Mesh] OR "gestational diabetes"[tw] OR ‘Pregnancy in Diabetics’[Mesh] OR "diabetes mellitus, type 1"[Mesh] OR "Type 1 diabetes"[tw] OR "Diabetes Mellitus, Type 2"[Mesh] OR "Pre-Eclampsia"[Mesh] OR "pre-eclampsia"[tw] OR "hypertension"[Mesh] OR hypertension[tw] OR "Adaptation, Physiological"[Mesh] OR "non-genetic"[tw] OR "maternal lifestyle"[tw] OR "Age Factors"[Mesh] OR "Maternal Age"[Mesh] OR "Age of Onset"[Mesh]) AND ("Pregnancy"[Mesh] OR "pregnancy"[tw] OR "Pregnancy, High-Risk"[Mesh] OR "Maternal Exposure"[Mesh] OR "Pregnancy Complications"[Mesh] OR "Preconception Care"[Mesh] OR "preconception"[tw] OR "inter pregnancy"[tw] OR "inter-pregnancy"[tw]) Filters: Meta-Analysis, Systematic Review, English

Embase

This is the search we used on 14 April 2021 via the Adelaide University Library platform (we searched from database inception to current).

('congenital malformation'/exp OR 'congenital malformation' OR 'congenital heart disease'/exp OR 'congenital heart disease' OR 'congenital heart diseases' OR 'congenital cardiac disease'/exp OR 'congenital cardiac disease' OR 'congenital cardiac diseases' OR 'congenital cardiac distress'/exp OR 'congenital cardiac distress' OR 'congenital cardiac distresses' OR 'congenital heart distress'/exp OR 'congenital heart distress' OR 'congenital heart distresses' OR 'congenital heart failure'/exp OR 'congenital heart failure' OR 'congenital heart failures' OR 'heart congenital disease'/exp OR 'heart congenital disease' OR 'heart congenital diseases' OR 'neonatal cardiopathy'/exp OR 'neonatal cardiopathy' OR 'persistent truncus arteriosus'/exp OR 'persistent truncus arteriosus' OR 'congenital heart malformation'/exp OR 'congenital heart malformation' OR 'congenital heart malformations' OR 'congenital heart anomaly'/exp OR 'congenital heart anomaly' OR 'congenital heart anomalies' OR 'congenital heart defect'/exp OR 'congenital heart defect' OR 'congenital heart defects'/exp OR 'congenital heart defects' OR 'heart right ventricle dysplasia'/exp OR 'heart right ventricle dysplasia' OR 'arrhythmogenic heart right ventricle dysplasia'/exp OR 'arrhythmogenic heart right ventricle dysplasia' OR 'arrhythmogenic right ventricular cardiomyopathy'/exp OR 'arrhythmogenic right ventricular cardiomyopathy' OR 'arrhythmogenic right ventricular dysplasia'/exp OR 'arrhythmogenic right ventricular dysplasia' OR 'cardiomyopathy, arrhythmogenic right ventricular'/exp OR 'cardiomyopathy, arrhythmogenic right ventricular' OR 'naxos disease'/exp OR 'naxos disease' OR 'naxos diseases' OR 'right ventricular cardiomyopathy'/exp OR 'right ventricular cardiomyopathy' OR 'right ventricular dysplasia'/exp OR 'right ventricular dysplasia' OR 'holt oram syndrome'/exp OR 'holt oram syndrome' OR 'atriodigital syndrome'/exp OR 'atriodigital syndrome' OR 'heart hand syndrome'/exp OR 'heart hand syndrome' OR 'leopard syndrome'/exp OR 'leopard syndrome' OR 'cardiocutaneous syndrome'/exp OR 'cardiocutaneous syndrome' OR 'lentiginosis profuse' OR 'lentigines syndrome' OR 'cardiomyopathic lentiginosis'/exp OR 'cardiomyopathic lentiginosis' OR 'mckusick kaufman syndrome'/exp OR 'mckusick kaufman syndrome' OR 'congenital heart block'/exp OR 'congenital heart block' OR 'congenital cardiac block'/exp OR 'congenital cardiac block' OR 'congenital cardial block'/exp OR 'congenital cardial block') AND ('smoking'/exp OR 'smoking' OR smok* OR tobacco* OR nicotiana* OR cigar* OR 'alcohol consumption'/exp OR 'alcohol consumption' OR 'drinking'/exp OR 'drinking' OR 'binge drinking'/exp OR 'binge drinking' OR 'maternal obesity'/exp OR 'maternal obesity' OR 'body mass'/exp OR 'body mass' OR 'underweight'/exp OR 'underweight' OR 'pregnancy diabetes mellitus'/exp OR 'pregnancy diabetes mellitus' OR 'maternal diabetes'/exp OR 'maternal diabetes' OR 'non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' OR 'insulin dependent diabetes mellitus'/exp OR 'insulin dependent diabetes mellitus' OR 'sedentary lifestyle'/exp OR 'sedentary lifestyle' OR 'preeclampsia'/exp OR 'preeclampsia' OR 'pregnancy induced hypertension'/exp OR 'pregnancy induced hypertension' OR 'hypertension'/exp OR 'hypertension' OR 'maternal age'/exp OR 'maternal age') AND ('pregnancy'/exp OR 'pregnancy' OR 'prepregnancy care'/exp OR 'prepregnancy care' OR 'inter-pregnancy' OR 'inter pregnancy' OR 'high risk pregnancy'/exp OR 'high risk pregnancy') AND 'review'/it AND [humans]/lim AND [english]/lim

Search strategy used in the two top up searches (on 27 May 2022 and 28 April 2023, same date limitations as used in the PubMed top-up searches were applied)

Embase (via Ovid)

1	'congenital malformation'.mp. or exp congenital malformation/	880428
2	exp congenital heart disease/	185157
3	'congenital heart failure'.mp.	102

4 'neonatal cardiopathy'.mp. 2

5 'persistent truncus arteriosus'.mp. 457

6 'congenital cardiac distress'.mp. 1

7 'congenital heart anomaly'.mp. 185

8 'congenital heart malformation'.mp. or exp congenital heart malformation/ 146183

9 'congenital heart defect'.mp. 3997

10 'congenital cardiac defect'.mp. 354

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 914432

12 exp maternal smoking/ or exp parental smoking/ or exp cigar smoking/ or exp cigarette smoking/ or exp pipe smoking/ or 'smoking'.mp. or exp "smoking and smoking related phenomena"/ or exp smoking/555156

13 'alcohol consumption'.mp. or exp alcohol consumption/ 168200

14 'alcohol drinking'.mp. or exp drinking behavior/ 58378

15 'binge drinking'.mp. or exp alcohol/ or exp binge drinking/ or alcoholism/369955

16 'maternal obesity'.mp. or exp obesity/ or exp maternal obesity/ or exp pregnancy/ or body mass/ or pregnancy complication/ 1662310

17 'maternal diabetes'.mp. or exp maternal diabetes mellitus/ 6332

18 'gestational diabetes'.mp. or exp pregnancy diabetes mellitus/ 45319

19 'non insulin dependent diabetes mellitus'.mp. or exp non insulin dependent diabetes mellitus/ 300739

20 'pregnancy induced hypertension'.mp. or exp maternal hypertension/ 29113

21 'maternal age'.mp. or exp maternal age/ 50154

22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 2706089

23 first trimester pregnancy/ or exp pregnancy complication/ or exp pregnancy/ or exp high risk pregnancy/ or 'pregnancy'.mp. 962417

24 11 and 22 and 23 65953

25 limit 24 to (human and english language) 48059

26 limit 25 to yr="2021 -Current" 4351

27 limit 26 to ("systematic review" and "reviews (maximizes sensitivity)") 277

Epistemonikos

Search used on 14 April 2021 (we searched from database inception to current), 27 May 2022 (searched from 2021 to current) and 28 April 2023 (searched from 2022 to current):

(title:((title:("congenital heart defect" OR "congenital malformation" OR "birth defect" OR "congenital abnormality") OR abstract:("congenital heart defect" OR "congenital malformation" OR "birth defect" OR "congenital abnormality"))) OR abstract:((title:("congenital heart defect" OR

"congenital malformation" OR "birth defect" OR "congenital abnormality") OR abstract:("congenital heart defect" OR "congenital malformation" OR "birth defect" OR "congenital abnormality"))))
Filters: Systematic review and English only

Figure S1 - PRISMA Study Flow Chart

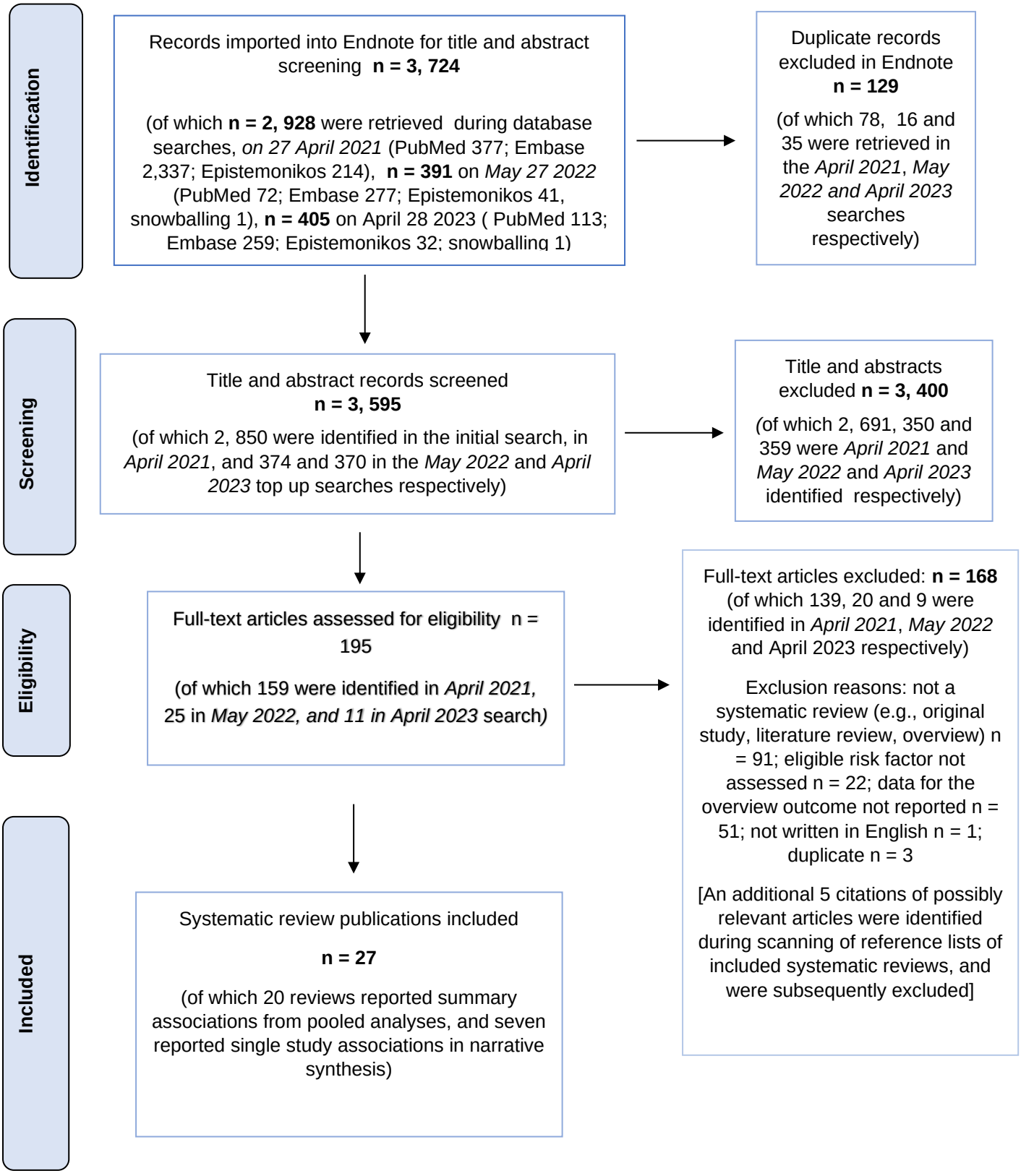


Table S2 Characteristics of included reviews

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
Ahn et al 2022 "Congenital anomalies, and maternal age: A systematic review and meta-analysis of observational studies. January 1989 to January 21, 2021 (English)	"... studies which reported both major (e.g neural tube defect) and minor (e.g hydrocele) congenital anomalies. Maternal age was classified into three groups: young mothers (<20 years old), reference group (20-34 years old) and older mothers (≥ 35 years old). Cohort, case-control and cross-sectional studies were eligible for inclusion"	Included in the review overall: 55 (15 cohort, 14 case control, 36 cross sectional); Included in the assessmnt of the overview exposure-outcome relationship: 8 (design, country setting, dates NR)	NR	**Advanced age**, ≥ 35 yrs (vs middle age, 20-34 yrs)	NOS tool
Cai et al 2014 "Association between maternal body mass index and congenital heart defects in offspring: A systematic review" January 1953 to February 2013 (English)	"participants were pregnant women...measured or estimated prepregnancy or early pregnancy weight was reported... the outcome was pregnancies with all CHDs combined or any specific defect"	Included in the review overall: 24 studies (6 cohort, 18 case control), of which 13 studies assessed overview relevant exposure-outcome association (Australia (1: 1997-2000), Netherlands (1: 1997-2008), Saudi Arabia (1: 1998-2005) Spain (1: 1976-2001), Sweden (3: 1982-1996; 1982-1996; 1992-2001), and USA (6: 1968-1980; 1992-2007; 1993-1997; 1993-2003; 1997-2002; 1997-2004)	39, 896 CHDs cases were involved in the 13 studies relevant to this overview (number of participants involved in these 13 studies is NR)	**Obesity** pre-pregnancy or in early pregnancy (vs normal weight) **Moderately obese** pre-pregnancy or in early pregnancy (vs normal weight) **Severe obesity** pre-pregnancy or in early pregnancy (vs normal weight)	NOS tool Modification of association by study quality was explored in pooled analyses

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
Chen et al 2019 "Risk of congenital heart defects in offspring exposed to maternal diabetes mellitus: an updated systematic review and meta-analysis" Database inception to 15 Dec. 2018 (Chinese or English)	"the exposure of interest was maternal DM; ... outcome of interest was CHDs...we relied on the exposure or outcome terminolgy in the original articles" "CHDs were identified as structural problems arising from malformations in the heart or major blood vessels"	52 (36 case control, 16 cohort) were included The 52 studies were performed in: Australia (1), Canada (2), China (16), Denmark (1), Hungary (2), Iran (2), Italy (1), Norway (1), Spain (2), Sweden (2), UK (2), USA (20) (publication dates reported as 1975 to 2018) 31 studies assessed PGDM-CHDs association 27 studies assessed GDM-CHDs association	NR	**PGDM** (vs no diabetes) **GDM** (vs no diabetes)	NOS tool Association modification by study quality was explored in pooled analysis
Hackshaw et al 2011 "Maternal smoking in pregnancy and birth defects: A systematic review based on 173 687 malformed cases and 11.7 million controls"	"…women who smoked during pregnancy (the exposure) … having a defect among pregnant smokers compared with non-smokers (the outcome)" Cardiovascular defects was one of the birth defect types considered in stratified analyses	101 studies were included in the review overall. 25 (12 case controls, 7 cohort, 6 retrospective surveys) reported data on our outcome of interest (cardiovascular birth defects overall) of which 17 studies were conducted in USA (17 studies: 1960-1967, 1974, 1974-1976, 1959-1966, 1959-1966, 1974-1977, 1976-1980, 1980-1983, 1984-1986, 1981-1983, 1981-1989, 1982-1983, 1998-1999,	2, 116, 757 participants 29, 288 CHDs (25 studies relevant to this overview)	**Any smoking** during pregnancy (vs no smoking)	NOS tool Potential influences of the methodological aspects of the studies on the findings of the main meta-analysis were investigated through sub-group analysis, however, these were performed for the primary outcome of the review, not the overview outcome of interest

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
1959 to February 2010 (English)		1987-1989, 1987-2003, 1999-2003, 1997-2002); 1 in Canada (1982-1984); 2 in UK (1958, 1965-1976); 1 in Finland (1982-1984); 1 in Sweden (1983-1996); 1 in Denmark (1997-2003); 1 in the Netherlands (2003); 1 in Israe1 (1974-1976); and 1 in China (2004-2005)			
Hedermann et al 2021 "Maternal obesity and metabolic disorders with congenital heart defects in the offspring: A systematic review" 1 January 1990 to 14 January 2021 (English)	"…exposures of interest were maternal overweight or obesity, hypertension, PE, diabetes, dyslipidaemia, and/or MetS; and...the outcome of interest was CHDs in the offspring..." Studies were excluded if they did not report CHDs referable to ICD-10 codes (DQ20-26) and/or did not have a healthy control group	32 studies (cohort n = 17, case-control n = 15) were included in the review. Among these, 17 dealt with maternal overweight or obesity, eight dealt with obesity only, 10 dealt with PGDM, , eight dealt with GDM, four dealt with hypertension, three dealt with PE, and none were about dyslipidaemia or MetS (as a diagnostic category). Except for the combination of PGDM and GDM, six studies investigated more than one maternal metabolic disorder (but not in combination), and one study assessed a combination of two conditions (obesity and GDM).	No of participants (range), cohort studies: 41, 013 – 4, 207, 898; and no. of case-controls: 525 –1, 124, 370)	**Obesity** prepregnancy or in early pregnancy (vs normal weight) **PGDM** (vs no diabetes) **GDM** (vs no diabetes) **Hypertension, any in pregnancy (treated or untreated)** (vs no hypertension) **Obesity and GDM** (vs normal weight and without GDM)	NOS tool Eligibility was restricted on study quality, to overall NOS score ≥7 and ≥ 15 CHD cases in total

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
Kankowski et al 2022 "The impact of maternal obesity on offspring cardiovascular health: a systematic literature review" 1946-October 2020 (English)	"We set a broad remit for the review…We included studies with any measure or estimate of maternal obesity set as the exposure of interest, and the outcome as any measures of offspring cardiovascular health at any age" Exclusions: primary focus of the study on other maternal conditions, e.g., gestational diabetes, hypertensive disorders of pregnancy; maternal BMI or other objective measure of obesity not recorded before or during pregnancy; primary focus of study not on maternal health; case reports	6 studies reported on out outcome of interest (i.e., CHDs overall) (5 case controls, 1 cohort) of which 4 were performed in the USA, 1 in Iran, and the remaining 1 in the UK (study dates NR)	NR	**Obesity prepregnancy or during pregnancy** (vs normal weight)	ROBINS-I tool
Kornosky & Salihu 2008 "Getting to the heart of the matter: epidemiology of cyanotic heart defects" January 1976 to March 2007 (English)	"…literature on the epidemiology of cyanotic CHD, with emphasis on the most current knowledge on identified risk/etiologic factors…. the 100 reports that contributed to this review describe risk factors such as infant sex, race, and ethnicity, environmental exposures, and maternal and paternal age… Studies conducted in developing countries were excluded" Exclusions: women in developing countries	100 "publications" were included overall, and reported associations observed between cyanotic CHDs (and in some cases CHDs) and a range of possible risk factors (infant sex, race, and ethnicity, environmental exposures, and maternal and paternal age); 3 studies (all case control) evaluated exposures relevant to this overview: alcohol (1 study, USA dates NR), smoking (2 studies, USA 1, dates not	NR	**Advanced age (**not further defined) (referent NR) **Obese** pre-pregnancy (not further defined) (referent NR)	_

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
		reported, 1 setting and dates NR) age			
Lassi et al 2014 "Preconception care: caffeine, smoking, alcohol, drugs and other environmental chemical/radiation exposure" Search dates: database inception to Dec 2012 (no language restriction)	"…preconception risks and interventions to prevent and avoid substance abuse and environmental and workplace exposure to chemicals and radiations for improved maternal, newborn and child health (MNCH) outcomes"	39 studies were included in the review overall, of which 4 (all case controls) assessed association between two relevant maternal exposures, alcohol (1 study, USA (1987–1988)) and smoking (2 studies, Greece (1, June 2006- June 2009), USA (1, October 1997 through December 2002, NBDPS database))	**Alcohol** NR **Smoking** 1 study NR, 1 study 365 (with CHDs NR)	**Any alcohol consumption** periconception (vs no alcohol use) **Any smoking** one month before conception through 1st trimester (not further defined) (vs no smoking) **Light smoking**, <14 cigarettes / day, periconception (vs heavy smoking, >25 cigarettes / day)	STROBE guidelines
Lee & Lupo 2013 "Maternal smoking during pregnancy and the risk of congenital heart defects in offspring: a systematic review and meta-analysis"	"…examined the association between maternal cigarette smoking anytime during pregnancy and CHDs overall or any one of the CHD subtypes in infants" Exclusions: mothers with a history of CHDs or diabetes	33 studies, 19 (5 survey/cross sectional, 10 case control 4 cohort) reported data relevant to this review Setting of 19 relevant studies: USA (9: 1960-1967; NR; 1980-1983; 1984-1986; 1981-1983; 1968-1980; 1998-1999; 1998-2004;1981-1989), UK (2: 1958; 1965-1976), Sweden (2: 1983-1996; 1992-2001), Greece (1: 2006-2009), China (1: 2004-	2, 687, 739 offspring were involved in the 19 relevant studies (i.e., the studies providing data for analyses measuring association between smoking and CHDs overall)	**Any smoking** during pregnancy (not future defined (vs no smoking) **	'We conducted a sensitivity analysis, restricting our analysis to studies with available information on exposure during the periconceptional period. Because heart anomalies develop during weeks 2–7 of gestation, we suspected that inclusion of studies that assessed exposure

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
1947 to July 2011 (English)		2005), Lithuania (1: 1999-2005), Netherlands (1: dates NR), Canada (1: 1982-1984), Finland (1: 1982-1984)			beyond the ''critical period'' may have biased our result toward the null. However, our sensitivity analysis showed no significant difference in the summary effect estimates" (data not provided in the review) (pg. 406) Studies examining… association of interest in certain subgroups, specified as "(e.g., mothers with CHDs, mothers with diabetes, or infants with Down syndrome) were excluded"
Liu et al 2019 "Maternal Body Mass Index and Risk of Congenital Heart Defects in Infants: A Dose-Response Meta-Analysis" Database inception to 31	"…studies on the relationship between maternal BMI and infants with CHDs…having clear BMI categories of prepregnancy or early pregnancy…CHDs or one of the CHD subtypes as outcome…in addition the study for dose-response analysis had to report the estimates of a least three BMI classifications"	19 studies (6 cohort, 13 case control) Australia (1: 1997-2000) Saudi Arabia (1: 1998-2005) Spain (1: 1976-2001) Sweden (3: 1982-1996; 1992-2001; 2001-2014) UK (1: 2003-2005)	2, 416, 546 participants (57,172 cases)	**Obesity** pre-pregnancy or in early pregnancy (vs normal weight)	NOS tool Modification of association by study quality was assessed in the pooled analyses. Studies with NOS score ≥ 7 only were eligible for inclusion in the meta-analysis

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
April 2018 (English)		USA (12: 1982-1983; 1984-1987; 1992-2007; 1993-2003; 1993-1997; 1997-2002; 1997-2008; 1998-2003; 1999-2004; 2002-2008; 2005-2012; 2011-2012)			
Nicoletti et al 2014 "Maternal smoking during pregnancy and birth defects in children: a systematic review with meta-analysis" 1950 to 2010 (no language restriction)	"…investigated the association between maternal smoking during pregnancy and birth defects in children … eligible…Studies that contemplated the association between maternal smoking and chromosomal abnormalities were ruled out" Exclusions: infants with chromosomal abnormalities "Cardiovascular system defects" was one of the birth defect types evaluated in stratified analysis	188 studies were included (159 retrospective case control, or cross-sectional, 29 prospective cohort or nested case control) A total of 29 studies were included in the assessment of the overview exposure-outcome of interest (study designs, country setting and dates NR)	13,564,914 participants (192,655 birth defect cases, 13,372,259 controls with no defects) involved in the 188 included studies 29 studies reporting on the overview outcome: 32, 340 cases contributed data for analysis	**Any smoking** during pregnancy (vs no smoking)	No tool was used to assess ROB, with the following justification: "…limitations of the tools currently available" *** Potential influences of the methodological aspects of the studies on the findings of the main meta-analysis were investigated through sub-group analysis, however, these were performed for the primary outcome of the review, not the overview outcome of interest
Papazoglou et al 2022 "Maternal diabetes mellitus and its impact on the risk of delivering a child with congenital	"…Pregestational diabetes melltus…and gestational diabetes…in accordance with globally respected diabetic diagnostic guidelines…association with CHDs…data for the whole spectrum of CHDs and not only the	15 studies included overall (6 case control, 9 cohort) of which all of which were included in the assessment of PGDM-CHDs association (Canada 3, USA 3 studies, Norway and UK 2 studies , and one study each in China, Denmark , France, Italy,	12, 461, 586 women were involved in the 15 studies included in the review, no. of participants included in each relevant meta-analysis is NA (CHD cases NR)	**PGDM** (vs no diabetes) **GDM** (vs no diabetes)	NOS tool

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
heart disease: a systematic review and meta-analysis" 1997 to 23 June 2020 (English) (the rational for 1997 cut off year is this is when the American Diabetes Association published updated guidelines for the diagnosis of diabetes mellitus)	specific ones…not predisposed participants"	Sweden. (Study settings and dates NR) 7 studies (3 case control, 4 cohort studies) were included in the assessment of GDM-CHDs association			
Parnell et al 2017 "Pre-pregnancy obesity as a modifier of gestational diabetes and birth defects associations: a systematic review" Database inception to Sept. 2013 (no	"…pregnant women, diabetes status of the women was reported and information on the presence of birth defects in the offspring was available" CHDs was one of several types of birth defects evaluated	5 case controls were included in the analysis relevant to this review (i.e., examining GDM-CHDs association) USA (3 studies: 1981-1987, 1997-2003, 1997-2004); Spain (2 studies: 1976-1985, 1976-2001)	Number of participants (CHDs cases and controls) not reported with the exception of for one study, for which the numbers are: controls 5, 673 and CHDs cases 6, 440	**GDM** (vs no diabetes)	Study design exclusion criteria intended to minimise bias: no information available in study report on the methods of determination of diabetes stats; no description of the ascertainment of and classification of birth defect(s)

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
language restriction)					
Patel & Burns 2013 "Non-genetic risk factors and congenital heart defects" 1990 to 2013 (no language restriction)	"risk of CHD for children after exposure to parental conditions or environmental exposures" Environmental exposure defined, as any factor that is not genetic, and more specifically to the fetal-placental-maternal environment; limited to the periconceptional period "Studies that evaluated broad categories of defects (e.g., conotruncal defects, septal defects, left-sided obstructive defects) were not included unless information regarding specific defects also was presented	**Alcohol** 1 study (case control) USA (1996-2005) **Smoking** 5 (case controls): 1 Baltimore-Washington USA (1981-1989), 1 Greece (2006-2009), 1 USA, 10 states (1997-2002), 1 Arkansas USA (1998-2004), 1 Sweden (1983-1996) **Hypertension** 5 studies (1 retrospective cohort, 4 cases controls): 1 California USA), 1 Hungary (1980-1996), 1 USA, 10 states (1997-2003), 1 USA Milwaukee (1997-1999), 1 Finland FRCM (1982-1983) **Diabetes** 7 studies (1 retrospective cohort, 6 case controls): 1 13 countries of Europe (1990-2005, 18 registries), 1 Hungary (1980-1996), 1 USA 10 states (1997-2003), 1 Milwaukee USA (1997-1999), 1 Baltimore-Washington USA (1981-1989,), 1 Washington State USA (1984-1991), 1 Sweden (1981-1986)	**Alcohol** 1, 185 (237)** **Smoking** 1, 430 927 (9 408)** **Hypertension** 517, 763 (17 202)** **Diabetes** 169, 529 (14 779)** **Obesity** 1, 492, 892 (42 4015)** **Age** 1, 774, 499 (14, 097)**	**Advanced age** periconception (not further specified) (referent NR) **Obesity** pre-pregnancy , **severe obesity** pre-pregnancy (referent NR) **PGDM** (vs no diabetes) **Hypertension** periconception (vs no hypertension) **Smoking** periconception (vs no smoking) **Any alcohol use** periconception (vs no alcohol use)	The reviewers generally describe restriction of study inclusion on quality, as follows: "each publication was assessed to determine the quality of information presented with respect to consistency of findings and study design"

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
		Obesity 8 studies 1 USA, 10 states (1997-2004), 1 Sweden (1995-2007), 4 USA (1993-1997; 1968-1980; 1992-2007; 1993-2003), 1 Australia (1997-2000), 1 Germany (1990-1994) **Age**, 6 studies (2 case controls, 4 NR (unclear): 1 Atlanta USA (1968-2005), 1 Poland (1998-2002), 1 Dallas USA (1988-1994,), 1 NSW/ACT Australia (1981-1984), 1 Baltimore Washington USA (1981-1989), 1 Finland (1982-1983)			
Ramakrishnan et al 2015 "Maternal hypertension during pregnancy and the Risk of Congenital Heart Defects in Offspring" 1978 to August 2013 (English)	"…examined the association between maternal hypertension or hypertensive medication and CHD overall or specific CHD subtypes (e.g., atrioventricular septal defects) in infants"	16 (9 case control, 7 cohort); Brazil (1 study: 2005-2007), Canada (2 studies: 2009-2010; 2002-2010), Europe (1 study: 1986-2003), Finland (2 studies: 1982-1983; 1996-2001), Hungary (3 studies: 1980-1996; 1980-1996; 1980-1996), Sweden (2 studies: 1995-2006; 1995-2001), USA (5 studies: 1981-1989; 1997-2003; 1985-2000; 1996-2000; 1995-2008)	4, 993, 996 (plus 1-10***) (with CHDs NR)	**Treated hypertension during pregnancy** (vs no hypertension) **Untreated hypertension during pregnancy** (vs no hypertension) **Any hypertension during pregnancy (treated or untreated)** (vs no hypertension)	NOS tool Modification of associations seen in the main analysis by study quality was performed
Simeone et al 2015	"…women with PGDM…contained one or multiple CHDs as outcome"	12 studies were included in relevant MA (i.e., assessed association between PGDM, and CHDs overall (rather than specific	1, 345, 484 (497 exposed offspring with CHDs)	**PGDM** (vs no diabetes)	Sensitivity analyses explored modification of

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
"A systematic review, meta-analysis, and modelling project" Database inception through Dec 2012 (English)	Exclusions: chromosomal and genetic defects	types of CHDs) (4 case control, 8 cohort) Australia (1 study: 1986-2000), Canada (1 study: 2005-06), Hungary (1 study: 1980-1996), Norway (1 study: 1999-2004), USA (7 studies: 1968-1990; 1981-1989; 1984-1991; 1991-2000; 1997-2004; 2000-2008; NR), UK (1 study: 1996-2008)			association by study quality Studies were excluded if they "did not exclude chromosomal and genetic defects from estimates of CHDs or did not include a study sample that was a representative population" (thus for e.g., studies whose participants were a group of women known to be at higher risk of CHDs (e.g., women older than 40 years, or women with a family history of CHDs) were not eligible
Slot et al 2019 "Congenital heart defects in offspring of women with Type 2 diabetes – a systematic review" 2007 to February 2018 (Language for inclusion unclear as NR)	"…offspring of women with Type 2 diabetes" (compared with) … of women with Type 1 diabetes…the risk of congenital heart defects"	5 cohort studies were included (1 study each in Canada, Denmark, Norway, Taiwan, USA; study dates NR)	23, 845 (CHDs cases NR)	**PGDM** (vs background population)	Study eligibility was restricted on study quality to: "cohort studies each including data on CHD in a minimum of 200 offspring of women with Type 2 diabetes from independent cohorts' ***

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
Stothard et al 2009 "Maternal overweight and obesity and the risk of congenital anomalies: A systematic review and meta-analysis" 1966 through May 2008 (English)	"Articles were included if the participants were pregnant women, a measure or estimate of prepregnancy or early pregnancy weight was reported, and the outcome was a congenital anomaly" "Cardiovascular anomalies" was one of the congenital anomaly subtypes assessed.	39 studies were included in the review (cohort or case controls); 7 (all case controls) contributed data for overview relevant analyses (USA 4 studies:1985-1987, 1968-1980, 1993-1997, 1997-2000; Sweden 2 studies: 1982-1986, 1992-2001; Spain 1 study: 1995-2001	For the 7 studies relevant to this review, total participant number is NR (13, 785 CHDs cases)	**Obesity** pre-pregnancy or in early pregnancy (vs recommended weight)	Sensitivity analysis examined the potential effects of varying methodological and inclusion criteria. Higher quality was defined as reported the inclusion of pregnancies ending in termination, excluded mothers with pregestational diabetes, and excluded cases that were chromosomal or syndromic. Sample size restriction for study inclusion in meta-analysis: ≥ 150 cases
Sun et al 2015 "Maternal alcohol consumption before and during pregnancy and the risks of congenital heart defects in offspring: A systematic review and Meta-analysis"	"…examined the association between maternal alcohol consumption and CHDs overall or any one of the CHD subtypes in infants…defined CHDs or one of the CHD subtypes as an outcome"	23 (19 case control, 4 cohort) Australia (1:1983-2007), USA (13: 2001-2004; 1968-1980; 1987-1988; 1981-1989; 1999-2003; 1998-2006; 1997-2002; 1996-2005; 1981-1989; 1991-1993; 1968-1980; 1997-1999; dates NR), Canada (2: 2002-2010; 1982-1984), Denmark (1: 1996-2002), Finland (1: 1982-1984), Lithuania (1: 1999-2005), Netherlands (2: 2008; 1996-	309, 980 (19, 160) (all studies) Cohort study no. offspring range: 26, 488 to 87, 260 (277 to 4, 123 with CHDs) Case control no. offspring range: 80 to 4, 075 (82 to 4, 392)	**Any alcohol** use before or during pregnancy (vs no alcohol)	NOS tool Modification of association by study quality was explored in the pooled analyses.

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
Database inception to 16 February 2015 (English)		2005), Spain (1: dates NR), Sweden (1: 1982-1996)			
Wu et al 2023 "Association between maternal factors and risk of congenital heart disease in offspring: A systematic review and meta-analysis" Database inception to May 2021 (whether language not reported)	"…all participants being pregnant women, with the number of CHD cases in children reported; (2) two or more studies investigating the same maternal factors including age, body mass index (BMI), alcohol intake, smoking history, diabetes, coffee intake, irradiation, and exposure to organic solvents; (3) outcomes including the risk of CHD, and atrial (ASD) and ventricular (VSD) septal defects in children…" (Maternal pregestational and gestational diabetes were not analysed separately, and thus the data from this review relating to diabetes were not considered in this overview)	64 studies reporting on one or more of the eligible maternal factors were included (46 case control, 18 cohort). Details for the maternal factors eligible in this review are reported below. **Advanced age**: 19 studies of which 16 cases control (7 USA, 2 UK, 1 each in Sweden, Finland, Egypt, Lithuania, Greece, Netherlands and China, study dates NR); 3 cohort (Canada, UK, Sweden, dates NR) **Obesity**:23 studies of which 4 cohort (Canada, Sweden, USA, UK, dates NR), and 19 case control (11 USA, 2 UK, 1 each in Australia, Hungary, Iran, Netherlands and Spain, dates NR) **Smoking:** 32 studies (33 cohorts) of which 5 cohort studies (2 performed in Sweden, and 1 each in Canada, China and the USA), and 28 cases controls (16 performed in the USA, 2 in Italy, 4 in the Netherlands, and 1 each	Authors reported that overall, all 64 of the included studies assessed a total of 182, 290 CHD cases in offspring. The number of participants (case/controls) involved in each study is listed in the table of included study characteristics, however the total numbers providing data in the pooled analysis for each of the review relevant maternal factors is not reported.	**Advanced age** assessed as "advanced maternal age" (not further specified) **Obesity** (timing not specified) (vs normal weight) **Any smoking** (vs none) **Any alcohol use** (vs none)	NOS tool The robustness of the overall conclusions was assessed by a sensitivity analysis that sequentially excluded individual studies (Tobias, 1999).

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
		in Hungary, UK, China, Greece, Lithuania and Sweden) **Alcohol**: 29 studies (32 cohorts) of which 6 cohort studies (2 each in Australia, Canada and Sweden), and 26 case controls (15 conducted in the USA, 3 in the Netherlands, and 1 each in Sweden, Spain, Lithuania, Italy, China, UK, Finland and Hungary, dates NR)			
Yang et al 2015 "Prenatal alcohol exposure and congenital heart defects: A meta-analysis" Database inception to March 2015 (English)	".. investigated the relationship between maternal alcohol exposure before or during pregnancy and the risk of overall CHDs or any CHDs subtypes" Exclusion: mothers of interest diagnosed with CHDs, diabetes, or other abnormal conditions, and infants of interest specified as with Down syndrome	20 (16 case control, 4 cohort) Australia (1:1983-2007), USA (9: 1968-1980; 1974-1977; 1976-1980; 1981-1989; 1987-1988; 1996-2005; 1997-2005; 1999-2004; 1998-2008;), Canada (1: 1982-1984), Denmark (1: 1996-2002), Finland (3: 1982-1983, 1982-1983, 1982-1983), Ireland (1994-1998), Italy (2008-2010), Lithuania (1: 1990-2005), Denmark (1: 2008; 1996-2002), Spain (1:1977-2001), Sweden (1: 1982-1996)	310, 919 (with CHDs NR)	**Any alcohol** use during pregnancy or periconception) (vs no alcohol) **Binge alcohol** use, assessed as ≥48g (i.e., ≥4 drinks) on one or more occasion, periconception or during pregnancy (vs no alcohol) **Heavy alcohol** use, defined as average consumption ≥24g on average per day, periconception or during pregnancy (vs no drinking)	NOS tool Sensitivity analysis assessed robustness of main meta-analysis findings to study quality.

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
Zhang et al 2017 "Is maternal smoking during pregnancy associated with an increased risk of congenital heart defects among offspring? A systematic review and meta-analysis of observational studies" Database inception to 24 July 2015 (English)	"…the exposure of interest was maternal smoking during pregnancy; (3) the outcome of interest was CHDs; and … We did not set any restriction to study setting, era, or locale" (Nine CHD types were excluded in the meta-analysis assessing the association between the relevant exposures and CHDs overall, as they were analysed in separate pooled analysis: atrial septal defect; atrioventricular septal defect; conotruncal heart defect; left ventricular outflow tract obstruction; right ventricular outflow tract obstruction; septal defect; transposition of the great arteries; tetralogy of Fallot; ventricular septal defect.	43 (38 case control studies, 5 cohort studies were included), of which 23 (19 case control 4 cohort studies) reported on our outcome of interest, CHDs overall 23 studies providing data for this overview: USA (11: 2001; 1982-1983; 2002-2008; 1988; 1997-2002; 1998-2004; 1998-2008; 1989-2011; 1997-2002; 1997-2006; 1998-1999; 1984-1986), Sweden (3: 1992-2001; NR; 1981-1986), Netherlands (3: 1997-2008; 2003-2006; 1996-2005), Italy (1: 2008-2010), United Kingdom (1: 1958) Greece (1: 2006-2009) Lithuania (1: 1999-2005) China (1: 2004-2005) India (1: 2004-2007)	74, 366 CHDs cases were involved in the 43 included studies 2, 612, 818 offspring were involved in the 23 studies relevant to this overview (contributing data on CHDs overall)	**Any smoking** during pregnancy (vs no smoking) Smoking on CHDs **dose response**	Authors reported that they: "…rated the biases of studies in 6 domains which were related to selection bias, measurement error, and statistics reasonability. Studies were rated as ''high risk'', ''low risk'', or ''unclear'' for each domain". Sensitivity analysis explored modification of association by study quality.
Zhang et al 2020 "Parental alcohol consumption and the risk of congenital heart	"…had use of parental alcohol consumption as the exposure of interest…CHDs as the outcome of interest"	45 (3 cohort and 42 case control) contributed data for the association between maternal alcohol consumption and CHD	55 included studies: 339, 334 offspring (41, 747 CHDs cases)	**Any alcohol** use periconception or during pregnancy (vs no alcohol)	NOS tool Robustness of association findings to study quality

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
diseases in offspring: An updated systematic review and meta-analysis" 1950 to 24 July 2019 (English or Chinese)	The reviewers noted that: "Because variations in the definition of exposures and outcomes exist across countries and cultures, it is extremely difficult to define uniform standards. Some of the included studies did not always define exposures and outcomes, and in such cases, we relied on the corresponding terminology in the original articles"	Australia 1 (1983-2007, cohort study), Canada 1 (1982-1984 cohort study), China 19 (2012-2013; 2012-2012; 2013-2014; 2015-2016; 2011-2017; 2008-2010; 2005-2006; 2009-2012; 2011-2014; 2011-2014; 2014-2016; 2013-2016; 2014-2016; 2004-2014; 2007-2008; 2009-2010; 2015-2016; 2017-2018; 1 NR), Denmark 1 (1996-2002 cohort study), Finland 1 (1982-1984), Lithuania 1 (1999-2005), Netherlands 5 (2003-2005; 2003-2008; 1997-2008; 2 dates NR), Spain 1 (1997-2002), Sweden 1 (1982-1996) USA 14 (1981-1989; 1985-1995; 1987-1988; 1968-1980; 1999-2003; 1981-1989; 1997-2007; 1982-1983; 1981-1989; 2001-2004; 1996-2005; 1997-2006; 1998-2004; 1997-2005)	45 reporting data for maternal alcohol exposure and CHDs overall: 332, 813 offspring of which 238, 037 were involved in the cohort studies, 94, 776 in the case controls (no. with CHDs NR)	**Binge alcohol use**, defined as ≥ 5drinks per sitting on any one or more occasion periconception or during pregnancy (vs no alcohol) Alcohol on CHDs **dose response**	was explored in pooled analyses.
Zhang et al 2022a "Risks of specific congenital anomalies in offspring of women with diabetes: A	"Population-based cross-sectional, case–control, and cohort studies that reported original data were eligible for inclusion if they (1) reported any CAs in offspring born to women with diabetes (i.e., pre-gestational [combined type 1 and 2] or gestational diabetes), (2) had a	59 studies were included (designs NR) Relevant to this review: 18 studies reported on the association between maternal PGDM and CHDs in offspring (1 study Australia: 1986-2000; 2	No. of participants in analyses relevant to this review is reported as < or ≥ 282, 260. For the assessment of PGDM: 3 studies <	**PGDM** (vs no diabetes) **GDM** (vs no diabetes)	ROBINS-I tool Robustness of the association findings seen in the overall analysis to study quality was explored through a range of sub-group analysis that restricted inclusion based

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
systematic review and meta-analysis of population-based studies including over 80 million births" Database inception to 15 October 2021 (no limitation on language)	comparison group that included mothers without diabetes, and (3) provided sufficient data from which a risk estimate could be calculated if a risk estimate was not reported."	studies Canada: 1998-2002; 2002-2013; 1 study Columbia:1981-1989; 1 study Denmark: 1978-2011, 1 study France: 2012; 1 study Hungary: 1980-1996, 5 studies USA: 1984-1991; 1997-2003; 1999-2015; 2006-2014; 2011-2018; 1 study Italy: 1997-2010; 1 study Norway: 1994-2009; 1 study UK: 1996-2008; 3 multi-country (European) studies: 1990-2005; 1999-2015; 2002-2003) 11 studies reported on the association between GDM and CHDs (1 study China: 2009-2011, 6 studies USA: 1981-1989; 1984-1991; 1997-2003; 1999-2015; 2006-2014; 2011-2018, 1 study France: 2012, 1 study Norway: 1994-2009, 1 study Denmark: 1978-2011, 1 study Hungary: 1980-1996)	282, 260, 15 studies ≥ 282, 260; For the assessment of GDM on CHDs: < 282, 260 participants 3 studies, ≥ 282, 260 participants in 8 studies. CHDs cases included in the review : 350, 051		on various study design criteria (e.g., sample size, adjustment for potential confounders).
Zhang et al 2022b "Hypertensive disorders in pregnancy are associated with congenital heart	"Eligibility criteria … included : …(ii) HDP were the exposure of interest including gestational hypertension, pre-eclampsia or eclampsia, chronic hypertension, and preeclampsia superimposed on chronic hypertension; (iii) CHDs or specific	24 studies were included (case control or cohort) Included for the analysis of our exposures of interest: gestational hypertension 6 studies (all cohort); and chronic hypertension	Overall number of participants involved was 40,394,699, and overall CHDs cases 477,839 Number of participants involved and cases of	**Pregestational hypertension** (specified as chronic hypertension, was defined as increased blood pressure (≥140/90 mmHg) before 20 weeks	NOS tool Robustness of the association findings seen was explored in sensitivity analysis which included removing poorer quality

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
defects in offspring: A systematic review and meta-analysis" Database inception to 30 April (English)	CHD phenotypes (e.g., ASD, VSD, TOF, etc.) were the outcomes of interest; (iv) the association between HDP and CHDs or specific CHD phenotypes were part of the main objective of the study (including studies that investigated other perinatal risk factors in addition to HDP); (v) reported odds ratios (ORs) or relative risks (RRs), with corresponding 95% confidence intervals (CIs) (or provided sufficient information to calculate effect value, such as β coefficient and standard error (se), or complete four grid table data (2 × 2 tables) sufficient to calculate their OR value or RR value)". The authors note that: "Some studies that focused on the treatment of HDP or special populations (e.g., very low birth weight preterm infants)…were excluded". However, also that: "it is difficult to accurately evaluate the effect of the management of these disorders or the use of antihypertensive treatment on the occurrence of complications because of the limited information from original studies.	12 studies (5 cohort, 6 case control, and 1 NR)	CHDs are not reported for our exposures of interest	gestation, but not associated with additional systemic features of preeclampsia (vs no hypertension) **Gestational hypertension** (Traditionally, gestational hypertension was defined as new-onset elevated blood pressure (≥140/90 mmHg) after 20 weeks of gestation, and recovery before 12 weeks of delivery) (vs no hypertension)	studies defined as NOS score < 7.

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
Zheng et al 2018 "Increased maternal Body Mass Index is associated with congenital heart defects: An updated meta-analysis of observational studies" Database inception to April 2018 (no language restriction)	"…the exposure of interest was maternal BMI …ascertainment the BMI category…the outcomes of interest were CHDs…total CDDs, but also …specific CHD phenotypes.	29 studies (6 cohort studies, 23 case control studies) Australia: 1 study Canada: 1 study China: 8 studies Iran: 1 study+ Netherlands: 1 study Saudi Arabia: 1 study Spain: 1 study Sweden: 3 studies UK: 1 study USA: 11 studies Study dates NR (all studies)	6, 467, 422 participants 99, 205 CHD cases	**Obesity** and c**lass I, II and III** pre-pregnancy or in early pregnancy (vs normal weight)	NOS tool Sensitivity analysis explored modification of association by study quality. Study eligibility was restricted to studies with diagnoses of cases based on reliable techniques (such as echocardiography, cardiac catherization, surgery, and autopsy)
Zhu et al 2018 "Association between maternal body mass index and congenital heart defects in infants: A meta-analysis"	"...maternal BMI and infant CHDs…the outcome was defined as CHDS or one of the CHD subtypes… BMI criteria were reported based on the definitions were established by the Centers for Disease Control"	17 (14 case control, 3 cohort); Australia 1 study (1997-2000); Netherlands 1 study (1990-2012); Spain 1 study (dates NR); Sweden 2 studies (1982-1996;1992-2001) UK 1 studies (2003-2005); USA 11 studies (NR; 1982-1983; 1998-2003; 1993-1997; 1993-2003; 1992-2007; 1997-2002; 1997-2008;	1, 154, 762 (43, 188 cases)	**Obesity** (timing not specified) (vs normal weight)	NOS tool Sensitivity analysis explored modification of association by study quality (case control vs cohort study, <10, 000 cases vs ≥ 10, 000 cases, overall NOS score <7 versus ≥7)

Review ID and title, and search dates (language restriction in eligibility criteria)	Review eligibility criteria for "types of participants, exposure(s) and outcomes"	Number of studies included (design) and their country setting(s) (dates) when reported in the reviews	Number of participants and CHD cases involved in the included studies relevant to this overview	Relevant overview maternal factor(s) assessed (referent)	Study quality assessment: tool used to assess ROB, pooled analysis, and limitations on quality in eligibility when reported
January 1980 to August 2017 (English)		1999-2004; 2005-2011; 2011-2012)			

Notes: * Results for light, moderate and heavy cigarette smoking during pregnancy were also reported in this review, which we have not included as we were unable to determine the quantification of the levels/categories light, moderate and heavy applied. **Single study results were reported in this review, we have added the number of cases and controls reported in the included studies**.** ** Single study results were reported in this review, we have added the number of cases and controls reported in the included studies**.** ***The authors report that the cohort size cut off for inclusion was a pragmatic choice made to minimise the uncertainty when evaluating the prevalence of rare events such as CHDs in a relatively small sample size.

Abbreviations: CAs: congenital anomalies; DM: diabetes mellitus, FE: fixed effects, FI: further information, GA: gestational age, GDM: gestational diabetes mellitus, MBDs: multiple birth defects, MA: meta-analysis, MetS: metabolic syndrome, NR, not reported; NOS: Newcastle-Ottawa Quality Assessment Scale, PE: preeclampsia; PDM: pre-gestational diabetes mellitus, RE: random effects, ROB: risk of bias, ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions, STROBE: International, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies, with the common aim of STrengthening the Reporting of OBservational studies in Epidemiology, WHO ICD: World Health Organisation International Classification of Disease.

Table S3 Risk of bias summary: reviewer judgements about bias in each included review

Systematic Review	Phase 2				Phase 3
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Overall risk of bias in the review
Ahn *et al.* (2022)	Low	Unclear [1]	Unclear [2]	Unclear [3]	Unclear
Cai *et al.* (2004)	Unclear [4]	Low	Low	Low	Low
Chen *et al.* (2019)	Unclear [5]	Unclear [6]	Unclear [7]	Unclear [8]	Unclear
Hackshaw *et al.* (2011)	Low	Unclear [9]	Low	Low	Low
Kankowski et al (2022)	Unclear [10]	Unclear [11]	Low	Low	Unclear
Hedermann *et al.* (2021)	Unclear [12]	Low	Low	Low	Low
Kornosky & Salihu (2008)	Unclear [13]	Unclear [14]	Unclear [15]	Unclear [16]	Unclear
Lassi *et al.* (2014)	Low	Low	Low	Low	Low
Lee & Lupo (2013)	Unclear [17]	Low	Low	Low	Low
Liu *et al.* (2019)	Unclear [18]	Low	Low	Low	Low
Nicoletti *et al.* (2014)	Low	Low	Unclear [7]	Unclear [8]	Unclear
Papazoglou *et al.* (2022)	Unclear [19]	Unclear [20]	Unclear [21]	Unclear [3]	Unclear
Parnell *et al.* 2017	Low	Low	Unclear [22]	Unclear [23]	Unclear
Patel & Burns (2013)	Low	Unclear [14]	Unclear [24]	Unclear [25]	Unclear
Ramakrishnan *et al.* (2015)	Unclear [5]	Low	Low	Low	Low
Simeone *et al.* (2015)	Unclear [26]	Low	Low	Low	Low
Slot *et al.* (2019)	Unclear [5]	Unclear [14]	Unclear [7]	Unclear [27]	Unclear
Stothard *et al.* (2009)	Unclear [16]	Low	Low	Low	Low
Sun *et al.* (2015)	Unclear [16]	Unclear [28]	Low	Low	Unclear
Wu *et al.* (2023)	Unclear [5]	Unclear [6]	Low	Low	Unclear
Yang *et al.* (2015)	Unclear [11]	Unclear [29]	Low	Low	Unclear
Zhang *et al.* (2017)	Unclear [18]	Low	Low	Low	Low
Zhang *et al.* (2020)	Unclear [18]	Low	Unclear [7]	Unclear [8]	Unclear
Zhang et al. (2022a)	Low	Low	Low	Low	Low
Zhang et al. (2022b)	Low	Low	Unclear [7]	Unclear [8]	Unclear
Zheng *et al.* (2018)	Unclear [18]	Low	Unclear [7]	Unclear [8]	Unclear
Zhu *et al.* (2018)	Unclear [18]	Low	Unclear [7]	Unclear [8]	Unclear

Explanation

[1] Publication date limited to 1989 or later, and search strategy not reported in full, thus we are unable to confidently assess risk of bias due to failure to identify all relevant published studies.

[2] No details are provided on key characteristics of studies included in the analyses assessing congenital heart defects in offspring and advanced maternal age, including no reporting of study design type, country setting (date), number of participants involved in each included study, or risk of bias assessments for these studies.

[3] Unable to confidently assess risk of bias in the interpretation of the evidence due to the limited information provided on included study characteristics.

[4] No protocol for this review is accessible, eligible studies restricted on language (English included only), and the timing aspect of the eligible exposures is specified generally as "early pregnancy".

[5] No protocol for this review is accessible, and the eligibility criteria are generally specified.

[6] Full database search strategies are not reported which makes confident assessment difficult, although comparison of the studies included in this review with those in other reviews with similar eligibility criteria suggests the search was comprehensive, therefore no serious concerns.

[7] Lack of details about potential confounder variables adjusted for or matched in included studies.

[8] In the absence of reporting of the variables adjusted (or matched on) in the studies included in each pooled analysis unable to assess confidently.

[9] During data extraction, when comparing the study inclusions of this review with other reviews with similar eligibility criteria reporting on the same maternal exposure (any smoking during pregnancy) (Lee et al 2013, Lassi et al 2014, Nicoletti 2014), we identified a few studies that may be eligible not included in the review.

[10] Eligibility criteria are broadly defined, and without further details we are not confident that it would be possible for other reviewers, to independently apply them and identify the same set of studies as that included in the review for our outcome of interest (CHDs overall)

[11] The search strategies are only broadly described in the review (in Table 2 of the review report), and after considering the number of studies included in this review against the numbers identified by other reviews included for the same factor (maternal obesity) published around the same time, we are not confident that the search identified all relevant studies (reporting data on the association between maternal obesity (referent normal weight) and CHDs). We have assessed the review as at unclear risk of bias overall due to the concern we have about possible missed studies.

[12] English language studies included only and start date for study inclusion limited to January 1990 with no justification.

[13] No protocol for this review is accessible, eligibility criteria generally specified, and eligibility was restricted on language (to English only) (with the limited details in the eligibility criteria, we cannot be certain that the study selection could be duplicated).

[14] Unable to confidently assess due to due to limited information provided on the search and study selection process of the review.

[15] Limited details are provided on the characteristics of the included studies; there is no characteristics of included studies providing details on the sample selection, exposure assessment, outcome ascertainment or confounder adjustment in the study includes, and no reporting of risk of bias in each included study.

[16] No concerns other than the comprehensiveness of the reporting of results (associations) in the narrative synthesis varies across studies and we are unable to confidently assess whether meta-analysis could have been utilised to increase precision due to the limited reporting of included study characteristics.

[17] No protocol for the review is accessible, eligibility restricted on language (to English included only), and general description of participant subgroups excluded means we are unable to confidently assess as high or low risk of selection bias.

[18] No protocol for the review is accessible and eligibility restricted on language, to English included only.

[19] Eligibility limited on language (English only), and publication date, to published since 1997.

[20] Search strategy is not reported in full, thus it is difficult to confidently judge whether the review is likely to have identified all relevant studies.

[21] No information is provided on the process of data extraction or risk of bias assessment and adjustment in each study included in the two relevant meta-analysis is not reported; additionally (despite quality scores based on NOS assessments provided by domain (selection, comparability, outcome detection)

[22] Data collection by one reviewer, which may or may not have introduced bias, and no reporting of risk of bias at included study level.

[23] Unable to confidently assess whether biases in primary studies were minimal or addressed in the synthesis due to no reporting of risk of bias in each study included in the relevant pooled analyses.

[24] Few details provided on the characteristics of included studies, including no reporting of adjustment or sources of controls for most of the studies, and no risk of bias report at the included study level.

[25] Unable to confidently assess the risk of bias with the limited information provided on risk of bias in the included studies and adjustment variables (although the reviewers do note that when available unadjusted results were included).

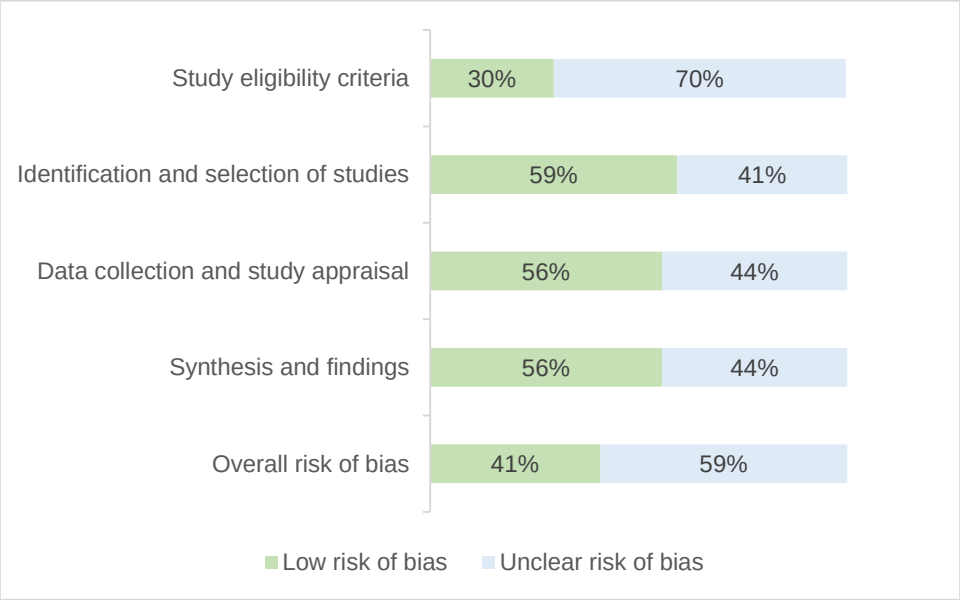
[26] No protocol for the review is accessible, no other concerns.

[27] The results of five included studies are summarised as a mean RR (range) measure of association without weighting or adjustment variables.

[28] Unable to confidently assess due to limited details provided on the strategy (database strategies not reported in full), and comparison of included studies with those included in another review with similar eligibility criteria (Yang et al 2015) suggests a couple of relevant studies may be eligible and not included.

[29] Unable to confidently assess due to limited details provided on the strategy (database strategies not reported in full), and comparison of included studies with those included in another review with similar eligibility criteria (Sun et al 2015) suggests a couple of relevant studies may be eligible and not included.

Figure S2 Risk of bias' graph: review authors' judgements about each bias item presented as percentages across all included reviews, expressed as percentage.



S2 References for supporting information

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