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Maternal modifiable factors and risk of congenital heart defects: systematic review and causality assessment

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ABSTRACT

Objective Primary prevention strategies are critical to reduce the global burden of congenital heart defects (CHDs); this requires robust knowledge of causal agents. We aimed to review associations between CHDs and maternal advanced age, obesity, diabetes, hypertension, smoking and alcohol consumption and assess the causal nature of the associations.

Design Systematic review of reviews with application of a Bradford Hill criteria score-based causal assessment system.

Data sources We searched PubMed, Embase and Epistemonikos (January 1990–April 2023).

Eligibility criteria Systematic reviews of original epidemiological studies reporting association (relative risk) between one or more of the above maternal factors and CHDs overall (any type) in subsequent offspring.

Data extraction and synthesis Two independent reviewers selected eligible reviews, assessed the risk of bias and assigned the strength of evidence for causality.

Results There was strong evidence of a causal relationship between CHDs and maternal obesity (prepregnancy and early pregnancy) and pre-existing diabetes (six of seven Bradford Hill criteria met). For pre-existing hypertension (strength and biological gradient not met), and advanced age (strength, consistency and biological gradient not met), causal evidence was moderate. Evidence for the causal contribution of gestational diabetes, gestational hypertension, smoking and alcohol consumption was weak (strength, consistency, temporality and biological gradient not met).

Conclusions CHDs can be reduced with stronger action to reduce maternal obesity and pre-existing diabetes prevalence. Investigating environmental exposures that have received limited attention, such as air pollutants and chemical exposures, is important to further inform prevention.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first systematic review of associations between modifiable maternal factors and congenital heart defects to assess causality and rank priorities for primary prevention strategy.
⇒ We performed a comprehensive search of relevant databases to identify relevant associations.
⇒ We used best practice systematic review methodology and an established method (Bradford Hill) to assess the weight of evidence for the causal nature of associations.
⇒ Unknown risk of publication bias is a limitation as reviews published in languages other than English and reviews in the grey literature were not eligible.

INTRODUCTION

Congenital heart defects (CHDs) are the most common class of congenital anomalies.[1] Live birth prevalence is 8–10 cases per 1000.[1 2] The impacts of CHDs on children, their families, the health system and society are wide-ranging. They are a leading cause of child mortality, often require complex treatment and are associated with long-term cardiovascular and neurological morbidity for afflicted children.[3 4] Having a child with a CHD can be distressing for the whole family, with negative effects on parent mental health and family functioning.[5 6] Over the last two decades, advancements in medical technology have greatly improved the rate of survival of children with critical CHD and led to a high proportion of individuals with CHD having near-normal life expectancy.[5–7] Thus, adverse health and economic impacts associated with this class of congenital anomalies are becoming more evident, and a strategy to mitigate risks associated with CHDs is a priority for global health policy.[7]

Genetic factors are present in 15%–40% of CHD cases.[8] For the remaining, environmental and chemical exposures are implicated, although causes are often not well understood.[9 10] In 2007, the American Heart Association published a scientific statement on non-inherited CHDs risk factors which identified maternal rubella, phenylketonuria, pre-existing diabetes mellitus (PDM), indomethacin for tocolysis and exposures to thalidomide, vitamin A congeners or retinoid, as definitive risk factors.[11]

Subsequently, there has been a marked expansion in research examining CHD

susceptibility, with a focus on reporting risks associated with maternal diseases and lifestyle.[12] This is drawn from observational studies, as it is unethical to obtain causal evidence through experimental studies. Limited attention has been paid to assessing causality.[12] However, inference of causation from observational studies has been achieved without human trials (eg, for thalidomide). Employing a comparable established strategy for imputing causation from observational studies of CHDs is crucial to target investment into areas that will have the greatest impact on CHDs reduction. Recent contributions in causal assessment[13–16] and systematic review methodology[17 18] facilitate implementing such an approach.

Therefore, here, we present a systematic review of CHDs risks associated with select, prevalent modifiable maternal factors (advanced maternal age, obesity, diabetes mellitus, hypertension, cigarette smoking and alcohol use) and assess causality using established criteria.

METHODS

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions,[19] with modifications for undertaking a review of exposures and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[20] The review protocol was not registered, however, it was approved, prospectively, by a panel of experts.

Eligibility criteria

Systematic reviews of original epidemiological studies published January 1990–April 2023 in English reporting associations (risk ratio (RR) or OR, summary or single study, adjusted or unadjusted) between one or more of the above maternal factors and CHDs overall (any specific type) in subsequent offspring were included. Our included factors are modifiable, prevalent, routinely collected and characterised by the debate over appropriate recommendations for women in the periconception period. Non-peer-reviewed systematic reviews were excluded (eg, those conducted for government or committees not published). See online supplemental table S1 for further details about the review eligibility criteria.

Search and study selection

To identify relevant systematic reviews, we systematically searched the databases PubMed, Embase and Epistemonikos, from database inception to 28 April 2023 (three searches, initial on 14 April 2021, with top-ups on 27 May 2022 and 28 April 2023). The database selection was informed by which combination of bibliographic databases is most efficient to retrieve systematic reviews in overviews of reviews.[21] We scanned included reviews to identify potentially relevant records not retrieved by the primary search. Database search strategies are in online supplemental material S1.

Two authors independently selected reviews for inclusion. Disagreements were resolved through consensus after discussion and consultation with a third author if necessary.

Data collection and analysis

Two authors independently extracted characteristics and data from the included reviews using a prespecified data extraction form tailored for this review. Characteristics extracted from the included reviews were: review title and authors; publication date, search dates and date review was last assessed as up to date; the number of included studies and number of participants in the studies and their characteristics (eg, countries where the studies were conducted, inclusion criteria); quality of the included studies (risk of bias and certainty as reported by reviewers); exposures and comparators (referents) relevant to this review; definition of the CHDs overall outcome (and whether this outcome was the primary or secondary outcome); any other characteristics relevant to assess review quality.

Statistical data extracted were: summary associations (including for eg, RRs, ORs, with 95% CI), the number of studies and participants contributing data, and statistics required for risk of bias assessments (eg, heterogeneity and publication bias statistics). When meta-analyses were not performed, we extracted single study results. We did not contact authors for unpublished information and data.

One author assessed the risk of bias of each included systematic review using the Risk of Bias in Systematic Reviews tool[22] with a second independently verifying the assessments.

We summarised associations by factor in narrative and tables, applied select Bradford Hill (BH) criteria[13] to assess the causal nature of associations and followed the score-based system used in two recent reviews of epidemiologic evidence[17 18] to classify the strength of causal evidence.

We assessed the BH criteria strength, consistency, temporality, biological gradient, plausibility, analogy and coherence. From the original Hill criteria, the specificity criterion was deemed non-applicable given known multifactorial causes of CHDs, and the experimental evidence criterion was deemed non-applicable as ethical considerations prevent the study of the maternal factors as the cause of disease under controlled conditions. We awarded 1 point for criterion satisfaction and rated overall scores 6–7, 4–5, 0–3 as strong, moderate or weak evidence of causality, respectively. We used knowledge gathered in purposive database searches to make plausibility, analogy and coherence judgments.

Required for BH criterion satisfaction:

- Strength of association—relative risk ≥2 with precision (we followed Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group recommendations).[14]

- Consistency of association—≥50% of included studies showed an association in the expected direction (we studied forest plots). When summary associations were reported without forest plots, we relied on the GRADE method[14 23] that focuses on unexplained inconsistency indicated by the I^2 heterogeneity statistic, and we required $I^2 \leq 50\%$ in most associations, including the one based on pooling data from the largest number of studies for criterion met.
- Temporality—included studies for the association established a temporal direction by design.
- Biological gradient—≥50% of tests for a dose–response relationship either showed a statistically significant trend or an apparent change in the magnitude of effect in the expected direction.
- Plausibility—Possible mechanisms underlying a causal relationship between the maternal factor (exposure) and CHDs in subsequent offspring exist.
- Analogy—Analogous relationships exist.
- Coherence of evidence—The association does not conflict with existing knowledge about CHDs and the maternal factor (eg, no conflicting patterns in prevalence and distribution).

For factors with strong causal evidence, we estimated the population attributable fraction (PAF) of CHD cases (range based on the lowest and highest pooled risk estimates reported). We used the Levin's formula as used previously,[24] which requires the RR estimate for the influence of the factor on CHDs, and the prevalence of the risk factor. For each factor, we calculated PAF estimates of CHD cases, one assuming the lowest RR indicated by our systematic review data, and the other assuming the highest. For maternal factor prevalence, we used the most recent robust global estimates we could identify in the literature, specifically 16.3% for obesity periconception[24] and 1% for pregestational diabetes mellitus.[25]

Patient and public involvement

None as this systematic review used study-level data and no individual-level data or participants were involved.

RESULTS

From 3724 records retrieved, we included 27 reviews[26–52] (online supplemental figure S1). Characteristics of the reviews are in online supplemental table S2, with the risk of bias assessments (by review, online supplemental table S3 and domain, online supplemental figure S2). 11 of the reviews, we assessed at low risk of bias[27 29 30 33–35 40 41 43 47 49] and the remaining[26 28 31 36–39 42 44–46 48 50–52] unclear risk of bias.

Overall, evidence of causal effect was strong for obesity and PDM and moderate for advanced maternal age and pre-existing hypertension. The remaining factors were assessed as having weak evidence of causality (table 1). The PAF was 2.7%–4.9% for maternal obesity and 2.1%–2.7% for PDM.

The assessment of each BH criterion is discussed below for each factor, except for coherence, which requires consideration of the evidence across all factors and is, therefore, at the end of the results.

Advanced age

One pooled association (unadjusted)[26] showed a modest elevated risk of CHDs in women ≥35 years (preconception or during pregnancy) compared with those younger (RR 1.15, 95% CI 1.06 to 1.25, I^2 54%, 8 studies). Another[45] did not show a significant elevation in risk of CHDs for advanced maternal age not further specified (OR 1.04, 95% CI 0.96 to 1.12; I^2 74%; 19 studies; confirmed in subgroup analysis restricted based on design and adjustment). Two further reviews[32 39] of case–control studies (n=7) reported single study conflicting results for advanced maternal age not further specified. Both pooled associations do not meet the strength criterion (summary effect size <2) and residual confounding cannot be ruled out.

The criterion for consistency is not met. Moderate heterogeneity was detected in the meta-analyses assessing age ≥35 years[26] and in the forest plot of the pooled association for advanced age not further specified[45] less than half of included studies indicated significant associations in the expected direction.

Temporality is met as advanced maternal age at conception precedes CHD development. The biological gradient criterion is not, as no review provided data to assess whether risk increases with age.

Several biological mechanisms could explain associations between advanced maternal age and CHDs. The risk of aneuploidy and other congenital anomalies increases dramatically with advanced age, which can give rise to CHDs occurring as part of a genetic syndrome (eg, Down syndrome).[53] Maternal ageing can induce changes to epigenome[54] that may influence the regulation of cardiac development.[55] The criterion for analogy is met as advanced maternal age is associated with other congenital anomalies of chromosomal and non-chromosomal origin.[26]

Obesity

Pooled risk estimates reported in six reviews[27 35 43 45 51 52] demonstrate a small, elevated risk of CHDs in women with obesity relative to normal weight (17%–32%), thus strength of association criterion is not met (table 2).

The criterion for consistency is with most associations significant in the expected direction and most I^2 statistics <50%.

The criterion for temporality is met as the pooled risk estimates were strengthened in the meta-analysis restricted to studies that assessed weight prepregnancy rather than early pregnancy (OR 1.44, 95% CI 1.23 to 1.68). There is also evidence of a biological gradient, for example, one review[35] found the risk of CHDs increased

Table 1 Bradford Hill criteria assessment of strength of evidence for causal nature of associations between prevalent maternal factors and CHDs

Factors	Assessments for criteria with data provided in the review				Assessments for criteria without data in the review			Interpretation
	Strength of association	Consistency of association	Temporality	Biological gradient	Plausibility	Analogy	Coherence of evidence	Strength of the evidence for causality (score)
Advanced age								
≥35 years vs younger	X	X	✓	X	✓	✓	✓	MODERATE (4)
Obesity								
Obesity vs normal weight	X	✓	✓	✓	✓	✓	✓	STRONG (6)
Diabetes								
Pre-existing DM vs no DM	✓	✓	✓	X	✓	✓	✓	STRONG (6)
GDM vs no GDM	X	X	X	X	✓	✓	✓	WEAK (3)
Hypertension								
Pre-existing vs none	X	✓	✓	X	✓	✓	✓	MODERATE (5)
Gestational vs none	X	X	X	X	✓	✓	✓	WEAK (3)
Pre-existing or gestational vs none								
Treated	X	✓	X	X	✓	✓	✓	MODERATE (4)
Untreated	X	✓	X	X	✓	✓	✓	MODERATE (4)
Any (treated or untreated)	X	✓	X	X	✓	✓	✓	MODERATE (4)
Smoking								
Any vs none	X	X	X	X	✓	✓	✓	WEAK (3)
Alcohol consumption								
Any vs none	X	X	X	X	✓	✓	✓	WEAK (3)
Heavy (≥2 drinks/day) vs none	X	X	X	X	✓	✓	✓	WEAK (3)
Binge (≥4 drinks on 1 occasion) vs none	X	X	X	X	✓	✓	✓	WEAK (3)

Continued

Table 1 Continued

Factors	Assessments for criteria with data provided in the review				Assessments for criteria without data in the review			Interpretation
	Strength of association	Consistency of association	Temporality	Biological gradient	Plausibility	Analogy	Coherence of evidence	Strength of the evidence for causality (score)

System used to classify strength of evidence for causality:
Required for Hill criterion satisfaction:

- Strength of association—relative risk≥2 with precision (we followed the widely used GRADE approach and guidance for integrating this with Bradford Hill's criteria for causation,[11 12] according to the GRADE working group, a strong association is indicated by an RR of 2–5 or 0.2–0.5.[12]
- Consistency of association—≥50% of included studies showed an association in the expected direction (we studied forest plots). When summary associations were reported without forest plots, we relied on the GRADE method that focuses on unexplained inconsistency indicated by the I^2 heterogeneity statistic, and we required $I^2 \leq 50\%$ in most associations, including the one based on pooling data from the largest number of studies for criterion met.
- Temporality—included studies for the association established a temporal direction by design.
- Biological gradient—≥50% of tests for a dose-response relationship either showed a statistically significant trend or an apparent change in the magnitude of effect in the expected direction.
- Plausibility—Possible mechanisms underlying a causal relationship between the maternal factor (exposure) and CHDs in subsequent offspring exist.
- Analogy—Analogous relationships exist.
- Coherence of evidence—The association does not conflict with existing knowledge about CHDs and the maternal factor (eg, no conflicting patterns in prevalence and distribution).

We awarded 1 point for criterion satisfaction (✓), nil for not satisfied (X) and computed an overall score out of 7. Overall score 7–6, 5–4, 3–0 we classified strong, moderate and weak respectively.

(1) From the original Hill criteria, the Specificity criterion was deemed non-applicable given known multifactorial causes of CHDs, and the Experimental Evidence criterion was deemed non-applicable as ethical considerations prevent the study of the maternal factors as the cause of disease under controlled conditions. (2) We included only the reviewed exposures for which pooled risk estimates were available in the causal assessment; there was one exposure for which data from only one study were available, moderate smoking (<14 cigarettes/day) (referent heavy smoking, defined as >25 cigarettes/day). (3) We conducted a purposive literature search for knowledge required to inform our assessments of the criteria plausibility, analogy and coherence of evidence.
CHD, congenital heart defects; DM, diabetes mellitus; GDM, gestational DM; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio.

Table 2 Summary associations between maternal obesity and CHDs

	Summary associations: OR unless otherwise specified (95% CI)	No. of studies (Offspring if reported)	Model: FE or RE, adjustment	Heterogeneity: $\chi 2$ I^2 (%)
Obesity (BMI>30 kg/m^2) (referent BMI 18.5–24.9 kg/m^2)				
Stothard (2009), weight assessment pre-pregnancy or early pregnancy				
Studies overall	1.30 (1.12 to 1.51)	7 (638, 983)	RE, none	I^2 58
Adjusted	1.27 (1.11 to 1.46)	3	RE, NR	NR
Higher quality*	1.51 (1.19 to 1.93)	2	RE, none	NR
Excluding chromosomal anomalies	1.36 (1.16 to 1.59)	6	RE, none	NR
Excluding PDM	1.35 (1.11 to 1.64)	4	RE, none	NR
Including terminations	1.51 (1.19 to 1.93)	2	RE, none	NR
Objective BMI measure	1.25 (0.94 to 1.65)	2	RE, none	NR
Cai (2014), weight assessment pre-pregnancy or early pregnancy				
Studies overall	1.23 (1.19 to 1.27)	13 (770, 251)	FE, none	I^2 49
Excluding PDM, included GDM	1.28 (1.18 to 1.39)	5	RE, none	NR
Excluding PDM and GDM	1.16 (1.08 to 1.23)	4	RE, none	NR
From the USA	1.25 (1.20 to 1.30)	7	FE, none	NR
From other countries	1.16 (1.09 to 1.25)	6	FE, none	NR
Live births, stillbirths, terminations	1.31 (1.18 to 1.46)	4	FE, none	NR
Liveborn or newborn infants	1.29 (1.07 to 1.99)	7	RE, none	NR
Zhu (2018), weight assessment maternal, not further specified				
Studies overall	1.17 (1.14 to 1.20)	17	FE, NR	I^2 25.5
USA	1.17 (1.14 to 1.20)	11	FE, NR	I^2 43
Not the USA	1.17 (1.10 to 1.25)	6	FE, NR	I^2 0
Published 2010 and earlier	1.18 (1.12 to 1.24)	9	FE, NR	I^2 24
Published after 2010	1.17 (1.14 to 1.20)	8	FE, NR	I^2 34
Case control	1.17 (1.14 to 1.21)	13	FE, NR	I^2 38
Cohort study	1.16 (1.10 to 1.22)	4	FE, NR	I^2 0
NOS score <7	1.17 (1.13 to 1.21)	5	FE, NR	I^2 37
NOS score ≥7	1.17 (1.13 to 1.21)	12	FE, NR	I^2 26
Zheng (2018), weight assessment prepregnancy or in early pregnancy†				
Studies overall	1.32 (1.21 to 1.43)	20	RE, 5 none; 15 adjusted or matched, variables NR	I^2 62
North America	1.31 (1.14 to 1.50)	7	NR	I^2 69
Europe	1.23 (1.13 to 1.34)	6	NR	I^2 50
Asia	1.94 (1.16 to 3.22)	6	NR	I^2 49
Oceania	1.34 (0.63 to 2.85)	1	NR	NA
Hospital-based sample	1.71 (1.24 to 2.34)	9	NR	I^2 54
Population-based sample	1.26 (1.17 to 1.35)	11	NR	I^2 62
Live births only	1.35 (1.19 to 1.54)	9	NR	I^2 71
Live births, stillbirths and or termination	1.37 (1.18 to 1.59)	10	NR	I^2 21
Case controls	1.40 (1.23 to 1.61)	14	NR	I^2 59
Cohort studies	1.28 (1.13 to 1.47)	6	NR	I^2 72
Singletons	1.40 (1.23 to 1.61)	7	NR	I^2 39
Singletons and multiples	1.28 (1.13 to 1.47)	4	NR	I^2 80
BMI assessed prepregnancy	1.44 (1.23 to 1.68)	16	NR	I^2 56
BMI assessed early pregnancy	1.28 (1.16 to 1.42)	4	NR	I^2 81
Adjustment or matching	1.37 (1.22 to 1.54)	15	NR	I^2 67

Continued

Table 2 Continued

	Summary associations: OR unless otherwise specified (95% CI)	No. of studies (Offspring if reported)	Model: FE or RE, adjustment	Heterogeneity: $\chi 2$ I^2 (%)
No adjustment	1.25 (1.06 to 1.49)	5	NR	I^2 20
Higher quality‡	1.30 (1.20 to 1.40)	17	NR	I^2 61
Lower quality	2.18 (0.91 to 5.21)	3	NR	I^2 63
Excl. PGDM and GDM	1.23 (0.96 to 1.57)	4	NR	I^2 34
PDM/GDM not excluded	1.36 (1.23 to 1.50)	8	NR	I^2 65
Liu (2019) (RR) (level I evidence), weight assessment prepregnancy or early pregnancy				
Studies overall	1.23 (1.17 to 1.29)	19	RE, Varied§	I^2 48
Cohort studies	1.22 (1.15 to 1.31)	6	RE, NR	I^2 53
Case controls	1.24 (1.15 to 1.33)	13	RE, NR	I^2 48
USA	1.24 (1.15 to 1.32)	12	RE, NR	I^2 48
Not the USA	1.22 (1.14 to 1.32)	7	RE, NR	I^2 52
Sample size <10 000	1.27 (1.08 to 1.49)	10	RE, NR	I^2 49
Sample size ≥10 000	1.21 (1.16 to 1.26)	9	RE, NR	I^2 38
Adjusted for maternal age	1.24 (1.17 to 1.31)	8	RE, NR	I^2 54
Not adjusted for maternal age	1.20 (1.08 to 1.33)	11	RE, NR	I^2 47
Adjusted for maternal smoking	1.24 (1.17 to 1.31)	7	RE, NR	I^2 58
Not adjusted for maternal smoking	1.20 (1.09 to 1.33)	12	RE, NR	I^2 42
Adjusted for maternal education	1.24 (1.17 to 1.33)	6	RE, NR	I^2 62
Not adjusted for maternal education	1.21 (1.11 to 1.31)	13	RE, NR	I^2 38
Wu (2023)				
Studies overall	1.29 (1.22 to 1.37)	23	RE, 16 adjusted, varied¶	I^2 47
Cohort studies	1.36 (1.23 to 1.50)	NR	RE	I^2 30
Case controls	1.27 (1.19 to 1.35)	NR	RE	I^2 41
Adjusted	1.27 (1.19 to 1.35)	NR	RE	I^2 54
Not adjusted	1.44 (1.26 to 1.65)	NR	RE	I^2 0
Moderate obesity (BMI 30.1–34.9 or 30.1–39.9 kg/m^2) (referent BMI 18.5–24.9 kg/m^2)				
Cai (2014), weight assessment pre-pregnancy or early pregnancy				
Studies overall	1.15 (1.11 to 1.20)	5 (735, 281)	FE, none	I^2 35
>500 infants	1.16 (1.11 to 1.21)	4	FE, none	NR
Excl. PGDM, including GDM	1.17 (1.12 to 1.23)	3	FE, none	NR
Excluded PGDM and GDM	1.12 (1.04 to 1.20)	2	FE, none	NR
From the USA	1.17 (1.12 to 1.23)	3	FE, none	NR
From other countries	0.99 (0.72 to 1.37)	2	FE, none	NR
Liveborn infants or newborn infants	1.14 (1.07 to 1.22)	4	FE, none	NR
Zheng (2018), weight assessment prepregnancy or early pregnancy				
Studies overall	1.15 (1.11 to 1.20)	2	FE, both studies adjusted, variables NR	I^2 0
Class II obesity (BMI 35 to <40 kg/m^2) (referent BMI 18.5–24.9 kg/m^2)				
Zheng (2018) (level I evidence), weight assessment prepregnancy or early pregnancy				
Studies overall	1.26 (1.18 to 1.34)	2	FE, both studies adjusted, variables NR	I^2 0.91
Class III obesity (BMI≥40 kg/m^2) prepregnancy or in early pregnancy (referent BMI 18.5–24.9 kg/m^2)				
Zheng (2018)[40] (level I evidence)				
Studies overall	1.42 (1.33 to 1.51)	5	FE, all studies adjusted or matched, variables NR	I^2 0

Continued

Table 2 Continued

	Summary associations: OR unless otherwise specified (95% CI)	No. of studies (Offspring if reported)	Model: FE or RE, adjustment	Heterogeneity: $\chi 2$ I^2 (%)
Severe obesity (BMI≥35.0 or ≥40 kg/m^2) (referent BMI 18.5–24.9 kg/m^2)				
Cai (2014), weight assessment prepregnancy or early pregnancy				
Studies overall	1.39 (1.31 to 1.47)	5 (665, 528)	FE, none	I^2 49
>500 infants	1.44 (1.34 to 1.54)	4		
Excluded PGDM, included GDM	1.46 (1.35 to 1.58)	3	FE, none	NR
Excluded PGDM and GDM	1.38 (1.20 to 1.59)	2	FE, none	NR
From the USA	1.45 (1.34 to 1.57)	3	FE, none	NR
From other countries	1.39 (1.21 to 1.61)	2	FE, none	NR
Liveborn infants or newborn infants	1.38 (1.30 to 1.47)	3	FE, none	NR

*Defined as excluded chromosomal anomalies and pregestational diabetes and included terminations.
†Subgroup analysis considered potential modification of associations seen in the overall analysis by the characteristics reported in the table above (ie, region; live birth, stillbirth terminations; design; plurality; timing of BMI assessment; adjustment; study quality; exclusion of participants with diabetes) and no differences were detected.
‡Defined as NOS overall score ≥7.
§included site, maternal age, race, insurance, maternal smoking, education, hypertension, parity, folic acid supplementation use, gestational diabetes, maternal alcohol use, PGDM, maternal height, early pregnancy, maternal country of birth, family situation, sex of offspring, payment method for healthcare, index of multiple deprivation, ethnicity, birth period, chronic illness and none.
¶included race, birth period, age, education, alcohol use, smoking, chronic illness, vitamin use, parity, ethnicity, smoking in the month prior to conception, folic acid supplementation in the month prior to conception, pregestational diabetes (1 study only), any cigarette smoking during pregnancy, index of multiple deprivation, infant gender, BMI, any alcohol consumption, dietary folic intake, caffeine intake, family history of a heart defect, residence of mother, any vitamin use. Gestational diabetes (1 study), any diabetes (1 study), urban/rural status, paternal age, family history of congenital anomalies and none (7 studies).
BMI, body mass index; CHDs, congenital heart defects; FE, fixed effect; GDM, gestational diabetes mellitus; NOS, Newcastle-Ottawa Scale; NR, not reported; PGDM, pregestational diabetes mellitus; RE, random effect.

by 7% for every 5 kg/m^2 increase in the maternal body mass index.

The criterion plausibility is met. Abnormal glucose metabolism in early pregnancy is strongly implicated in CHD development in human and animal studies (described in more detail below). Both type 2 and gestational diabetes mellitus (GDM are increased in women with prepregnancy obesity, as is mild glucose intolerance in the absence of overt diabetes.[56] Even small increases in maternal glucose levels in early pregnancy confer increased CHDs risk,[57] which may explain why risk is attenuated but remains elevated with maternal obesity in meta-analyses that exclude women with pre-existing or GDM. Fetal cardiac development may be adversely affected by other metabolic and inflammatory disturbances present with maternal obesity including abnormal lipid metabolism, hyperinsulinaemia, insulin resistance, increased oxidative stress, endothelial cell dysfunction and subclinical inflammation which can impair placental function with detrimental effects on fetal vascular circulation.[58 59] Additionally, a poor diet during pregnancy, particularly low intake of micronutrients such as folate, is more common

among women with obesity and may contribute to risk of CHDs.[60]

The criterion for analogy is met as maternal obesity is associated with other congenital anomalies (eg, neural tube defects, cleft lip).[43 60]

Diabetes mellitus (pre-existing including types 1 and 2 or gestational: treated or untreated)

For PDM, the criteria for strength and consistency are met. Pooled estimates in five reviews[28 37 41 42 49] demonstrate that women with PDMs mellitus (type 1 or 2) have a 3–4 fold increase in risk of having a baby with a CHD compared with women without diabetes (table 3).

The direction of effect is very consistent, with >50% of the studies in review analyses showing significant associations in the expected direction. However, significant heterogeneity was detected. Subgroup analysis[28] indicated a higher risk among women in North America than in Asia, Europe or Oceania. The high heterogeneity could also reflect the inclusion of mothers with either type 1 or 2 diabetes[28] and/or differences in management.

Criteria for strength and consistency were not met for GDM, with pooled estimates in reviews[28 37 49] typically not exceeding 2. Substantial heterogeneity was identified, which may reflect differences in the rate of maternal obesity across studies reporting on GDM. While no pooled analyses examined potential modification of GDM-CHDs association by maternal weight, one review[37] reported that elevated risk associated with GDM was present only in women with GDM and obesity (OR 3.47, 95% CI 1.7 to 7.0; data from one study).[61]

For PDM, the temporality criterion is met, as by definition the disease diagnosis predates pregnancy. The criterion for biological gradient is not met as no review

Table 3 Summary associations between maternal diabetes mellitus, hypertension and CHDs

	Summary OR unless otherwise specified (95% CI)	No. of studies (offspring)	Model: FE or RE, adjustment	Heterogeneity: $\chi 2$ I^2 (%)	Summary associations: OR or RR (95% CI)	No. of studies (offspring)	Model: FE or RE, adjustment	Heterogeneity: $\chi 2$ I^2 (%)
PGDM (treated or untreated) (referent no PGDM)					GDM (treated or untreated) (referent no GDM)			
Chen (2019), timing of exposure assessment not specified								
All	3.18 (2.77 to 3.65)	31 (NR)	RE, 16 adjusted, variables NR	I^2 79	1.98 (1.66 to 2.36)	27 (NR)	RE, 11 adjusted, variables NR	I^2 90
Adjusted	2.95 (2.48 to 3.51)	16	RE, adjustment NR	I^2 84	1.50 (1.35 to 1.67)	11 (NR)	RE, adjustment NR	I^2 25
Unadjusted	3.57 (2.76 to 4.61)	15	RE	I^2 72	2.18 (1.64 to 2.92)	16 (NR)	RE, adjustment NR	I^2 93
Case control	3.08 (2.48 to 3.82)	18	RE, adjustment NR	I^2 74	2.12 (1.69 to 2.65)	19 (NR)	RE, adjustment NR	I^2 91
Cohort	3.41 (2.89 to 4.03)	13	RE, adjustment NR	I^2 76	1.74 (1.27 to 2.38)	8 (NR)	RE, adjustment NR	I^2 87
North America	3.81 (3.17 to 4.57)	17	RE, adjustment NR	I^2 70	1.52 (1.39 to 1.65)	12 (NR)	RE, adjustment NR	I^2 34
Asia	1.72 (1.19 to 2.50)	3	RE, adjustment NR	I^2 29	3.67 (3.07 to 4.38)	10 (NR)	RE, adjustment NR	I^2 37
Europe	2.92 (2.36 to 3.61)	10	RE, adjustment NR	I^2 79	1.42 (1.21 to 1.64)	4 (NR)	RE, adjustment NR	I^2 0
Oceania	2.84 (1.89 to 4.26)	1	RE, adjustment NR	NA	1.40 (1.12 to 1.75)	1 (NR)	RE, adjustment NR	NA
Population based	3.33 (2.90 to 3.81)	24	RE, adjustment NR	I^2 78	1.66 (1.47 to 1.89)	18 (NR)	RE, adjustment NR	I^2 77
Hospital based	2.61 (1.63 to 4.17)	7	RE, adjustment NR	I^2 70	3.33 (2.25 to 4.94)	9 (NR)	RE, adjustment NR	I^2 77
Papazoglou (2021), timing of exposure assessment not specified								
All	3.48 (2.36 to 4.61)	15	RE, adjustment NR	I^2 97	1.55 (1.48 to 1.61)	7 (NR)	RE, adjustment NR	I^2 80
Zhang (2022) (RR), timing of exposure assessment not specified, summary RR reported								
All	3.46 (2.77 to 4.32)	18	RE, adjustment varied†	I^2 98	1.50 (1.38 to 1.64)	11	RE adjustment varied‡	I^2 81
Simeone (2015), timing of exposure assessment not specified								
All	3.8 (3.0 to 4.9)	12 (NR)	RE, no adjustment	NR				
Slot (2019), timing of exposure assessment not specified, type 2 diabetes only								
All	Mean RR (range) 3.83 (2.53 to 5.49)	4 cohort studies	Mean (range) unweighted					
Pre-existing hypertension†† treated or untreated) (referent no pre-existing hypertension)					Gestational hypertension‡‡ (treated or untreated) (referent no gestational hypertension)			
Zhang 2022b								
All	1.68 (1.49 to 1.89)	12 (NR)	RE, 6 adjusted, variables NR	I^2 54	1.16 (1.02 to 1.31)	6 (NR)	RE, 5 adjusted, variables NR	I^2 27
Treated hypertension (referent no treated hypertension)					Untreated hypertension (referent no untreated hypertension)			
Ramakrishnan (2015 (RR), timing of exposure assessment not reported								

Continued

Table 3 Continued

	Summary OR unless otherwise specified (95% CI)	No. of studies (offspring)	Model: FE or RE, adjustment	Heterogeneity: $\chi 2$ I^2 (%)	Summary associations: OR or RR (95% CI)	No. of studies (offspring)	Model: FE or RE, adjustment	Heterogeneity: $\chi 2$ I^2 (%)
All	2.03 (1.54 to 2.6)	8 (NR)	RE, adjustment varied§	NR	1.38 (1.15 to 1.6)	7 (NR)	RE, adjustment varied¶	NR
beta-blockers	2.10 (1.64 to 2.7)	3	RE, adjustment NR	NR				
ACE inhibitors (RR)	2.12 (0.76 to 5.93)	4	RE, adjustment NR	NR				
Calcium channel blockers	1.16 (0.86 to 1.55)	3	FE, adjustment NR	NR				
Any hypertension (pre-existing or gestational, treated or untreated hypertension) (referent no hypertension)								
All	1.8 (1.5 to 2.2)	15 (NR)	RE, adjustment varied**	NR				

*Adjusted variables differed across the studies in this meta-analysis and included maternal age (16 studies), race/ethnicity (6 studies), BMI (4 studies), education (3 studies), smoking/alcohol consumption (4 studies), parity (6 studies), pregnancy complications (4 studies) and none (2 studies).
†Adjusted variables differed across the studies in this meta-analysis and included maternal age (10 studies), race/ethnicity (5 studies), BMI (4 studies), education (4 studies), smoking/alcohol consumption (4), parity (4), pregnancy complications (4) and none (1 study).
‡In the Chen 2019 review, test for subgroup differences (TSD) was conducted and considered geographical region, whether the studies were adjusted, study design and sample source, groups as listed in the table. For the association between PGDM and CHDs, geographical region (TSD: I^2=79.9%) and whether the confounding factors were adjusted (TSD: I^2=31.2%) were identified as the first two of the most relevant heterogeneity moderators. There were statistically significant differences in the risk of CHDs associated with PGDM between different geographical regions (χ^2=14.95, p<0.00001). For the association between GDM and CHDs, geographical region (TSD: I^2=96.6%), sample source (TSD: I^2=90.8%) and whether the confounding factors were adjusted (TSD: I^2=81.2%) were identified as the first three of the most relevant heterogeneity moderators. These differences in risk of CHDs associated with GDM were statistically significant across geographic regions (χ^2=87.90, p<0.00001), sample sources (χ^2=10.83, p=0.001) and whether the confounding factors were adjusted (χ^2=5.32, p=0.02).
§Adjusted variables differed across the studies in this meta-analysis and included maternal age, maternal illness, maternal smoking, maternal occupation, race/ethnicity, therapeutic drugs, lifestyle exposure (not further specified), parity, income quartile, tobacco use, previous miscarriage, maternal BMI, diabetes mellitus (pre-existing or gestational), medically assisted conception, none.
¶Adjusted variables differed across the studies in this meta-analysis and included maternal age, maternal illness, maternal ultrasound examination, hypertension prior to index pregnancy, maternal smoking, maternal deodorant use, race/ethnicity, maternal occupation, alcohol consumption, therapeutic drugs, lifestyle exposure (not further specified), region of birth, parity, multiple gestation pregnancy, tobacco use, maternal BMI, maternal diabetes mellitus (pre-existing or gestational), medially assisted conception, folic acid consumption during pregnancy, infant sex.
**Adjusted variables differed across the studies in this meta-analysis and included maternal age, maternal illness, maternal ultrasound examination, hypertension prior to index pregnancy, maternal smoking, maternal deodorant use, maternal occupation, race/ethnicity, maternal alcohol consumption, maternal therapeutic drug use, lifestyle exposure (not further specified), region of birth, parity, multiple gestation pregnancy, maternal tobacco use, maternal BMI, diabetes mellitus (pre-existing or chronic), medically assisted conception, folic acid consumption during pregnancy infant sex, none;
††Chronic hypertension was defined as increased blood pressure (≥140/90 mm Hg) before 20 weeks gestation but not associated with additional systemic features of pre-eclampsia.
‡‡Gestational hypertension was defined as new-onset elevated blood pressure (≥140/90 mm Hg) after 20 weeks of gestation and recovery before 12 weeks of delivery.[21 22]
BMI, body mass index; FE, fixed effects; GDM, gestational diabetes mellitus; NA, not applicable; NR, not reported; PE, pre-eclampsia; PGDM, pregestational diabetes mellitus; RE, random effects; RR, risk ratio; TSD, test for subgroup differences.

reported CHDs risk according to indicators of diabetes severity, for example, based on degree of hyperglycaemia. No reviews examined differences in risk based on treatment of diabetes.

For GDM, temporality and biological gradient criteria are not met as GDM is commonly diagnosed mid-pregnancy, and no review examined risk by disease severity.

Animal studies provide compelling evidence linking maternal hyperglycaemia during embryogenesis to cardiac malformations via a number of pathways including overexpression of glucose transporter proteins, impaired left-right axis formation, altered expression of genes such as Pax3, increased oxidative stress leading to apoptosis and altered cardiac cell proliferation and dysregulation of signalling pathways critical for cardiac development.[62 63] Several of these pathways have also been linked to increased risk of a wide range of other congenital anomalies in diabetic pregnancies,[64] thus also satisfying the criteria for analogy. Based on the available data, it seems that the major organ systems affected by PDM are the cardiovascular and the central nervous systems, which could be related to their embryonic origin in the neural crest.[64] In the case of GDM, although it is diagnosed mid-pregnancy, it is possible that subclinical changes in glucose metabolism arise earlier in pregnancy[65] contributing to elevated risk. Early antenatal scans suggest heart of fetus carried by women who go on to develop GDM are subtly different to those who did not, suggesting early glycaemic changes or other factors related to maternal risk profile may be at play.[66] PDM and GDM may also lie on a common pathway, either directly genetic or via shared mediator such as obesity. Alternatively, the association between GDM and CHDs could reflect a degree of misclassification of undiagnosed PDM as GDM, as a large proportion of women with GDM are diagnosed with type 2 diabetes in the postnatal period.[67] Thus, for PDM and GDM, plausibility criterion is met.

Hypertension (pre-existing or gestational or either: treated or untreated and either/overall)

For pre-existing hypertension (treated or untreated) the strength criterion is not met, with the one summary RR<2; however, the consistency criterion is, as 8 of the 12 studies in this meta-analysis[50] showed a significantly elevated risk. Temporality was satisfied by definition (table 3).

For gestational hypertension, also reported in one pooled analysis,[50] the strength and consistency criterion is not satisfied. Additionally, as gestational hypertension is the onset of hypertension after 20 weeks of gestation, the criterion for temporality is not met.

No data were identified to support a biological gradient for pre-existing or gestational hypertension.

Three reviews[30 39 40] reported data for any hypertension in pregnancy, comprising of either pre-existing or gestational, treated or untreated, and one[40] reported treated and untreated separately.

For treated hypertension, the pooled association[40] showed a doubling in risk but with considerable imprecision. Further, on stratification by treatment type variation in risk based on treatment type was seen, such that there remained a significant association for women treated with beta-blockers, however, not ACE inhibitors or Calcium channel blockers. Notably, covariates adjusted for varied, and very few studies reported adjustment for maternal diabetes. Thus, the criterion for strength is not met. The criterion for evidence consistency is, however, as forest plot examination showed all but one study indicating significant risk elevation.

For untreated hypertension assessed at any time during pregnancy, a criterion for strength is not met, with a pooled risk of 1.5 reported,[40] and variation in the degree of control for confounding. The criterion for consistency is met, with most studies pooled showing significant risk elevation.

With the uncertainty surrounding the timing of hypertension onset in the studies included in the analyses, the temporality criterion is not satisfied, for either treated or untreated hypertension. Neither is the criterion for biological gradient, with no data on the severity of these hypertensions in relation CHDs risk provided.

For any hypertension during pregnancy (treated and untreated combined), the criterion for strength is not met as the pooled risk estimate[40] indicated a 1.8-times increased risk of CHDs. The magnitude of risk elevation suggested by most of the single studies reported in the other two reviews was similar.[30 39] The criterion for consistency is clearly met with most studies indicating similar risk elevations.

The plausibility criterion is met for hypertension that predates the time of cardiac development in the fetus, whether treated or not. Maternal hypertension is associated with poor placentation, placental insufficiency and chronic hypoxia, which contribute to increased oxidative stress and angiogenic imbalances, with direct evidence of altered expression of angiogenic factors including VEGF (vascular endothelial growth factor) and hypoxia-inducing genes in human fetal hearts with CHD.[68] In addition, there may be shared genetic risks predisposing to both maternal hypertension and fetal CHD.[69] Further, animal studies indicate there may be direct teratogenic effect of medications such as beta-blockers.[70] Criteria for analogy are met as maternal hypertension (untreated and treated) has been associated with an increased risk of other types of birth defects including hypospadias.[71]

Smoking

The criterion for strength is not met. Pooled associations[29 34 36 47] suggest smoking during pregnancy is associated with increased risk in the order of 10%–20%. One review only specifically examined smoking in very early pregnancy[33] and reported an imprecise association suggesting a 3-fold risk elevation (OR 2.80; 95% CI 1.7 to 4.4; 1 study, 365 participants). Criterion for consistency is not met, due to a high degree of heterogeneity and

Table 4 Summary associations between maternal smoking and CHDs

Level I evidence (OCEBM)	Relative effect: Summary OR (95% CI) (unless otherwise specified)	No. of studies (offspring if reported)	Model: FE or RE, adjustment	Heterogeneity: $\chi 2$ I^2 (%)
Any smoking during pregnancy (referent no smoking)				
Hackshaw (2011), smoking any time during pregnancy				
All	1.09 (1.02 to 1.17)	25 (2, 116, 757)	RE, 11 no adjustment, variables adjusted or matched varied across remaining studies included*	I^2 64
Lee (2013) (RR), smoking any time during pregnancy				
All	1.11 (1.02 to 1.21)	19 (18, 282 cases)	RE, 7 no adjustment, 12 adjusted for various variables, included† or matched cases and controls on some characteristics‡	I^2 NR
Nicoletti (2014), smoking any time during pregnancy				
All	1.11 (1.03 to 1.19)	29 (32, 000 cases)	RE, adjustment variables NR	I^2 58
Zhang (2017)§ (RR), smoking any time during pregnancy				
All	1.11 (1.04 to 1.18)	23	RE, 14 no adjustment, 9 adjusted, variables varied across remaining included¶	I^2 69
Europe	1.12 (0.99 to 1.26)	10	RE	I^2 74
USA	1.10 (1.03 to 1.18)	11	RE	I^2 59
Asia	6.60 (2.13 to 20.59)	2	RE	I^2 0
Case control	1.11 (1.03 to 1.20)	19	RE	I^2 67
Cohort studies	1.13 (0.98 to 1.29)	4	RE	I^2 79
Age adjusted	1.11 (1.02 to 1.20)	10	RE	I^2 74
BMI adjusted	1.04 (0.97 to 1.11)	3	RE	I^2 45
Alcohol adjusted	1.04 (0.98 to 1.10)	4	RE	I^2 24
Vitamin B-adjusted	1.05 (0.97 to 1.12)	5	RE	I^2 40
Social factor adjusted	1.05 (0.98 to 1.13)	4	RE	I^2 12
Wu (2023), smoking any time during pregnancy				
All	1.16 (1.07 to 1.25)	32 studies (33 cohorts)	RE, 17 no adjustment, variables varied across remaining, included**	I^2 71
Adjusted	1.16 (1.06 to 1.27)	NR	RE	I^2 73
Not adjusted	1.15 (0.99 to 1.34)	NR	RE	I^2 70
Cohort	1.08 (0.98 to 1.20)	NR	RE	I^2 50
Case control	1.17 (1.06 to 1.29)	NR	RE	I^2 73

*Maternal age, parity or gravidity, social class, race/ethnicity, maternal alcohol use, birth month or year, location or study centre, marital status, maternal or paternal education, previous induced abortions, mother's occupation, caffeine, infant gender, kidney a/dysegenesis of infant, maternal diabetes, BMI, periconceptional multivitamin supplementation including folic acid, dietary folate intake, family history of malformations and location (rural/urban setting).
†Maternal age, maternal race/ethnicity, marital status, maternal education, parity, alcohol consumption, coffee consumption, infant's year/month of birth, maternal diabetes (pregestational or gestational), interval between end of pregnancy and blood collection, homocysteine levels, folic acid intake/dietary folate, infant gender, maternal BMI, family history of CHDs, maternal occupation, infant race/ethnicity, therapeutic drug use, influenza-like illness, paternal smoking, cases and controls matched on birth hospital/geographic region, birth month/age, influenza-like illness, paternal smoking.
‡Cases and controls matched on birth hospital/geographical region, birth month/age race or sex (2 studies).
§This review excluded the following CHD types in the overall meta-analysis: ASD, AVSD, CHD, CTD, LVOTO, RVOTO, SPD, TGA, TOF, VSD.
¶Included maternal age, education level, folic acid use, periconceptional alcohol consumption, time interval between end of pregnancy and blood collection, serum homocysteine, folate, H vitamin B_{12} level, race, homocysteine, methionine, occupation, M MTHFR:677 C>T, vitamin B_{12}, CysGly or cysteine, BMI, birth year, maternal education, therapeutic drug exposure during pregnancy, pregestational diabetes, influenza-like illness in the first trimester, parity, paternal smoking, offspring gender, prematurity, diabetes, adenosine, GluCys, study centre, birth defect history in first-degree relative, gravidity.
**Included education, ethnicity, maternal age, coffee, maternal vitamin use, alcohol use, gravidity, year of birth, parity, gestational age, birth weight, diabetes, maternal BMI, infant gender, folic acid intake, hypertension, any binge drinking and smoking interaction term, low socioeconomic status, stress, family income, socioeconomic deprivation of the area of residence, pesticide exposure, organic solvents, family history of congenital anomalies, paternal age and paternal smoking.
ASD, atrial septal defect; AVSD, atrioventricular septal defect; BMI, body mass index; CHD, congenital heart defect; CTD, conotruncal heart defect; FE, fixed effects; LVOTO, left ventricular outflow tract obstruction; RE, random effects; RR, risk ratio; RVOTO, right ventricular outflow tract obstruction; SPD, septal defect; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

variation in direction of associations across studies in the reviews (table 4).

Criterion for temporality is not met as the vast majority of studies assessed smoking at any time in pregnancy and, therefore, could not confirm that exposure occurred in the critical period of fetal cardiac development.

The available evidence also does not satisfy the criterion for biological gradient, as no clear differences were reported in reviews that attempted to look at dose-response effects.[33 34 47] Important caveats when interpreting this finding are imprecision and reporting bias problems that plague research on the effects of smoking

(and alcohol), (other than in those using rare methodologies (eg, cotinine studies)).

Criteria for plausibility are met. Animal studies demonstrate nicotine exposure during embryogenesis increases oxidative stress in fetal hearts in a dose-dependent manner, altering gene expression related to cardiomyocyte growth resulting in reduced cell proliferation and altered epithelial to mesenchymal transition.[72] It has also been postulated that toxins in cigarette smoke may induce epigenetic changes in the fetus and placenta altering micro RNA expression with effects on fetal development.[73] Smoking also causes prematurity, which frequently co-occurs with congenital anomalies, presenting another plausible common pathway between smoking and cardiac defects.[74]

Smoking is associated with an increased risk of other congenital anomalies, including cleft lip and/or palate[75] therefore, criterion for analogy is met.

Alcohol

Strength criterion is not met for any alcohol consumption, prepregnancy or during pregnancy, with all pooled associations <2.[44–46 48] Criterion for consistency is not met as there was high variation in direction of risk estimates and substantial heterogeneity. This likely reflects variation in adjustment for confounding, which typically included sociodemographic factors and multivitamin/folic acid use but not for concurrent chronic disease (table 5).

For heavy (≥2 drinks/24 g per day) and binge (≥4 or 5 drinks/any one occasion) drinking, one review 2015[46] reported marked risk elevation (2–3 fold) with either, but with considerable imprecision. Another[48] reported only a modest increase in risk with binge drinking, and the forest plot revealed variation in the direction of effect estimates. Thus, the criteria for strength and consistency are not met. As with smoking, the variation in risk estimates and imprecision found likely reflects variation in methods for ascertainment of exposure and degree to which this is influenced by recall and social desirability bias.

The temporality criterion is not met. One review only[48] reported risk estimates associated with drinking during the periconception period, specifically the first trimester, and there was wide variation, suggesting possible bias in measurement related to recall and stigma. Criterion for biological gradient is not met. Dose-response analysis showed a non-linear relationship between alcohol and CHDs risk overall such that 'when maternal alcohol consumption was more than 116 g/day, the risk of total CHDs in offspring significantly increased, by 42% (OR 1.42, 95% CI 1.07 to 1.88)' (p 413).[48] However, the variation in risk estimates reported for binge versus any drinking does not support a clear dose–response relationship.

Criteria for plausibility and analogy are met. Animal studies demonstrate reduced expression of genes that encode signalling molecules in embryonic hearts after pregnant mice are exposed to binge dose of alcohol.[76] In addition, alcohol consumption during pregnancy is known to cause fetal alcohol spectrum disorder (FASD), which includes structural brain abnormalities, and there is some evidence that CHDs occur more frequently in children with FASD than the general population.[77]

For all risk factors, the criterion for coherence is satisfied. The available evidence does not conflict with knowledge about the natural history of CHD, which is widely considered to be of multifactorial origin. For several risk factors we examined there are distinct causal mechanisms (eg, chromosomal abnormalities arising with advanced maternal age, fetal alcohol toxicity). It is also possible that there are shared underlying mechanisms, for example, hyperglycaemia underpins the excess risk of CHDs in diabetic pregnancies and may amplify effects in women with obesity, which, in turn, may be influenced by shared genetic risks for metabolic diseases and CHD. Risk may be amplified by the presence of several maternal risk factors, as metabolic disease risk factors often cluster together (eg, advanced age, hypertension and diabetes), however, none of the reviews formally examined potential additive effects.

Further, the rise in global birth prevalence of CHDs in the last 40 years[1 78] coincides with increases in the later onset of childbearing and in the prevalence of obesity and diabetes in pregnancy, globally.[79] Notably, the highest increase in CHDs has occurred in the Asia region,[1] which also has had high rates of increase in hyperglycaemia in pregnancy.[79]

With regard to smoking and alcohol, there has been an overall reduction in smoking in pregnancy in the past 30 years, however, tobacco use in pregnancy continues to vary widely between regions.[80] For example, in some low-income and middle-income countries, rates have plateaued and, in others, increased.[81] Studies estimating global and regional prevalence in alcohol use around pregnancy, including any or binge, similarly, point to high variation in rates between regions.[82 83] Further, any observed reductions in the use of alcohol and tobacco in pregnancy do not preclude a causal effect as women may cease to use only when a pregnancy is identified, which for some, may be after the critical period for development of most CHDs, particularly in pregnancies that are unplanned. Importantly, however, evidence suggests quitting smoking in pregnancy may reduce prematurity and by implication, risk of cardiac and other birth defects.[84]

DISCUSSION

We conclude that there is strong evidence of a causal relationship between maternal obesity and PDM and the development of CHDs. A causal relationship may be present between CHDs and pre-existing maternal hypertension (untreated or treated) and advanced maternal age, as for these factors causal evidence is moderate. For other maternal factors including GDM, gestational hypertension, smoking and alcohol consumption the evidence for causality was weak.

Table 5 Summary associations between maternal alcohol consumption and CHDs

Level I evidence (OCEBM)	Relative effect: summary OR (95% CI) (unless otherwise specified)	No. of studies (offspring if reported)	Model: FE or RE, adjustment	Heterogeneity: χ^2 I^2 (%)
Heavy alcohol consumption (referent no alcohol)				
Yang (2015), alcohol consumption before or during pregnancy				
≥24 g (2 drinks)/day	3.76 (1.00 to 14.10)	4 studies (122, 559)	RE adjustment variables varied*	NR
≥4 drinks on any 1 occasion	2.49 (1.04 to 5.97)	2 studies (6,491)	RE, NR	I^2 40
Zhang (2020), alcohol consumption periconception or during pregnancy				
≥5 drinks on any 1 occasion	1.16 (1.02 to 1.32)	10 studies	RE, 6 studies adjusted (variables NR)	I^2 12
Any alcohol drinking (referent no alcohol)				
Sun (2015), alcohol consumption before or during pregnancy unless otherwise specified				
All	1.13 (0.96 to 1.29)	23 studies	RE, adjustment varied, included†	I^2 88
Case control	1.00 (0.95 to 1.06)	19 studies	RE, NR	I^2 16
Cohort	1.35 (0.93 to 1.97)	4 studies	RE, NR	I^2 94
North America	1.10 (0.89 to 1.36)	15 studies	RE, NR	I^2 92
Europe	1.09 (0.99 to 1.19)	7 studies	RE, NR	I^2 0
Australia	1.69 (1.23 to 2.33)	1 study	RE, NR	NA
Prepregnancy or until pregnancy known	0.95 (0.88 to 1.04)	6 studies	RE, NR	I^2 0
During pregnancy	1.12 (0.96 to 1.30)	22 studies	RE, NR	I^2 89
Trimester 1	1.12 (0.96 to 1.30)	22 studies	RE, NR	I^2 89
Trimester 2	1.22 (0.98 to 1.52)	12 studies	RE, NR	I^2 90
Trimester 3	1.22 (0.98 to 1.52)	12 studies	RE, NR	I^2 90
Adjustment for smoking	1.27 (0.86 to 1.87)	4 studies	RE, NR	I^2 94
No adjustment for smoking	1.04 (0.96 to 1.13)	19 studies	RE, NR	I^2 39
Yang (2015), alcohol consumption before or during pregnancy unless otherwise specified				
All	1.06 (0.93 to 1.22)	8 studies	RE, adjustment variables varied‡	I^2 42
Higher quality (NOS score≥7)	1.11 (0.88 to 1.40)	3 studies	RE, adjustment unclear§	I^2 69
North America	0.99 (0.85 to 1.14)	4 studies	RE	I^2 0
Europe	1.22 (0.93 to 1.60)	4 studies	RE	I^2 57
Cohort	1.05 (0.88 to 1.25)	2 studies	RE	I^2 0
Case control (population based)	1.08 (0.85 to 1.39)	5 studies	RE	I^2 61
Case control (hospital based)	1.00 (0.81 to 1.23)	1 study	RE	NA
First trimester drinking	1.12 (0.93 to 1.34)	4 studies	RE	I^2 53
During pregnancy drinking	1.09 (0.82 to 1.46)	2 studies	RE	I^2 34
Periconception drinking	0.80 (0.58 to 1.10)	1 study	RE	NA
Before pregnancy drinking	1.01 (0.61 to 1.69)	1 study	RE	NA
Sample size <1000	0.97 (0.74 to 1.28)	3 studies	RE	NR
Sample size ≥1000	1.11 (0.96 to 1.29)	5 studies	RE	NR
Zhang (2020), alcohol consumption periconception or during pregnancy unless otherwise specified				
All	1.16 (1.05 to 1.27)	45 studies	RE, 16 studies adjusted (variables NR)	I^2 74
Adjusted	1.60 (1.29 to 1.97)	16 studies	RE	I^2 84

Continued

Table 5 Continued

Level I evidence (OCEBM)	Relative effect: summary OR (95% CI) (unless otherwise specified)	No. of studies (offspring if reported)	Model: FE or RE, adjustment	Heterogeneity: χ^2 I^2 (%)
Not adjusted	1.00 (0.93 to 1.09)	29 studies	RE	I^2 39
Cohort	1.15 (0.87 to 1.53)	3 studies	RE	I^2 89
Case control	1.15 (1.04 to 1.27)	42 studies	RE	I^2 69
Norther America	0.96 (0.90 to 1.02)	15 studies	RE	I^2 20
Asia	1.03 (0.94 to 1.13)	10 studies	RE	I^2 75
Europe	1.51 (1.31 to 1.73)	1 study	RE	NA
Oceania	2.21 (1.58 to 3.09)	19 studies	RE	I^2 0
Pregnancy drinking (any time)	0.91 (0.73 to 1.14)	5 studies	RE	I^2 0
Prepregnancy and pregnancy	1.18 (0.98 to 1.42)	15 studies	RE	I^2 64
First trimester drinking	1.20 (1.06 to 1.36)	25 studies	RE	I^2 81
Lower quality (NOS score <7)	1.13 (0.87 to 1.48)	8 studies	RE	I^2 44
Higher quality (NOS score ≥7)	1.16 (1.05 to 1.29)	37 studies	RE	I^2 77
Wu (2023), alcohol consumption any time during pregnancy				
All	1.08 (0.95 to 1.22)	29 studies (32 cohorts)	RE, 17 studies adjusted, variables included¶	I^2 86
Adjusted	1.16 (0.96 to 1.41)	NR	RE	I^2 90
Not adjusted	0.97 (0.91 to 1.05)	NR	RE	I^2 0
Cohort	1.31 ((0.99 to 1.72)	NR	RE	I^2 91
Case control	0.99 (0.93 to 1.06)	NR	RE	I^2 16

In Sun 2015, subgroup analyses were preformed to investigate sources of heterogeneity and considered the characteristics listed in the table (study design, timing of alcohol assessment, adjustment for smoking) and were largely consistent with the findings of the overall analysis. In Zhang 2020, subgroup analyses for the risk estimates between any maternal alcohol consumption and CHDs were conducted. The risk of total CHDs associated with maternal alcohol exposure was significantly different for different geographical regions (χ2=55.01; p<0.00001) as well as whether the confounding factors were adjusted (χ2=16.30; p<0.00001). When data were restricted to studies from Asia (χ2=2.21; 95% CI 1.58 to 3.09), and studies controlling the confounding factors (χ2=1.60; 95% CI 1.29 to 1.97), the risk of total CHDs was further increased.
*3 studies no adjustment; 1 study adjusted for maternal smoking, race, maternal multivitamin use and education.
†Maternal age, maternal race/ethnicity, marital status, maternal education, parity, smoking, coffee consumption, infant's year/month of birth, intake of multivitamin, stress, folic acid intake/dietary folate, infant gender, maternal BMI, family history of CHDs, maternal residence, maternal occupation, insurance.
‡Maternal age, smoking, coffee, organic solvents and 'so on'; birth year; race, multivitamin use, education, none (5 of the 8 studies).
§Smoking; B, race; C, multivitamin use; D, education.
¶Included organic solvents at work, maternal age, education, ethnicity, smoking, coffee intake, year of birth, parity, maternal cigarette smoking, multivitamin supplementation, infant gender, BMI, dietary folate intake, folic acid intake, family history of heart defect, place of residence, household occupational status, any binge drinking and smoking interaction, insurance, birth order, low socioeconomic status, organic solvents, pesticide exposure, family history of congenital anomalies.
BMI, body mass index; CHD, congenital heart defect; FE, fixed effects; NA, not applicable; NOS, Newcastle-Ottawa Scale; NR, not reported; RE, random effects; RR, risk ratio.

Our findings are broadly consistent with a recent overview[12] which did not formally assess causality, although we found stronger evidence for a causal implication of maternal obesity and PDMs. The earlier overview[12] argues that further research on all potentially non-genetic modifiable factors is required to provide more powerful sequential evidence. Contrarily, we suggest that research examining maternal obesity and PDM is not necessary based on the strength of available evidence including coherence with animal studies which identify hyperglycaemia as a primary teratogen and implicate other metabolic disturbances (eg, insulin resistance) as causal mechanisms. Our study questions the value of further research on maternal alcohol use and smoking using current published methodologies due to the difficulties involved in gathering precise estimates of these exposures in early pregnancy.

Further research on maternal hypertension is, however, warranted to distinguish the impacts of disease severity and antihypertensive medications on CHD susceptibility and thereby optimise treatment recommendations in early pregnancy. Additional synthesis of evidence concerning maternal age could provide more precise estimates of risk according to specific age categories. Future

original research on environmental exposures that have received limited attention but have broad levels of population exposure, including air pollutants, environmental chemicals and solvents is important. This would allow for the development of precise recommendations about specific exposures rather than current general advice, to avoid or reduce exposure to 'hazardous substances' during pregnancy. Consideration of how environmental exposures and maternal factors cluster together and interact is also important to advance understanding of CHD development.[10]

In this overview, we focused on the outcome any CHDs. As this outcome is heterogeneous, future research replicating our analysis for CHD groups based on suspected shared causal pathways (eg, left-sided obstructive lesions, conotruncal defects) would be beneficial.

Our PAF calculations suggest that, globally, approximately 2% of cases of CHD are attributable to PDMs and just under 5% to maternal obesity. These estimates are more conservative but broadly consistent with existing studies, which attribute 4% of cases to PDMs and up to 8% to obesity.[84] With approximately 1.78 million babies born annually with a CHD,[85] these findings suggest that even modest improvements in reducing the prevalence of maternal obesity and PDMs would translate to significant reductions in the number of babies born with CHD.

Evidence suggests that to reduce the burden of maternal obesity, the current predominant lifestyle intervention during pregnancy approach[86] must be accompanied by a public health approach that addresses the broad determinants of obesity, interpregnancy weight retention and chronic disease in women of reproductive age, which are rooted in social disadvantage.[87 88] This requires much stronger multisector investment and action to address current inequities in access to healthy foods and opportunities for physical activity.[89] There is presently no effective population intervention to reduce obesity in any population so the existing repertoire of strategies is unlikely to be effective in reducing pre-pregnancy BMI.

In addition to primary prevention, among those with PDMs, preconception care programmes that focus on optimal diabetes management can dramatically reduce the risk of CA.[90] Yet access to preconception care is highly variable, even among women with pre-existing disease.[91] At a minimum, encouraging providers of healthcare for women with chronic diseases to routinely ask about pregnancy intention would be a major step forward.[92]

Strong evidence suggests a protective effect of folic acid supplementation during the periconceptional period on cardiac anomalies.[93–95] Thus, providing all women with access to this is also a CHDs prevention strategy priority.[96]

Strengths and limitations

We used best practice overview methodology to identify and summarise relevant associations[19] and an established approach to assign strength of causal evidence.[13–18] This is the first systematic review of associations between maternal modifiable factors and CHDs to assess causal nature of associations using BH perspectives and draw implications for primary prevention strategy. Management of overlapping studies in reviews of reviews is an unresolved issue.[97] We adopted the approach of including all reviews meeting eligibility criteria except exact duplicates to ensure comprehensive coverage of the evidence base and were guided by the findings of the most recent review when assessing causality.

Assessment of risk of bias in reviews was difficult due to infrequent reporting of items required for comprehensive assessment, including confounding variables used in adjustment in included studies. We did not access 'grey literature' reviews which may contain smaller studies with null results not accepted for publication, and reviews not published in English (which may or may not exist) were not eligible. Most of the included reviews did not specifically search for 'grey literature' studies, although most did assess publication bias (eg, through use of funnel plots) and found no such bias.

We did not consider two criteria originally recommended by BH: experimental evidence, which was deemed not applicable as it is not ethical to obtain evidence through experimental studies of maternal risk factors (eg, smoking); and specificity, which was due to the multifactorial nature of CHD development. This approach is consistent with other BH assessments on topics which rely solely on observational evidence.[17 18] We considered an RR>2.0 with precision to indicate a strong association, which is consistent with the GRADE approach widely used to assess experimental evidence.[14 15] Nevertheless, other assessments have considered an RR cut-off of ≥1.2,[98] thus, our assessments of strength of association may be conservative.

CONCLUSION

There is more than sufficient causal evidence now to advocate for increased resources and policy action to tackle the prevalent maternal CHDs risk factors obesity and PDM. Research should be directed towards environmental and chemical exposures, to further inform strategy for prevention of the most common type of congenital abnormality.

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initial manuscript and critically reviewed the manuscript. Professor AR contributed to the conceptualisation and design of the review, supervised the data extraction and analysis, critically reviewed the analysis, contributed to the drafting of the initial manuscript and critically reviewed and revised the manuscript. Professor VM contributed to the conceptualisation of the review, contributed to the initial analysis and critically reviewed and revised the manuscript. Dr RF collected data, contributed to the initial analysis and critically reviewed and revised the manuscript. Associate Professor LCG, and Professors LG and MD critically reviewed and revised the manuscript. JG and AR were responsible for the overall content as guarantors. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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