Front. Med. 2025, 19(6): 968−980
https://doi.org/10.1007/s11684-025-1170-2

REVIEW

Risk assessment of congenital heart defects based on maternal factors in early pregnancy—a systematic review and meta-analysis

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Abstract **Congenital heart defect (CHD) is a leading cause of neonatal mortality, with early maternal risk factors playing a significant role in its development. This systematic review and meta-analysis investigated the relationship between maternal factors during the first trimester and CHD. The study protocol was registered on PROSPERO (CRD42023476855). MEDLINE, Embase, and Cochrane TRIALS were systematically searched for eligible cohort and case-control studies. The primary outcome was the risk of the fetus developing CHD under the effects of maternal factors. The outcome was estimated by odds ratios (ORs) and 95% confidence interval (CI) using the random-effects model. Seventy-eight studies with 393 534 cases and 29 493 495 controls were included. Maternal pre-pregnancy diabetes (OR 2.91, 95% CI 2.10–4.03), obesity (OR 1.23, 95% CI 1.13–1.33), active (OR 1.28, 95% CI 1.03–1.57) and passive smoking (OR 2.67, 95% CI 1.30–5.46), and chronic hypertension (OR1.39, 95% CI 1.02–1.90) significantly increased the risk of overall CHD in offspring. While underweight was not associated with overall CHD, it showed a slight association with ventricular septal defect (OR 1.10, 95% CI 1.02–1.18). These findings emphasize the importance of optimizing maternal health and lifestyle before and during pregnancy and provide evidence for public health strategies to reduce the risk of CHD.**

Keywords alcohol consumption; BMI; CHD; diabetes; hypertension; meta-analysis; smoking

Introduction

Congenital heart defect (CHD) is one of the most common birth anomalies, affecting approximately 1% of all live births and contributing significantly to neonatal mortality [1,2]. CHD arises from structural abnormalities in the fetal heart and great vessels during early embryogenesis [3]. Despite the good prognosis of surgery for the majority of CHD, with improved short- and long-term survival rates and low rates of reoperation, millions of children are still waiting for surgical treatment [4,5]. Therefore, studying the prevention of fetal cardiac development abnormalities during pregnancy seems to be more important and meaningful at this stage.

Understanding the underlying etiology of CHD is crucial for its prevention. CHD is recognized as a multifactorial anomaly, with contributions from genetic factors, environmental exposures, and gene-environment interactions [6,7]. In CHD cases, approximately 15% are linked to genetic factors, while up to 30% are associated with environmental exposures [8]. Notably, these environmental factors encompass a wide range of non-genetic influences, including socioeconomic status, maternal health conditions, and medication use, emphasizing the critical role of risk factors within the fetal-placental-maternal environment [9,10].

Embryonic heart development occurs between weeks 2 and 7 of gestation, with most CHD phenotypes forming in the late first and early second trimesters of pregnancy, making the first trimester a widely recognized critical

Received April 1, 2025; accepted August 14, 2025
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window for environmental influences on CHD risk [10,11]. Previous meta-analyses have investigated associations between individual maternal risk factors and CHD, such as maternal diabetes [12–16], obesity and underweight [17–20], smoking [21–23], alcohol consumption [18,24–27], and chronic hypertension [28]. Although these studies demonstrated that certain maternal conditions are associated with elevated CHD risk, however, the findings are often inconsistent, phenotype-specific risk assessments are frequently overlooked, and only one study to date has comprehensively evaluated multiple risk factors within a uniform methodological framework. Therefore, we aimed to perform a comprehensive systematic review and meta-analysis to investigate the relationship between maternal factors present during the first trimester and CHD (including its specific phenotypes).

Materials and methods

We conducted our systematic review and meta-analysis under the guidance of PRISMA 2020 and the Cochrane Handbook for Systematic Reviews of Interventions. The study protocol was registered on PROSPERO (registration number CRD42023476855). Although air pollution is considered an important potential risk factor for CHD, inconsistencies in air pollutant definitions, measurement methods, and exposure time complicate accurate assessment. In detail, most studies rely on indirect environmental monitoring data, making it difficult to quantify individual exposure levels, and standardized thresholds for high versus low exposure levels remain uncertain. Furthermore, studies on air pollution involve multiple confounding factors and require complex statistical adjustments, which increase the difficulty of synthesizing overall effects across studies. In contrast, the maternal factors included in this meta-analysis were generally assessed through clinical diagnosis or self-report, with more standardized and comparable measurements that facilitate more reliable pooling of effect estimates across studies. Therefore, to ensure the scientific rigor, consistency, and appropriate scope of our study, our interdisciplinary leadership board decided to exclude air pollution from this systematic review and meta-analysis.

Search strategy

A systematic search was conducted in three databases: MEDLINE (via PubMed), Embase, and TRIALS (via the Cochrane Library). The search key was divided into three domains. The first domain contained pregnancy terms and their synonyms. The second domain was maternal factors. The third domain included the terms of general CHD and its 10 specific phenotypes. We only used title, abstract, and keyword filters in the Embase database; no time or language restrictions were applied. Specific search keys for each database are provided in Supplementary Material 1. The search cutoff date was November 16, 2023. The search was supplemented by the citation chasing of the eligible articles in January 2024.

Eligibility criteria

The inclusion criteria were as follows. (1) Population (P) —pregnant women with their singleton infants. (2) Maternal factors (E)—diabetes, obesity, underweight, smoking, alcohol consumption, and hypertension. Detailed definitions of risk factors are presented in Table S1. (3) Outcome (O) —CHD and its 10 most common phenotypes: ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), Tetralogy of Fallot (ToF), pulmonary artery stenosis (PAS), coarctation of the aorta (CoA), pulmonary atresia (PA), transposition of the great arteries (TGA), hypoplastic left heart syndrome (HLHS), and atrioventricular septal defect (AVSD) (Table S2). (4) Only human cohort and case-control studies were accepted.

Study selection

All articles were downloaded into the reference management software EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) for automatic and manual removal of duplicates. The article screening tool for systematic review Rayyan was used by two independent reviewers (ZS and ÁJ) to select the articles by title and abstract and full text. If disagreements arose between the two reviewers, a third reviewer (AR) resolved them. Cohen's κ coefficient was used to assess the consistency between two independent reviewers in the article screening process.

Data extraction

Two independent reviewers (ZS and ÁJ) performed data extraction using a predesigned spreadsheet. Discrepancies were resolved by a third independent reviewer (AR). The following data were extracted: first author, year of publication, DOI, study design, study period, country, number of singleton infants, exposure factors, definition of exposure, baseline characteristics of population, case and total numbers in the exposure and non-exposure groups, incidence/prevalence of CHD, unadjusted and adjusted odds ratio (OR)/relative risk (RR) and their upper and lower 95% confidence intervals (CIs), and confounding factors adjusted in the multivariate model. For articles that only contained figures without precise data, we used the WebPlotDigitizer tool (Ankit Rohatgi, Pacifica, CA, USA) to extract data from the figures.

Risk of bias (RoB) assessment

The Quality in Prognostic Studies (QUIPS) tool recommended by Cochrane Collaboration was applied to assess the quality of eligible studies. The QUIPS tool assesses RoB across six domains: Study Participation, Study Attrition, Prognostic Factor Measurement, Outcome Measurement, Study Confounding, and Statistical Analysis and Reporting. For each domain, RoB was rated as low, moderate, or high based on the number of unmet considerations. Overall RoB was determined by aggregating domain-level assessments. The detailed rating criteria are presented in Supplementary Material 2. The rating criteria and prompting items and considerations in each domain were strictly referenced from Hayden *et al*. [29]. Two review authors (ZS and ÁJ) performed the RoB assessment independently. Any disagreements were resolved in discussion with the third reviewer (AR) to reach a final consensus. Publication bias was assessed using the Egger's test and visualized using funnel plots. These methods are only applicable when the number of studies included in the analysis exceeds 10.

Data synthesis

ORs were used as effect size measure with their 95% CIs. Pooled OR and their 95% CIs were calculated from unadjusted or adjusted ORs using random-effects models. The inverse variance weighting method was used to calculate pooled ORs. The analysis was performed separately by CHD phenotypes under different maternal factor exposures. In cases where only RRs were available in some studies, and where the incidence of CHDs in the study population was less than 10%, the RR served as an approximation for the OR [30,31]. I^2-statistic and Cochran's Q tests were used to assess the statistical heterogeneity among included studies. To estimate the heterogeneity variance (τ^2), we used the restricted maximum-likelihood estimator with the Q profile method for CIs [32,33]. ORs and 95% CIs of each study and pooled effects were visualized using forest plots.

Subgroup analysis was based on the results of the RoB assessment, where the effect of each maternal factor on overall CHDs was analyzed according to three levels of RoB: high, intermediate, and low. For a specific maternal factor, the requirement to perform a subgroup analysis was that each RoB subgroup should contain at least three studies. All statistical analyses were performed by R software (version 4.2.2; R Core Team, Vienna, Austria), specifically employing the "metagen" function (for meta-analysis) and "forest" function (forest plot generation) from the meta package. In statistical analyses, the P-value $\leqslant 0.05$ indicated statistical significance. All statistical methods were performed by Mikolt Bakony, a certified statistician at the Centre for Translational Medicine, Semmelweis University, Budapest, Hungary.

Results

Study selection and characteristics

Fifty-nine studies met our inclusion criteria, with an additional 19 from citation chasing, resulting in 78 studies in total. The PRISMA flow diagram is shown in Fig. 1.

The table of basic characteristics of included studies is shown in Table S3. A total of 26 cohort studies and 52 case-control studies were included. A total of 393 534 infants with CHD and 29 493 495 infants without CHD were included in this analysis. The distribution of risk factors and CHD phenotypes in included studies is shown in Table S4.

Maternal risk factors

Maternal diabetes

In comparison to non-diabetic pregnant women, the offspring of women with diabetes before pregnancy had almost three times the odds of CHD (OR 2.91, 95% CI 2.10–4.03) (Fig. 2), with considerable heterogeneity (I^2 = 87%). Offspring of pregnant women with type 1 and type 2 diabetes (Fig. S1), respectively, had an approximately three times (OR 2.96, 95% CI 1.90–4.62) and two times (OR 2.27, 95% CI 1.21–4.27) increased risk of CHD compared to the offspring of mothers without diabetes. By the analysis of various phenotypes of CHD, the pooled ORs indicated that pre-pregnancy diabetes in pregnant women significantly increased the risk of their offspring developing ASD (OR 2.63, 95% CI 1.20–5.74), VSD (OR 2.45, 95% CI 1.26–4.74), AVSD (OR 5.35, 95% CI 1.73–16.55), CoA (OR 3.21, 95% CI 1.41–7.33), or TGA (OR 2.83, 95% CI 1.78–4.50) (Fig. S2). However, no significant association could be detected between pre-pregnancy diabetes and the risk of the offspring developing HLHS (OR 1.98, 95% CI 0.19–20.28) or ToF (OR 2.63, 95% CI 0.77–8.95) (Fig. S2). The strong association between maternal diabetes and overall CHD and several phenotypes highlights the urgent need for preconception counseling and glycemic control in diabetic women to reduce fetal cardiac risks. For phenotypes that could not be included in the meta-analysis due to insufficient data, Table S5 records the effects of pre-pregnancy diabetes and its subtypes on non-poolable offspring CHD phenotypes.

Maternal obesity

There was an association between maternal obesity and the development of CHD in their infants (OR 1.23, 95% CI 1.13–1.33), with high heterogeneity (I^2 = 73%)

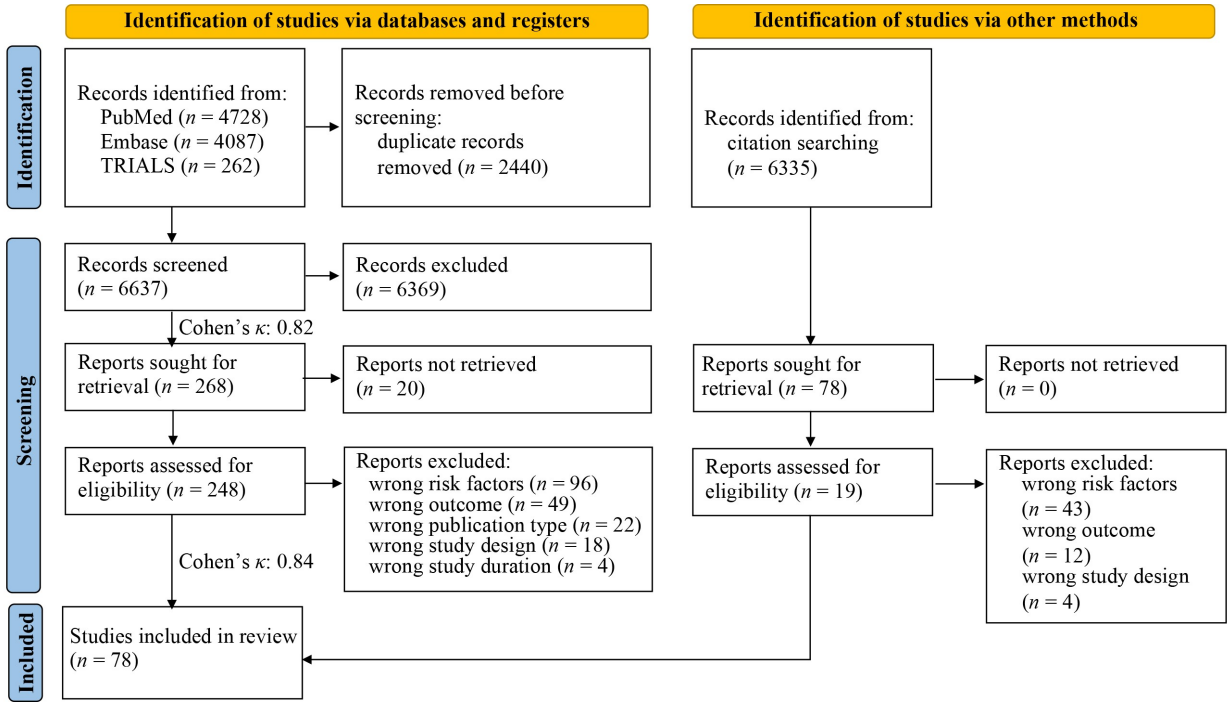

Fig. 1 PRISMA 2020 flowchart of the study selection process.

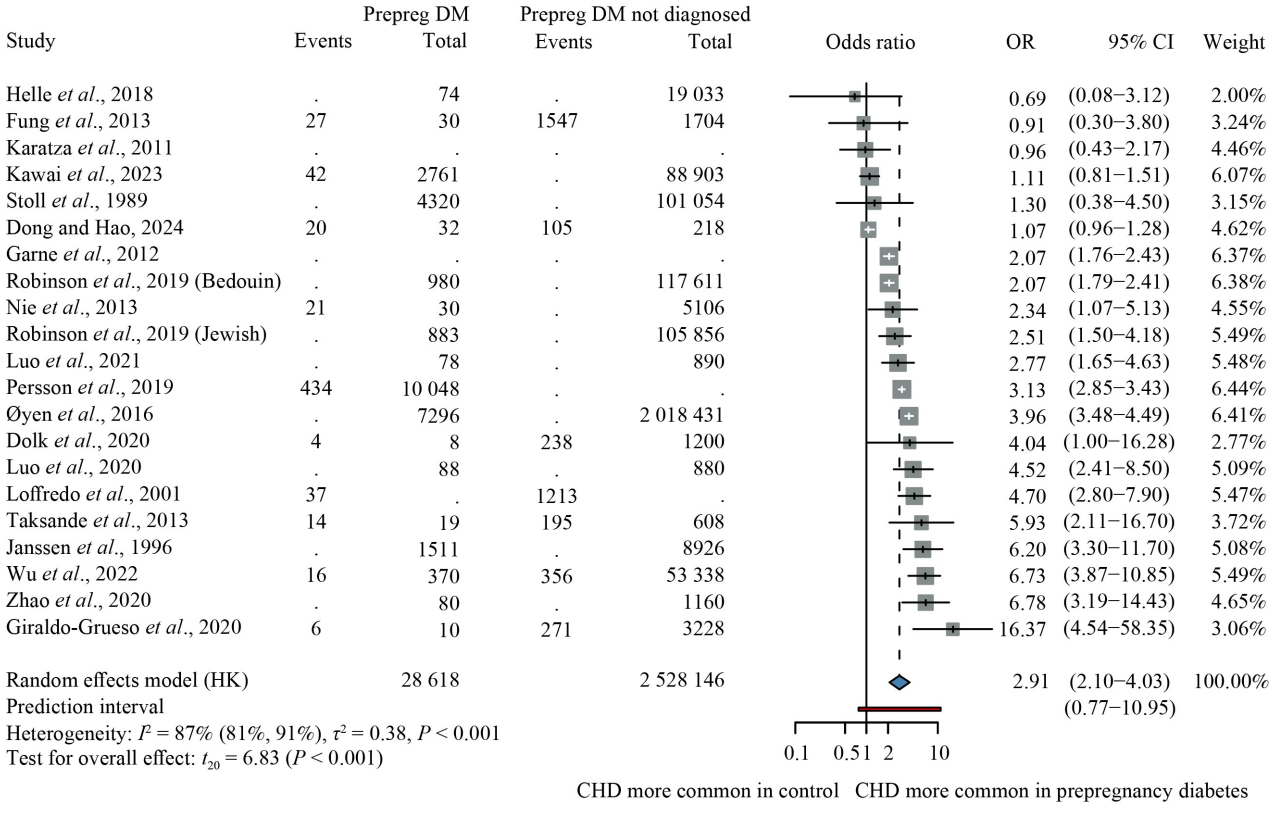

Fig. 2 Forest plot of ORs for the association between maternal pre-pregnancy diabetes and risk of offspring CHD. Prepreg DM, pre-pregnancy diabetes mellitus; OR, odds ratio; CI, confidence interval.

(Fig. 3A). Phenotype analysis revealed that maternal obesity also increased the risk of infants having ASD (OR 1.14, 95% CI 1.07–1.22) and ToF (OR 1.26, 95% CI 1.02–1.58) (Fig. S3). However, most offspring CHD phenotypes, including VSD (OR 1.12, 95% CI 0.89–1.41), AVSD (OR 0.93, 95% CI 0.49–1.73), CoA (OR 1.10, 95% CI 0.91–1.32), HLHS (OR 1.38, 95% CI 0.98–1.93), and TGA (OR 1.10, 95% CI 0.90–1.33), were not associated with maternal obesity (Fig. S3).

Some studies classified maternal obesity into different categories (Table S1). Class I (OR 1.18, 95% CI 1.09–1.28) and class II maternal obesity (OR 1.32, 95% CI 1.16–1.49) (Fig. S4) were associated with CHD in offspring. In contrast, maternal class III did not affect CHD development in offspring (OR 1.41, 95% CI 0.67–2.95) (Fig. S4). The observed association between maternal obesity and overall CHD in offspring, and particularly ASD and ToF, emphasizes the importance of weight optimization before pregnancy through lifestyle and nutritional interventions. The effects on other non-poolable offspring CHD phenotypes are shown in Table S5.

Maternal underweight

In comparison to pregnant women with normal weight, being underweight did not affect CHD development in their offspring (OR 1.02, 95% CI 0.97–1.08) (Fig. 3B). A low heterogeneity was found across studies (I^2 = 27%). Although this association was not significant for overall CHD, maternal underweight was slightly associated with only VSD in the offspring (OR 1.10, 95% CI 1.02–1.18) (Fig. S5). There was no association between maternal underweight and other offspring CHD phenotypes including ASD (OR 1.03, 95% CI 0.80–1.34), ToF (OR 1.08, 95% CI 0.84–1.40), CoA (OR 1.05, 95% CI 0.83–1.33), HLHS (OR 1.01, 95% CI 0.78–1.31), TGA (OR 1.07, 95% CI 0.76–1.51), and PA (OR 1.40, 95% CI 0.45–4.34) (Fig. S5). Mills *et al*. [34] and Gilboa *et al*. [35] reported the same finding, indicating that maternal underweight had a significant effect on the incidence of AVSD in offspring (Table S5). Although overall CHD risk was not significant, the association with VSD suggests that maternal undernutrition may affect specific cardiac structures, warranting nutritional support in underweight women planning pregnancy.

Maternal smoking

Active smoking

Smoking in the first trimester of pregnancy increased the risk of CHD in the offspring (OR 1.28, 95% CI 1.03–1.57), with high heterogeneity (I^2 = 83%) (Fig. 4A). Furthermore, when offspring CHD phenotypes were examined, it was found that compared to non-smoking pregnant women, smoking in the first trimester of pregnancy increased the odds of the offspring developing ASD by 48% (OR 1.48, 95% CI 1.11–1.98) and VSD by 22% (OR 1.22, 95% CI 1.03–1.45). However, no association was found between maternal smoking in the first trimester of pregnancy and other phenotypes of CHD in offspring (Fig. S6A). The significant association between active smoking and overall CHD and specific phenotypes in offspring highlights the critical role of smoking cessation programs in preconception and pregnancy for preventing fetal heart malformations.

Passive smoking

Notably, the risk of CHD in the offspring of pregnant women exposed to passive smoking in early pregnancy was 2.67 times higher (OR 2.67, 95% CI 1.30–5.46) compared with pregnant women who were not exposed to passive smoking (Fig. 4B). High heterogeneity was found across studies (I^2 = 77%). No association was found in ASD (OR 1.73, 95% CI 0.85–3.50), VSD (OR 1.70, 95% CI 0.48–5.94), or AVSD (OR 1.42, 95% CI 0.27–7.37) (Fig. S6B). The increased overall CHD risk in offspring associated with passive smoking indicates the need for public health efforts to minimize pregnant women's exposure to secondhand smoke. The effects of active and passive smoking on other offspring CHD phenotypes that could not be pooled are shown in Table S5.

Maternal alcohol consumption

In the first trimester, the effect of maternal alcohol consumption on the risk of CHD in the offspring was not mathematically significant (OR 1.22, 95% CI 0.89–1.66) (Fig. 5). There was considerable heterogeneity between the studies (I^2 = 69%). Similarly, maternal alcohol consumption had no effect on ASD (OR 1.24, 95% CI 0.36–4.28) and VSD (OR 1.01, 95% CI 0.91–1.12) phenotypes in offspring (Fig. S7). The association between maternal alcohol consumption and other non-poolable offspring CHD phenotypes is shown in Table S5.

Maternal hypertension

The analysis reported that pregnant women with chronic hypertension had higher odds of CHD in the offspring compared to pregnant women with normal blood pressure (OR 1.39, 95% CI 1.02–1.90), with high heterogeneity (I^2 = 86%) (Fig. 6). However, this significant increase in risk was not detected for ASD (OR 1.04, 95% CI 0.47–2.28) or VSD (OR 1.19, 95% CI 0.91–1.54) in offspring (Fig. S8). The significant association between chronic hypertension and overall offspring CHD underscores the necessity of blood pressure control and cardiovascular monitoring before and during pregnancy. Furthermore, the effects of chronic hypertension on

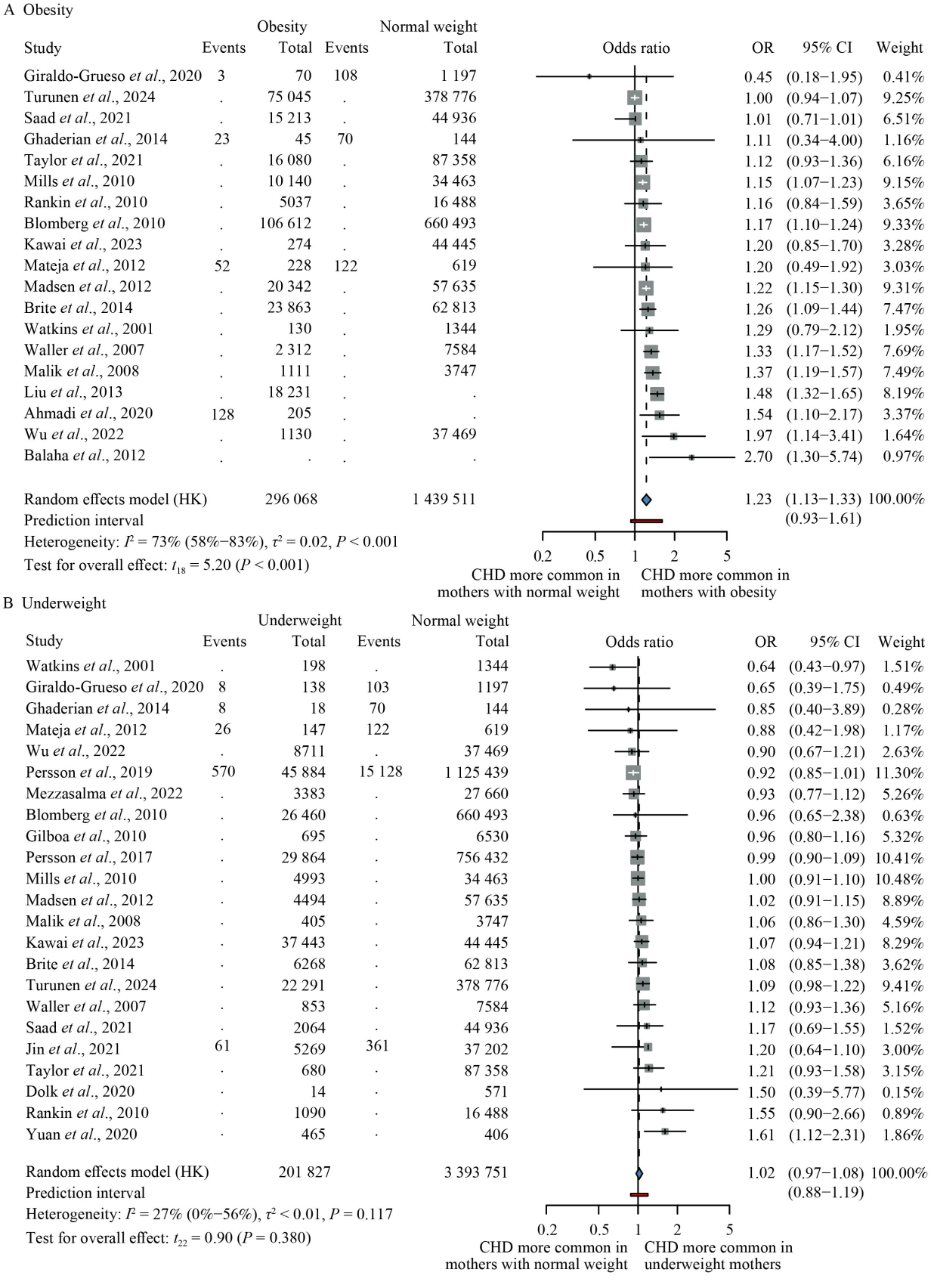

Fig. 3 Forest plot of ORs for the association between maternal (A) obesity/(B) underweight and risk of offspring CHD. OR, odds ratio; CI, confidence interval.

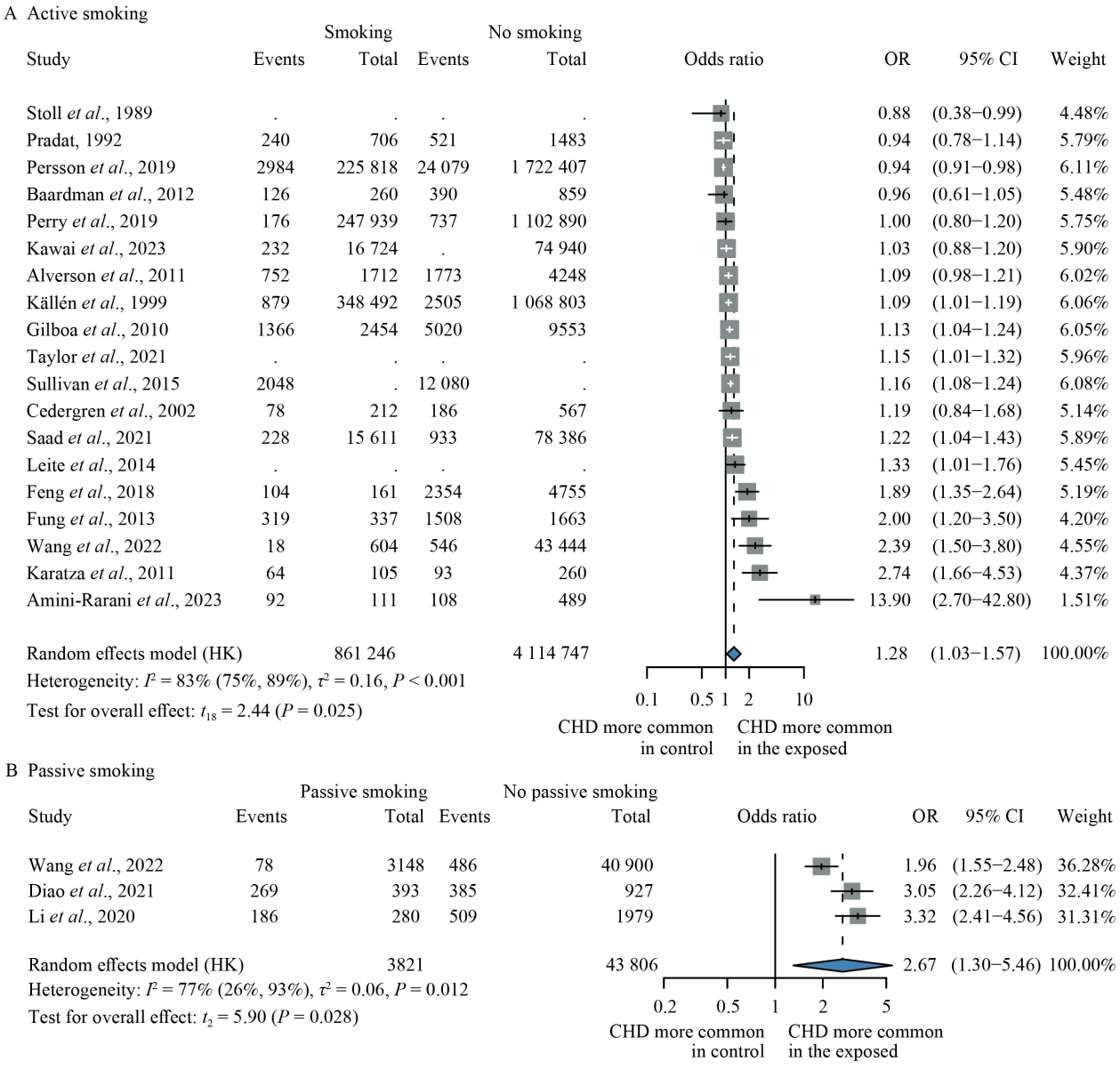

Fig. 4 Forest plot of ORs for the association between maternal (A) active smoking/(B) passive smoking and risk of offspring CHD. OR, odds ratio; CI, confidence interval.

non-poolable offspring CHD phenotypes are presented in Table S5.

Summary of main findings

To facilitate comparison across different maternal factors, Table 1 summarizes the effect sizes of associations between each maternal factor and risk of offspring overall CHD, as well as its phenotypes.

Results of RoB assessment

Of the 78 included eligible studies, 37 studies had a low RoB, 24 studies had a moderate RoB, and 17 studies had a high RoB. The results of the RoB assessments are presented in Table S6. The primary cause of high RoB was the omission of confounding factors, which affected 15 studies. In the study by Giraldo-Grueso *et al*. [36], there was a serious risk of bias due to the small number of mothers with diabetes, underweight, or obesity in the case group. Although the studies by Mateja *et al*. [37] and Karatza *et al*. [38] did not have any domains of high risk of bias, they were considered to have an overall high risk of bias as they were evaluated as moderate risk in three domains.

Results of publication bias assessment

Egger's test revealed asymmetry in the funnel plots for

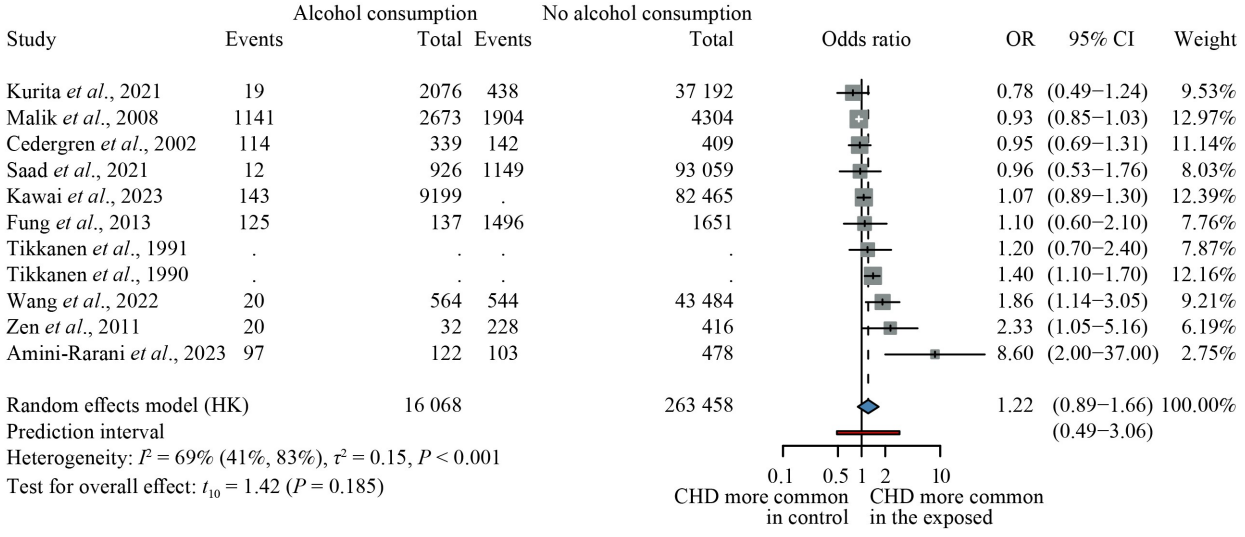

Fig. 5 Forest plot of ORs for the association between maternal alcohol consumption and risk of offspring CHD. OR, odds ratio; CI, confidence interval.

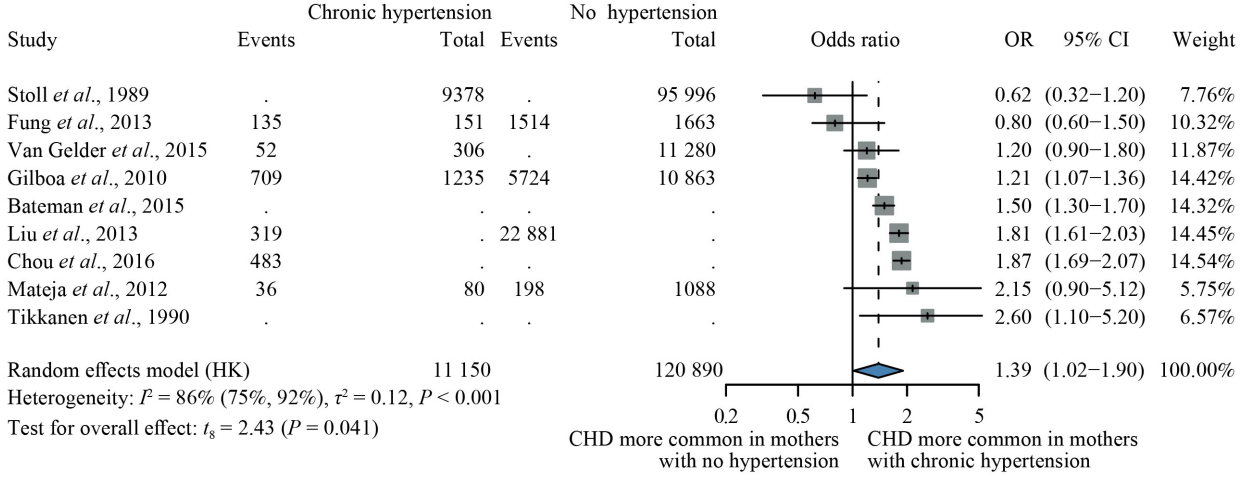

Fig. 6 Forest plot of ORs for the association between maternal hypertension and risk of offspring CHD. OR, odds ratio; CI, confidence interval.

active smoking (P = 0.001), indicating potential publication bias in the meta-analysis (Fig. S9).

Results of subgroup analysis

Maternal obesity, underweight, pre-pregnancy diabetes, and active smoking met the requirement for subgroup analysis. The results of subgroup analysis based on RoB levels for each eligible risk factor are presented in Fig. S10. There was no significant difference in effect size between subgroups with different levels of RoB.

Discussion

Principal findings

This comprehensive meta-analysis investigated the effect of maternal factors on CHD and their 10 specific phenotypes in offspring. To achieve this objective, we included approximately 394 000 children with CHD and about 29.5 million control group infants. Overall, the following maternal factors in a clinically relevant and statistically significant way increased the risk of CHD in offspring: diabetes (OR 2.91, 95% CI 2.10–4.03), obesity (OR 1.23, 95% CI 1.13–1.33), active smoking (OR 1.28, 95% CI 1.03–1.57), passive smoking (OR 2.67, 95% CI 1.30–5.46), and hypertension (OR 1.39, 95% CI 1.02–1.90). By contrast, maternal underweight was not associated with the incidence of overall CHD (OR 1.02, 95% CI 0.97–1.08); however, it showed a slight association with VSD (OR 1.10, 95% CI 1.02–1.18). Similarly, maternal alcohol consumption (OR 1.22, 95% CI 0.89–1.66) was not associated with the incidence of CHD in offspring.

Table 1 Pooled ORs (with 95% CI) for associations between maternal factors and CHD, including overall CHD and specific phenotypes

Maternal factor	Overall CHD OR (95% CI)	CHD phenotypes OR (95% CI)
Diabetes	2.91 (2.10–4.03)*	ASD 2.63 (1.20–5.74)*
		VSD 2.45 (1.26–4.74)*
		AVSD 5.35 (1.73–16.55)*
		CoA 3.21 (1.41–7.33)*
		TGA 2.83 (1.78–4.50)*
		HLHS 1.98 (0.19–20.28)
		ToF 2.63 (0.77–8.95)
Obesity	1.23 (1.13–1.33)*	ASD 1.14 (1.07–1.22)*
		ToF 1.26 (1.02–1.58)*
		VSD 1.12 (0.89–1.41)
		AVSD 0.93 (0.49–1.73)
		CoA 1.10 (0.91–1.32)
		HLHS 1.38 (0.98–1.93)
		TGA 1.10 (0.90–1.33)
Underweight	1.02 (0.97–1.08)	VSD 1.10 (1.02–1.18)*
		ASD 1.03 (0.80–1.34)
		ToF 1.08 (0.84–1.40)
		CoA 1.05 (0.83–1.33)
		HLHS 1.01 (0.78–1.31)
		TGA 1.07 (0.76–1.51)
		PA 1.40 (0.45–4.34)
Active smoking	1.28 (1.03–1.57)*	ASD 1.48 (1.11–1.98)*
		VSD 1.22 (1.03–1.45)*
		AVSD 1.16 (0.86–1.56)
		CoA 0.90 (0.70–1.17)
		HLHS 1.02 (0.91–1.13)
		PDA 1.37 (0.92–2.05)
		ToF 1.26 (0.74–2.15)
		TGA 1.15 (0.75–1.77)
Passive smoking	2.67 (1.30–5.46)*	ASD 1.73 (0.85–3.50)
		VSD 1.70 (0.48–5.94)
		AVSD 1.42 (0.27–7.37)
Alcohol consumption	1.22 (0.89–1.66)	ASD 1.24 (0.36–4.28)
		VSD 1.01 (0.91–1.12)
Chronic hypertension	1.39 (1.02–1.90)*	ASD 1.04 (0.47–2.28)
		VSD 1.19 (0.91–1.54)

*Statistically significant OR at $P < 0.05$. CHD, congenital heart defect; CI, confidence interval; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; ToF, tetralogy of Fallot; CoA, coarctation of the aorta; PA, pulmonary atresia; TGA, transposition of the great arteries; HLHS, hypoplastic left heart syndrome; AVSD, atrioventricular septal defect.

Comparison with existing literature

The findings of our study are consistent with those of existing meta-analyses. For the risk factor of maternal diabetes, five existing meta-analyses agree that pre-pregnancy diabetes significantly increase the risk of CHD in the offspring [12–16]. In maternal diabetes, the primary teratogenic factor for the fetus is hyperglycemia. It is noteworthy that maternal glucose is transported to the fetus via the placenta through facilitated diffusion mediated by glucose transporters (GLUTs) [39,40]. Therefore, the fetal blood glucose level mainly depends on maternal glucose levels. When the fetal heart is exposed to elevated glucose levels, various molecular pathways crucial for cardiac development are disrupted, including increased oxidative stress during embryonic development, altered expression of antioxidant enzyme genes, and disrupted cardiac developmental signaling pathways [39–41].

Previous meta-analyses also reported a strong association between maternal obesity and CHD in the offspring, with findings similar to our study [17–20]. However, the specific mechanisms by which maternal obesity leads to CHD in the fetus remain widely debated. Excessive weight gain leads to the overexpansion and accumulation of adipose tissue, which impairs insulin signaling and reduces the number of functional β cells, ultimately resulting in type 2 diabetes [42]. Thus, the teratogenic mechanism of maternal obesity may be linked to the glycemic dysregulation mentioned above. However, in the cohort study by Brite *et al*. [43], even after adjusting for glycemic status, obese mothers still showed a higher risk of developing CHD in their offspring. On the basis of this result, they believed that the abnormal glucose metabolism due to obesity only partially explains the teratogenic mechanism of obesity on the fetal heart [43]. Another explanation is that maternal obesity can lead to endothelial dysfunction, which may extend into the fetal circulatory system through the maternal-fetal connection, thereby continuously affecting fetal development [44]. In our analysis, maternal class III obesity showed no effect on CHD, a surprising result that conflicts with the findings of Zheng *et al*. [19] and Cai *et al*. [17]. Upon investigation, we found that one of the included studies, specifically Dolk *et al*. [45], did not include cases of transitory ASD. Interestingly, however, most previous studies included such transitory forms. Previous meta-analyses and also ours showed that maternal obesity significantly increases the risk of ASD in the offspring [17,19]. Therefore, the reason for this discrepancy is that certain forms of ASD were excluded from the study population. In our analysis, although maternal underweight did not affect CHD in offspring, this conclusion was also confirmed by previous meta-analyses

[17–20]. Nevertheless, our analysis suggests that maternal underweight is a risk factor for VSD. Inadequate intake of nutrients during pregnancy may be responsible for fetal malformations. Two studies from China highlighted that adequate egg and dairy intake and increasing dietary diversity during pregnancy could help reduce the risk of VSD in the fetus [46,47]. Therefore, the potential protective effects of a diverse and nutrient-rich diet during pregnancy on the fetus should not be overlooked.

Maternal passive smoking in early pregnancy appears to pose a higher risk for fetal CHD development compared to active smoking. Previous meta-analyses that included passive smoking also noted this point [22,23]. An animal experiment indicated that in pregnant mice exposed to nicotine, the expression of genes critical for embryonic heart development was downregulated, impairing cell proliferation and the epicardial epithelial-to-mesenchymal transition (EMT) process [48]. Epicardial EMT plays a crucial role in the formation of cardiac fibroblasts, vascular smooth muscle cells, subsets of coronary endothelial cells, and subsets of cardiomyocytes [49]. In addition, nicotine exposure due to smoking increases oxidative stress and alters intracellular calcium concentrations, promoting embryonic cell apoptosis and disrupting normal embryonic development [50]. As for why passive smoking has a greater risk to fetal cardiac development, we speculate that the incomplete combustion of tobacco and the prolonged dispersion of smoke exhaled by smokers and produced by burning tobacco in confined spaces may lead to pregnant women being exposed to higher levels of harmful substances, which may adversely affect embryonic development. We suggest that future observational studies strive to improve data validity by distinguishing passive smoking exposure in household, occupational, and environmental settings. Exploring how exposure intensity and duration of passive smoking influence the risk of CHD in the fetus will contribute to a more accurate assessment.

As to whether alcohol consumption during pregnancy is a risk factor for CHD, previous meta-analyses have shown considerable discrepancies. Of the existing five meta-analyses, three studies were consistent with our findings [18,25,26], while the other two considered maternal alcohol consumption to be a risk factor for causing CHD [24,27]. Notably, only studies by Wen *et al*. [26] and Zhang *et al*. [27] specified the time of maternal alcohol exposure, which was limited to the three months before pregnancy and the first trimester of pregnancy (i.e., periconceptional period). However, the other studies only mentioned "during pregnancy" as the period. We strongly recommend that future studies should specifically define the exposure period of alcohol consumption in the first trimester of pregnancy to make the research findings more valuable. Some evidence from animal studies suggests that alcohol exposure leads to upregulation of cardiomyocyte apoptosis and enhancement of the Wnt/β-catenin pathway, which inhibits early cardiogenesis [51,52]. Therefore, although our study did not find a statistically significant association, existing biological evidence suggests potential adverse effects of alcohol on fetal heart development. Given the broader health risks associated with alcohol consumption during pregnancy, caution is advised, and further research is needed to clarify its specific impact on CHD risk.

A previous meta-analysis reported that untreated maternal chronic hypertension increases the risk of CHD in the fetus, which is consistent with our findings [28]. Chronic hypertension may lead to placental dysfunction, impairing blood supply during fetal development and increasing the risk of certain cardiovascular malformations, especially when it occurs in early pregnancy [53–55]. In detail, changes in vascular resistance within the placental vascular bed alter the balance of blood flow within the fetal heart, significantly affecting intracardiac blood distribution. For example, a severe reduction in left heart blood flow may lead to CHD such as HLHS [56]. Future research should focus on the impact of antihypertensive drugs on pregnancy outcomes in mothers with chronic hypertension, ensuring both safety and efficacy to minimize health risks for both the mother and fetus.

Our subgroup analysis showed minimal differences in the effect of risk factors on overall CHD between groups with varying levels of RoB, which were not clinically significant. Thus, we conclude that the RoB in the studies included is unlikely to significantly affect the overall effects. Instead, a larger sample size increases the precision of these effects. Despite this, heterogeneity among studies in the low RoB group remained moderate to high, suggesting that the heterogeneity is not due to study quality or bias. We speculate that it is due to differences in study designs (a mix of cohort and case-control studies) and variations in the clinical characteristics of the populations involved.

Strengths and limitations

Our study has several strengths. First, our study investigated six risk factors with detailed subcategories, assessing their effects not only on overall CHD but also on specific phenotypes in offspring. A previous comprehensive meta-analysis by Wu *et al*. [18] on maternal factors and CHD focused solely on overall offspring CHD, without assessing the risks associated with specific phenotypes. By addressing this gap, our study offered a more nuanced understanding of how different maternal risk factors contribute to various CHD phenotypes, potentially improving early risk stratification

and preventive strategies. Second, our study included chronic diseases (such as diabetes and chronic hypertension) and nutrition status (including obesity and underweight) as risk factors. This may help women preparing for pregnancy and pregnant women enhance the adjustment and optimization of their health and nutritional status in order to reduce the risk of CHD in the fetus. Finally, this study adopted an innovative grouping approach by conducting a subgroup analysis based on RoB levels to assess the impact of different study qualities on the pooled results. The subgroup results indicated that the study findings exhibit overall good robustness.

However, some limitations in this study should be highlighted. First, the definitions and cut-off values of certain risk factors vary across countries and populations, posing challenges for quantitative analysis. Additionally, in some studies, risk factors such as maternal diabetes, smoking, and alcohol consumption were self-reported, which may introduce recall and information bias. Second, some studies have not adequately considered potential confounders, such as the coexistence of obesity and diabetes, which may introduce bias or underestimate certain risk factors. Additionally, socioeconomic status, healthcare accessibility, and lifestyle factors may also significantly influence the risk of CHD in offspring. Therefore, future research should apply multivariable analysis methods to consider interactions between multiple risk factors, enabling a more accurate assessment of their combined effects on offspring CHD. Lastly, the presence of potential publication bias may lead to an overestimation of the association between maternal factors and the risk of CHD in offspring.

Implications

The findings in this study may have implications for clinical practice, research, and society [57,58].

From the clinical perspective, the strong association between maternal factors and increased CHD risk highlights the importance of optimizing maternal health and lifestyle both before and during pregnancy. Measures including, but not limited to: preconception counseling, effective management of chronic diseases (e.g., diabetes and hypertension), smoking cessation programs, and nutritional support should be available to pregnant women.

Future research should conduct prospective longitudinal studies to investigate the impact of both treated and untreated maternal diseases on the risk of CHD in offspring. In addition, large-scale population-based studies on demographic factors are needed to identify vulnerable subgroups and inform targeted public health interventions. Finally, studies investigating the mechanisms of how maternal risk factors contribute to CHD are critical as well. These future studies will deepen our understanding of the teratogenic effects of maternal factors and support the development of more precise CHD prevention strategies.

In terms of policy, these findings support the development of public health guidelines and maternal education aimed at reducing modifiable risk exposures, such as smoking, during early pregnancy.

Conclusions

In summary, we identified maternal diabetes, obesity, smoking, and chronic hypertension as key risk factors for CHD in offspring, with maternal underweight showing a slight association with VSD phenotype. These findings highlight the importance of optimizing maternal health and lifestyle prior to and during pregnancy to reduce the risk of CHD in offspring. Future research plans should include longitudinal studies comparing the impact of treated and untreated maternal diseases on CHD, population-based studies examining demographic effects, and mechanistic studies investigating the relevant teratogenic pathways. Policymakers should promote public health strategies and maternal education to minimize maternal risk exposures. Limitations include heterogeneous exposure definitions, potential recall and publication bias, and unmeasured confounding, which may affect the comparability and interpretation of pooled estimates.

Acknowledgements

All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Compliance with ethics guidelines

Conflicts of interest Zihan Suo, Anett Rancz, Árpád Ágoston Jankó, Péter Hegyi, Zoltán Klárik, Ágnes Mayer, Márton Vezér, and Nándor Ács declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

Electronic supplementary material Supplementary material is available in the online version of this article at https://doi.org/10.1007/s11684-025-1170-2 and is accessible for authorized users.

Funding note Open access funding provided by Semmelweis University.

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