Ultrasound Obstet Gynecol 2024; **64**: 294–307
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.27659.

Maternal prepregnancy weight as an independent risk factor for congenital heart defect: systematic review and meta-analysis stratified by subtype and severity of defect

N. SALMERI[1,2], A. SEIDENARI[3,4], P. I. CAVORETTO[1,2], M. PAPALE[1,2], M. CANDIANI[1,2] and A. FARINA[3,4]

[1]*Gynecology and Obstetrics Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [2]*Vita-Salute University, Milan, Italy;* [3]*Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum-University of Bologna, Bologna, Italy;* [4]*Obstetric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*

KEYWORDS: body mass index; diabetes; CHD; congenital heart defect; congenital malformation; meta-analysis; obesity; overweight; risk factor

CONTRIBUTION

What are the novel findings of this work?
Women who are overweight or obese before pregnancy have a higher risk of congenital heart defect in their offspring. This risk rises in tandem with increasing maternal body mass index and is independent of the mother's diabetic status before or during pregnancy.

What are the clinical implications of this work?
Advocating preconception weight management is key to reducing congenital heart defects in offspring. Women with higher body mass index should receive routine fetal echocardiography during pregnancy.

ABSTRACT

Objective *To assess the association between increased maternal prepregnancy body mass index (BMI) and the risk of congenital heart defect (CHD) in offspring.*

Methods *This systematic review and meta-analysis searched PubMed/MEDLINE, Web of Science and Scopus from inception to 20 April 2023. Risk estimates were abstracted or calculated for increased BMI categories (overweight, obesity, moderate obesity and severe obesity) compared with normal weight (reference). Fixed-effects or random-effects models were used to combine individual study risk estimates based on the degree of heterogeneity. Sensitivity analyses were conducted to weight pooled estimates for relevant moderators, particularly diabetes before and during pregnancy. Subgroup analyses for specific CHD subtypes were conducted if there were at least two studies with available data. Findings were presented for groups of defects, categorized using severity and topographic–functional criteria, and for individual defects. The certainty of the evidence for each effect estimate was evaluated according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines.*

Results *Overall, 31 studies comprising 4 861 693 patients and 86 136 CHD cases were included. The risk of CHD increased progressively from moderate to severe obesity (pooled odds ratio (OR), 1.15 (95% CI, 1.11–1.20) and 1.39 (95% CI, 1.27–1.53), respectively). Sensitivity analysis indicated that this effect persisted independently of maternal diabetes status before or during pregnancy. In the subgroup analysis, obesity was associated with up to a 1.5-fold increase in the risk of severe CHD (pooled OR, 1.48 (95% CI, 1.03–2.13)). Severe obesity was associated with an even higher risk, with 1.8-times higher odds compared with the reference group for specific CHD subtypes, including tetralogy of Fallot (pooled OR, 1.72 (95% CI, 1.38–2.16)), pulmonary valve stenosis (pooled OR, 1.79 (95% CI, 1.39–2.30)) and atrial septal defect (pooled OR, 1.71 (95% CI, 1.48–1.97)).*

Conclusions *Maternal weight is a crucial modifiable risk factor for CHD, particularly for severe forms of defect. Further research is needed to investigate whether weight management before pregnancy might serve as a preventive measure against CHD. In pregnant women with obesity,*

Correspondence: Dr P. I. Cavoretto, Gynecology and Obstetrics Unit, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy (e-mail: cavoretto.paolo@hsr.it)

Accepted: 26 March 2024

fetal echocardiography should be a routine diagnostic procedure.

INTRODUCTION

In recent decades, the proportion of women of reproductive age who are overweight or obese has increased significantly[1]. According to the World Health Organization (WHO), a body mass index (BMI) over 25 kg/m^2 is considered overweight, while 30 kg/m^2 or higher is considered obese[2]. In Europe, the prevalence of obesity before pregnancy ranges from 7.8% to 25.6%[3], and in the USA, it is nearly 3 in 10 women[4]. Pregnancy in women who carry excess weight has been linked to adverse outcomes for both the mother and the newborn[5–11]. Furthermore, women with obesity face an increased likelihood of delivering an infant with congenital anomaly[12], such as neural tube defect[13], orofacial cleft[14] and cardiovascular anomaly[15,16].

Congenital heart defects (CHD) are the most prevalent congenital malformation among neonates, affecting up to 1% of all live births worldwide[17,18]. CHD has been identified as a significant cause of neonatal morbidity and mortality globally, thereby posing a major public health challenge[19]. The interpretation of previous meta-analyses investigating the association between maternal weight and CHD has been hindered by overlapping maternal conditions, such as diabetes, which act as residual confounders or mediators. Consequently, although detailed fetal anatomical ultrasound scans are recommended for women with obesity, fetal echocardiography is typically reserved for cases with a high suspicion of cardiac abnormality[20]. This practice is reflected in the guidelines of the American Society of Echocardiography and the International Society of Ultrasound in Obstetrics and Gynecology, which currently do not classify obesity as a maternal factor associated directly with CHD[21,22]. However, timely detection of CHD through fetal echocardiography and early referral to a specialized center that is experienced in fetal and pediatric cardiovascular care are critical steps in improving neonatal outcome.

The primary objective of this meta-analysis was to quantify the risk of CHD in the offspring of women with varying degrees of increased prepregnancy BMI. We considered relevant confounding factors, particularly gestational diabetes mellitus (GDM) and pregestational diabetes mellitus (PDM)[23]. Furthermore, we aimed to provide specific risk estimates for the most common subtypes of CHD, according to the severity of maternal obesity.

METHODS

Study design

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[24,25]. The study protocol was registered prospectively in the publicly accessible PROSPERO database (CRD42023405393).

Search strategy and eligibility criteria

A systematic search of English language articles published in peer-reviewed journals was conducted on PubMed/MEDLINE, Web of Science and Scopus from inception to 20 April 2023. The search strategy is provided in detail in Appendix S1. Reference lists of relevant publications were also screened. Duplicate records were removed using EndNote software (Clarivate Analytics, Philadelphia, PA, USA). Two independent reviewers (A.S., M.P.) screened titles and abstracts, followed by a full-text review of manuscripts. Any disagreements were resolved by a third reviewer (N.S.).

To be eligible for inclusion, studies were required to meet the following criteria: (1) available data on prepregnancy or early-pregnancy BMI in the standard format of kg/m^2; (2) incidence of CHD is reported as the primary outcome; (3) incidence of CHD is discernible from that of other non-cardiac fetal malformations; and (4) absence of known chromosomal or genetic anomalies. Studies included in the quantitative synthesis also met the following criteria: (1) reporting of risk estimates (odds ratios (ORs) or risk ratios) with corresponding 95% CI, or provision of sufficient raw data to calculate the specific measure of risk according to BMI categories; and (2) inclusion of a reference category of normal bodyweight.

The exclusion criteria were as follows: (1) inclusion of multiple pregnancy; (2) overlapping study periods from the same research groups (only the largest was included); (3) studies published in languages other than English; and (4) descriptive studies or those that do not present original findings.

Data extraction

Two independent reviewers (A.S., M.P.) extracted the following data: study identifiers (first author, publication year), study period, study design and setting, exposure definition and categorization, outcome definition and classification (diagnostic methods and subtypes of CHD) and potential moderators. Maternal BMI was classified into categories based on WHO guidelines[2]: 18.5–24.9 kg/m^2 (reference group), 25.0–30.0 kg/m^2 (overweight) and $>$ 30.0 kg/m^2 (obese). Moderate and severe obesity were defined as a BMI of 30.1–34.9 kg/m^2 and $\geq$ 35.0 kg/m^2, respectively. In studies reporting risk estimates for BMI categories not conforming to the WHO guidelines, effect estimates were grouped with the nearest conventional BMI category, as per a prior publication[26]. These studies were omitted from sensitivity analyses to control for potential exposure misclassification bias.

The risk of bias within and across studies was evaluated independently by two authors (A.S., M.P.)

using the Risk of Bias In Non-randomized Studies of Exposures (ROBINS-E) tool, in accordance with the updated Cochrane collaboration guidelines[27,28].

Data synthesis

Original outcome data were extracted by an independent reviewer (N.S.). Risk estimates were calculated and pooled according to predefined BMI categories. The pooled estimates were obtained using a random-effects model with restricted maximum likelihood estimation method, which accounted for between-study variability. In cases in which study homogeneity was reasonable, a fixed-effects model using the Mantel–Haenszel method was preferred. Heterogeneity was assessed using the I^2 index[29], which was interpreted as follows: 0–25%, insignificant; 26–50%, low; 51–75%, moderate; > 75%, high[30]. To examine the potential influence of publication bias and small-study effects, funnel plots were obtained by plotting the logarithm of study-specific effect sizes against their corresponding standard errors. Funnel plot asymmetry was assessed using the linear regression-based method described by Egger *et al.*[31] and the adjusted rank correlation test proposed by Begg and Mazumdar[32].

To assess the robustness of the overall findings and to evaluate the impact of study-level covariates on the pooled estimates, the following sensitivity analyses planned *a priori* were conducted: (1) exclusion of cases with PDM and/or GDM; (2) assessment of the effect of study location; (3) evaluation of the effect of study design; (4) evaluation of the impact of the publication year (≤ 2013 or > 2013), taking into account advancements over the past decade in the detection of CHD and potential confounders, with the selection of the cut-off year based on the WHO criteria for GDM established in 2013; and (5) exclusion of studies reporting risk estimates for BMI categories not conforming to the WHO guidelines. Subgroup analyses were undertaken when a minimum of two studies supplied data regarding the risk of specific subtypes of CHD based on maternal BMI. Risk estimates for individual CHD subtypes were presented both as groups of defects, categorized using a severity criterion[33] and a topographic–functional criterion[34], as well as individual defects when sufficient data were available. Pooled risk estimates were provided for the following: severe CHD, according to Dolk *et al.*[33]; conotruncal defects (CTD), encompassing tetralogy of Fallot (TOF) and transposition of the great arteries (TGA); septal defects (SD), including ventricular septal defects (VSD), atrial septal defects (ASD) and atrioventricular septal defects (AVSD); left ventricular outflow tract obstruction (LVOTO), consisting of hypoplastic left heart syndrome (HLHS), aortic valve stenosis (AS) and coarctation of the aorta (CoA); right ventricular outflow tract obstruction (RVOTO), including pulmonary valve stenosis (PVS); and other defects, including single ventricle and anomalous pulmonary venous return. The certainty of the evidence for each effect estimate was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines[35]. STATA version 17 software (Stata Corp., College Station, TX, USA) was used for statistical analysis.

RESULTS

Study characteristics

After removal of duplicates, the literature search identified 3289 results, of which 31 publications were eligible for qualitative synthesis[36–66]. The selection process and reasons for exclusion are illustrated in Figure 1. The 31 studies included in the systematic review consisted of a population of 4 861 693 pregnancies, with a total of 86 136 cases of CHD. The characteristics of the included studies are presented in Table 1.

Figure S1 presents the risk-of-bias assessment for each of the included studies using the ROBINS-E tool[27,28]. Of the 31 studies, 21 (67.74%) were case–control studies and 10 (32.26%) were cohort studies. The study years ranged from 1964 to 2019, whereas the publication years ranged from 1969 to 2021, with only four studies published in the last 5 years. Most reports were from the USA (15 studies), followed by Europe (11 studies). A total of 26 studies reported data on maternal glycemic status (PDM and/or GDM).

Twenty studies were included in the meta-analysis. Of those 20 studies, only nine provided enough raw data to compute risk estimates for individual CHD subtypes, with a median number of studies included in subgroup analyses of 4 (range, 2–6). Studies included in the

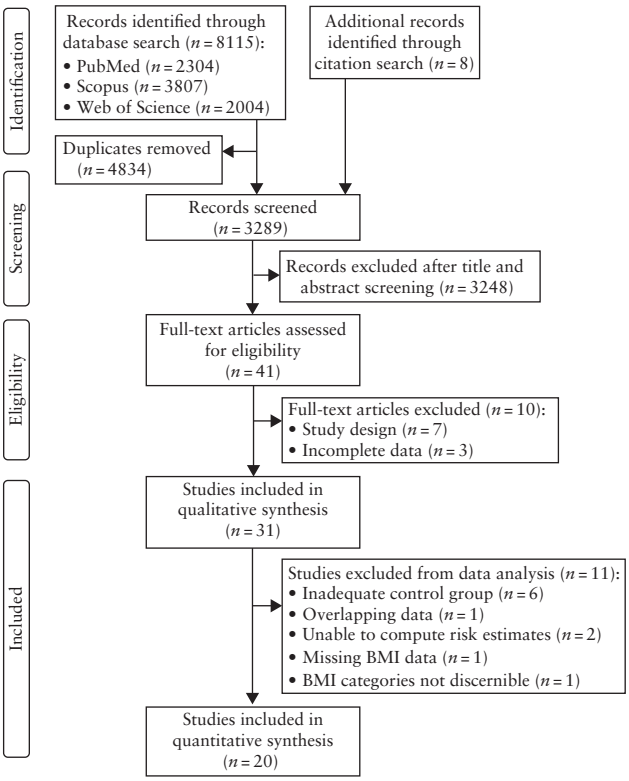

Figure 1 PRISMA flowchart summarizing inclusion of studies in systematic review and meta-analysis. BMI, body mass index.

Table 1 Characteristics of 31 studies included in systematic review

Study	*Study type*	*Study location*	*Maternal diabetes*	*Study period*	*BMI classification*	*Diagnostic approach for CHD*	*CHD subtypes*
Arias (2010)[36]	Case–control	USA	Included PDM, excluded GDM	2007–2009	Obesity: ≥ 30.0 kg/m^2	—	SD, CTD, obstructive defects
Baardman (2012)[37]	Case–control	Europe	Excluded PDM, included GDM	1997–2008	Overweight: 25.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	Neonatal examination, prenatal/postnatal echocardiography	SD, CTD, OFTD§
Block (2013)[38]	Case–control	USA	Excluded PDM, included GDM	2004–2009	Overweight: 25.0–29.9 kg/m^2; obesity class I: 30.0–34.9 kg/m^2; obesity class II: 35.0–39.9 kg/m^2; obesity class III: ≥ 40.0 kg/m^2	—	TOF, VSD, PVS, PA, TGA, HLHS, CoA, AS
Blomberg (2010)[39]	Case–control	Europe	Included PDM and GDM	1995–2007	Overweight: 25.0–29.9 kg/m^2; moderate obesity: 30.0–39.9 kg/m^2; severe obesity: ≥ 40.0 kg/m^2	Neonatal examination, postnatal echocardiography	TOF, TGA, HLHS, common truncus
Brite (2014)[40]	Cohort	USA	Excluded PDM and GDM*	2002–2008	Overweight: 25.0–29.9 kg/m^2; moderate obesity: 30.0–40.0 kg/m^2; severe obesity: ≥ 40.0 kg/m^2	—	CTD, ASD, VSD
Cedergren (2002)[41]	Case–control	Europe	—	1982–1996	Overweight: 26.0–28.9 kg/m^2; obesity: ≥ 29.0 kg/m^2	Neonatal examination	—§
Cedergren (2002)[42]	Case–control	Europe	—	1982–1996	Overweight: 26.0–28.9 kg/m^2; obesity: ≥ 29.0 kg/m^2	Neonatal examination	ASD, VSD, ECD, SV, TOF, common truncus, TGA, HLHS, PVS, CoA§
Cedergren (2003)[43]	Case–control	Europe	Excluded PDM, included GDM	1992–2001	Overweight: 26.1–29.0 kg/m^2; moderate obesity: 29.1–34.9 kg/m^2; severe obesity: ≥ 35.0 kg/m^2	Neonatal examination, postnatal echocardiography	HLHS, TOF, TGA, CoA, VSD, ASD, AVSD
Cedergren (2006)[44]	Cohort	Europe	—	1992–2001	Overweight: 25.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	Neonatal examination, postnatal echocardiography	—§
García-Patterson (2004)[45]	Cohort	Europe	All cases had GDM	1986–2002	First tertile: 15.43–21.91 kg/m^2; second tertile: 21.92–24.77 kg/m^2; third tertile: 24.78–47.07 kg/m^2	Neonatal examination	—§
Ghaderian (2014)[46]	Case–control	Middle East	Excluded PDM and GDM	2011–2012	Overweight: 25.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	—	VSD, ASD, PVA, AS, PVS, CoA, AVSD, TOF, TGA, PA, SV, tricuspid atresia§

Continued over.

Table 1 *Continued*

Study	*Study type*	*Study location*	*Maternal diabetes*	*Study period*	*BMI classification*	*Diagnostic approach for CHD*	*CHD subtypes*
Gilboa (2010)[47]	Case–control	USA	Excluded PDM, included GDM	1997–2004	Overweight: 25.0–29.9 kg/m^2; moderate obesity: 30.0–34.9 kg/m^2; severe obesity: ≥ 35.0 kg/m^2	Postnatal echocardiography, cardiac surgery	EBS, CTD, OFTD, HLHS, PA, SV, TOF, TGA, APVR, AS, PVS, AVSD, SD, CoA, VSD, ASD
Khalil (2008)[48]	Case–control	Middle East	Excluded PDM and GDM	1998–2005	Overweight: 25.0–29.9 kg/m^2; moderate obesity: 30.0–34.9 kg/m^2; severe obesity: ≥ 35.0 kg/m^2†	Neonatal examination, postnatal echocardiography	ASD, VSD, PA, PVA, AS, PVS, CoA, TOF, TGA, complete heart block, EBS, hypoplastic right heart§
Madsen (2013)[49]	Case–control	USA	Excluded PDM, included GDM	1992–2007	Overweight: 25.0–29.9 kg/m^2; moderate obesity: 30.0–34.9 kg/m^2; severe obesity: ≥ 35.0 kg/m^2	Postnatal echocardiography	ASD, VSD, AVSD, ECD, CoA, HLHS, TGA, TOF, PVS, LVOTO, PA, obstructive defects, DORV, EBS, SV, coronary artery anomaly, APVR, PVA§
Martínez-Frías (2005)[50]	Case–control	Europe	Excluded PDM and GDM	1976–2001	Overweight: 25.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	Neonatal examination	—§
Mikhail (2002)[51]	Cohort	USA	Excluded PDM and GDM	1981–1994	Obesity: ≥ 27.0 kg/m^2	—	HLHS, TOF, TGA, DORV
Mills (2010)[52]	Case–control	USA	Excluded PDM and GDM	1993–2003	Overweight: 25.0–29.9 kg/m^2; moderate obesity: 30.0–39.9 kg/m^2; severe obesity: ≥ 40.0 kg/m^2	—	HLHS, CTD, TOF, TGA, CoA, DORV, PVS, OFTD, APVR, AS, SD, VSD, ASD, AVSD
Moore (2000)[53]	Cohort	USA	Excluded PDM and GDM	1984–1987	Obesity: ≥ 28.0 kg/m^2	—	HLHS, SD
Oddy (2009)[54]	Case–control	Australia	—	1997–2000	Overweight: 25.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	Postnatal echocardiography	CTD
Persson (2017)[55]	Cohort	Europe	Included PDM and GDM	2001–2014	Overweight: 25.0–29.9 kg/m^2; obesity class I: 30.0–34.9 kg/m^2; obesity class II: 35.0–39.9 kg/m^2; obesity class III: ≥ 40.0 kg/m^2	Neonatal examination, prenatal and postnatal echocardiography	—§
Persson (2019)[56]	Cohort	Europe	Included PDM and GDM*	1992–2012	Overweight: 25.0 29.9 kg/m^2; obesity class I: 30.0–34.9 kg/m^2; obesity class II: 35.0–39.9 kg/m^2; obesity class III: ≥ 40.0 kg/m^2	Neonatal examination, prenatal and postnatal echocardiography	TOF, TGA, AVSD, aortic arch defects, SV, ASD, VSD, PVA, valve defects, right ventricular defects
Richards (1969)[57]	Case–control	Europe	—	1964–1966	—	—	SD, PVA, aortic anomalies

Continued over.

Table 1 *Continued*

Study	*Study type*	*Study location*	*Maternal diabetes*	*Study period*	*BMI classification*	*Diagnostic approach for CHD*	*CHD subtypes*
Rutkowski (2021)[58]	Cohort	USA	Excluded PDM, included GDM	2005–2016	Overweight: 25.0–29.9 kg/m^2; obesity class I: 30.0–34.9 kg/m^2; obesity class II: 35.0–39.9 kg/m^2; obesity class III: ≥ 40.0 kg/m^2	—	Truncus arteriosus, HLHS, TOF, PA, TGA, APVR, RVOTO, EBS, CoA, SV§
Shaw (2000)[59]	Cohort	USA	Included PDM and/or GDM	1987–1988	Obesity: ≥ 29.0 kg/m^2	Neonatal examination	—§
Shaw (2008)[60]	Case–control	USA	Excluded PDM and GDM	1999–2004	Overweight: 25.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	Postnatal echocardiography	TGA, TOF
Waller (1994)[61]	Case–control	USA	Excluded PDM, included GDM	1985–1987	Overweight: 27.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	Prenatal ultrasonography	—§
Waller (2007)[62]	Case–control	USA	Excluded PDM, included GDM	1997–2002	Overweight: 25.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	Postnatal echocardiography	—§
Watkins (2001)[63]	Case–control	USA	Excluded PDM and GDM	1968–1980	Overweight: 26.1–28.9 kg/m^2; obesity: ≥ 29.0 kg/m^2	Neonatal examination	OFTD, TGA, TOF, ASD, VSD§
Watkins (2003)[64]	Case–control	USA	Excluded PDM, GDM not specified	1993–1997	Overweight: 25.0–29.9 kg/m^2; obesity: ≥ 30.0 kg/m^2	Neonatal examination	LVOTO, HLHS, CoA, RVOTO, ASD, VSD, TOF, TGA, OFTD
Wu (2022)[65]	Cohort	China	Included PDM and GDM	2017–2019	Overweight: 24.0–27.9 kg/m^2; obesity: ≥ 28.0 kg/m^2‡	Prenatal echocardiography, pediatric neonatal examination	Heterotaxia, CTD, AVSD, APVR, LVOTO, RVOTO, SD and complex CHD§
Yuan (2020)[66]	Case–control	China	Excluded PDM and GDM	2010–2015	Overweight: ≥ 24.0 kg/m^2‡	Prenatal and postnatal echocardiography	SD, VSD, CTD, LVOTO, RVOTO, APVR

Only first author of each study is given. *Subgroup analysis for subtype of congenital heart defect (CHD) was reported excluding pregestational diabetes mellitus (PDM). †Study reported comparisons between obese and normal weight only. ‡Non-standard ranges for body mass index (BMI) categories due to ethnicity. §Excluded from subgroup analysis because of lack of or insufficient raw data to compute risk estimates for individual CHDs. APVR, anomalous pulmonary venous return; AS, aortic valve stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; CTD, conotruncal defect; DORV, double outlet right ventricle; EBS, Ebstein's anomaly; ECD, endocardial cushion defect; GDM, gestational diabetes mellitus; HLHS, hypoplastic left heart syndrome; LVOTO, left ventricular outflow tract obstruction; OFTD, outflow tract defect; PA, pulmonary atresia; PVA, pulmonary valve atresia; PVS, pulmonary valve stenosis; RVOTO, right ventricular outflow tract obstruction; SD, septal defects; SV, single ventricle; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

systematic review but excluded from the meta-analysis are detailed in Table S1.

Findings from meta-analysis

The quantitative findings for the risk of CHD subtypes across BMI categories are presented in Figures 2, 3 and S2. Table S2 summarizes the GRADE evidence profile for quality assessment.

Maternal overweight BMI was associated with a pooled OR of 1.05 (95% CI, 1.03–1.07) when compared with the reference category. The analysis showed low heterogeneity ($I^2 = 30.62\%$) and non-significant publication bias (Begg's test, $P = 0.327$; Egger's test, $P = 0.052$). The risk estimate for pregnant women with obesity compared with the reference category was higher than that for overweight BMI (pooled OR, 1.42 (95% CI, 1.18–1.70)), despite high heterogeneity ($I^2 = 97.94\%$) and some evidence of publication bias (Begg's test, $P = 0.002$; Egger's test, $P = 0.888$). Pooled OR for women with moderate and severe obesity compared with the reference category were 1.15 (95% CI, 1.11–1.20) and 1.39 (95% CI, 1.27–1.53), respectively. Heterogeneity was low for the analysis of women with moderate obesity ($I^2 = 47.69\%$) and higher for the estimate of severe obesity ($I^2 = 74.39\%$). No publication bias was detected in either of the two comparisons.

Table 2 summarizes the results of sensitivity analyses stratified by study attribute to identify sources of heterogeneity. The pooled effect estimates yielded a similar trend to that of the main analysis, with an overall decrease in heterogeneity. The analysis specifically restricted to study populations excluding PDM determined the OR of CHD for pregnant women considered overweight and those with obesity, moderate obesity and severe obesity to be 1.06 (95% CI, 1.03–1.10), 1.26 (95% CI, 1.22–1.30), 1.17 (95% CI, 1.13–1.23) and 1.48 (95% CI, 1.39–1.57), respectively.

Subgroup analyses

Subgroup analyses of BMI categories and individual CHD subtypes are reported in Table 3 and Figure S3. Compared with the reference category, women with obesity showed a significantly higher risk of severe CHD (pooled OR, 1.48 (95% CI, 1.03–2.13)). Moreover, this risk increased progressively from moderate to severe obesity (pooled OR, 1.18 (95% CI, 1.10–1.27) and 1.45 (95% CI, 1.25–1.68), respectively).

All categories of increased BMI were associated with a significantly higher risk of CTD, with a trend toward progressively increasing risk with rising BMI. Particularly, the severe obesity category was associated with an elevated risk of both TGA (pooled OR, 1.39 (95% CI, 1.10–1.74)) and, to an even greater extent, TOF (pooled OR, 1.72 (95% CI, 1.38–2.16)).

Increased BMI categories were also associated with a significantly higher risk of LVOTO. In particular, all increased BMI categories were associated with an elevated risk of HLHS, again with a progressive effect. None of the BMI categories was associated with an increased risk of AS.

All categories of increased BMI were associated with a significantly higher risk of RVOTO, with pooled OR progressively escalating as BMI increased. Of note, the risk of PVS increased for all BMI categories, again with a progressive effect.

Compared with the reference category, women with moderate and severe obesity had a significantly higher overall risk of SD. Specifically, the risk of VSD and AVSD increased only in women with severe obesity, whereas the risk of ASD increased in all categories of increased BMI.

DISCUSSION

Main findings

This systematic review and meta-analysis found a progressive increase in the risk of CHD in offspring with rising maternal prepregnancy BMI (overweight to moderate obesity to severe obesity), compared with pregnancy with normal weight. When women with PDM and/or GDM were excluded from the analysis, the association persisted, emphasizing the effect of increased adiposity (as measured by BMI) on the risk of CHD, even in the absence of glycemic alteration. Not only was the combined risk of CHD elevated, but also several specific subtypes of CHD exhibited a trend of progressively increasing risk as maternal BMI increased.

Interpretation

The mechanism by which maternal obesity influences crucial phases of cardiac development is likely to be multifactorial. First, the impact of maternal obesity on fetal cardiac development is linked closely to alterations in the metabolic environment. Pregnant women with obesity exhibit elevated concentrations of glucose and insulin, and these molecules can cross the placental barrier, exerting an impact on fetal development[67]. It is possible that some of the effects of obesity may be mediated by teratogenic processes, promoted by glycemic dysregulation during embryonic development. Moreover, a wide range of metabolic abnormalities are present in women with obesity, including dyslipidemia and oxidative stress[68]. Obesity is associated closely with a state of chronic low-grade inflammation, which can give rise to the generation of reactive oxygen species, ultimately exerting detrimental effects on cells and tissues. Placental villous tissues from overweight and obese women were found to have a 6- and 14-fold increase in reactive oxygen species production, respectively[69]. Exposure to this oxidative stress during fetal development can interfere with normal heart development.

Maternal obesity can directly influence the functionality of the placenta, which has been identified as a contributing factor to the changes in fetal growth and organ development associated with maternal obesity[70]. Women with obesity exhibit inefficient placental blood flow and

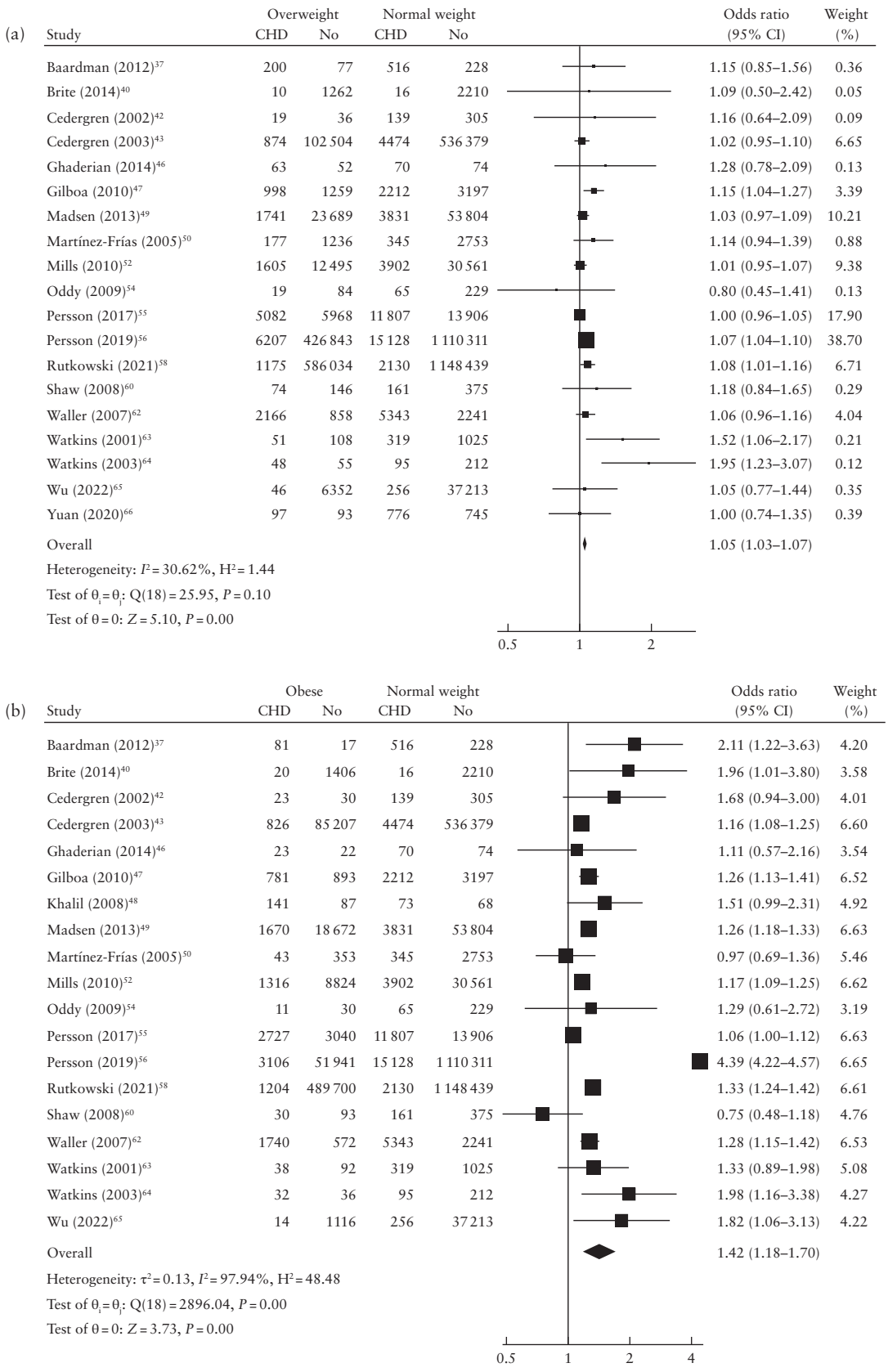

Figure 2 Forest plots showing risk of congenital heart defect (CHD) according to maternal body mass index category: (a) overweight; and (b) obesity. Only first author is given for each study.

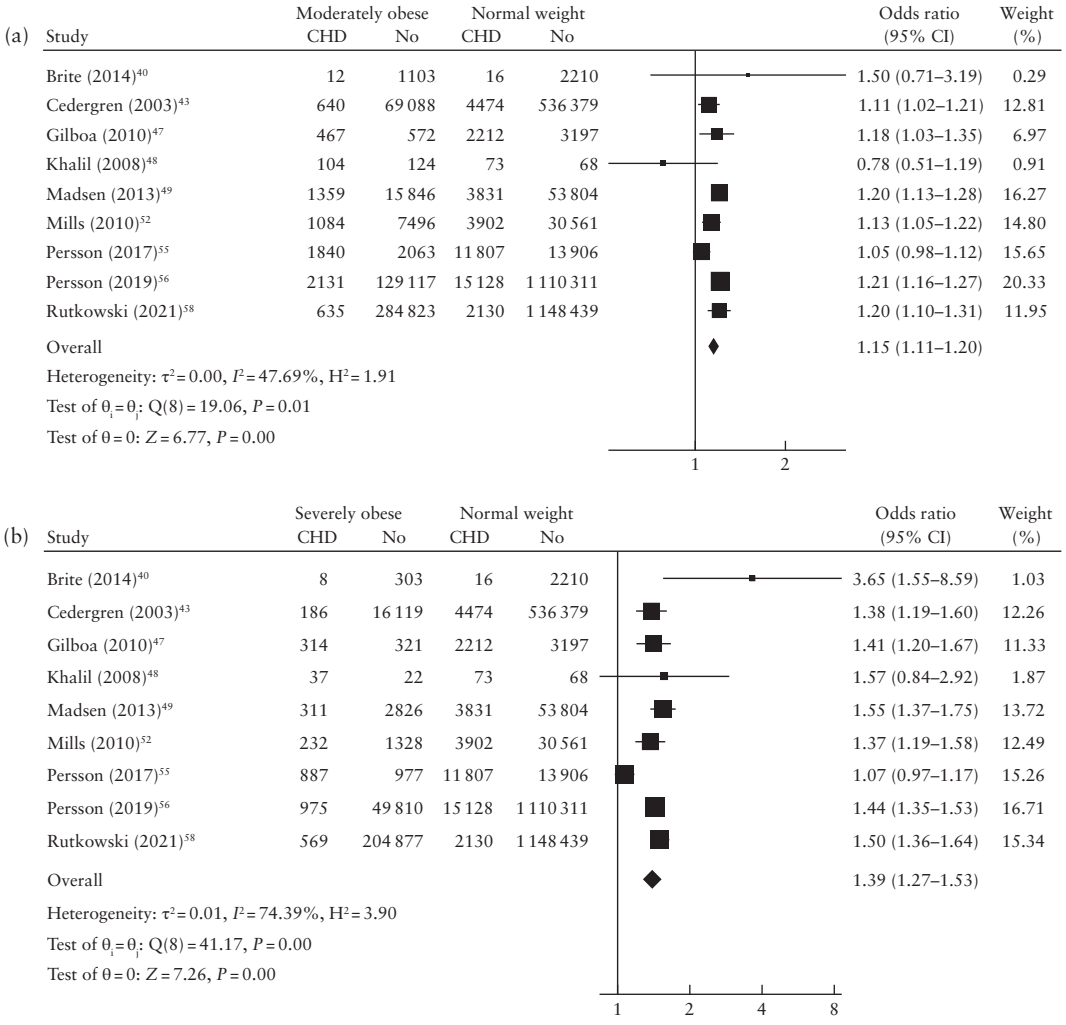

Figure 3 Forest plots showing risk of congenital heart defect (CHD) according to maternal body mass index category: (a) moderate obesity; and (b) severe obesity. Only first author is given for each study.

compromised delivery of oxygen and nutritional factors that are important for fetal cardiac development[71].

In addition, women with obesity frequently exhibit diminished levels of circulating adiponectin during pregnancy[72], which has been linked to the development of placental insulin resistance[73] and increased placental nutrient transfer[74]. This is particularly significant because cardiac development primarily occurs during the first trimester, a period in which the fetus is unable to regulate glucose. Therefore, the fetus may be particularly vulnerable to adiponectin-related dysfunction in placental glucose transport of women with obesity during this critical window.

Strengths and limitations

Our meta-analysis has several strengths. First, it provides an up-to-date summary of the available evidence, which is important for monitoring disease trends over time. Previous meta-analyses have suggested a higher risk of CHD with an increasing maternal BMI[12,15]. However, inconsistent findings emerged as a result of the limited number of published reports at that time, significant heterogeneity in comparisons, and residual confounding by maternal glycemic status. Second, we employed rigorous methods for data synthesis, including extensive methods to pool individual data and assess heterogeneity and publication bias. Third, we stratified results according to several covariates, including maternal diabetes, to control for potential confounders. Finally, we explored the association between maternal BMI and several subtypes of CHD, representing, to our knowledge, the most extensive investigation of this topic to date. Additionally, by adopting severity and topographic–functional criteria when summarizing estimates, we enhanced the feasibility of applying our findings in a clinical setting.

There are also some limitations. First, the GRADE quality assessment rated most comparisons as low to very low, because of the inclusion of case–control studies, which offer less reliable risk estimates than prospective population-based studies. Additionally, the studies included may have underestimated the prevalence of CHD in the population, considering that non-critical CHD may not cause symptoms at birth and might only be diagnosed later in life. Furthermore, decreased sensitivity of ultrasound for cardiac anatomy has been

Table 2 Sensitivity analyses for maternal body mass index (BMI) categories and risk of all congenital heart defects (CHD)

Maternal BMI category	*Studies* (n)	*Pooled OR (95% CI)*	I^2 *(%)*	P
Overweight				
Overall	19*	1.05 (1.03–1.07)	30.62	0.001
Diabetes				
Excluded PDM and GDM	7*	1.03 (0.98–1.09)	21.44	0.236
Excluded only PDM	7*	1.06 (1.03–1.10)	0	0.001
Study location				
USA	9*	1.04 (1.01–1.08)	23.82	0.017
Europe	6*	1.06 (1.02–1.10)	16.28	0.002
China	2*	1.03 (0.82–1.27)	0	0.820
Study design				
Case–control	14*	1.06 (1.02–1.08)	29.41	0.003
Cohort	5*	1.05 (1.95–3.25)	0	0.009
Publication year				
≤ 2013	12*	1.05 (1.02–1.10)	22.69	0.001
> 2013	7*	1.04 (1.03–1.07)	8.59	0.001
BMI cut-off				
> 25 kg/m^2	14*	1.05 (1.03–1.07)	19.89	0.001
> 26 kg/m^2	3		0	0.275
Obesity				
Overall	19†	1.42 (1.18–1.70)	97.94	0.001
Diabetes				
Excluded PDM and GDM	7*	1.16 (1.09–1.24)	33.51	0.001
Excluded only PDM	7*	1.26 (1.22–1.30)	23.08	0.001
Study location				
USA	9†	1.63 (1.04–2.54)	99.32	0.033
Europe	6*	1.25 (1.21–1.29)	21.47	0.001
Middle East	2*	1.38 (0.96–1.97)	0	0.078
Study design				
Case–control	14*	1.22 (1.17–1.26)	5.19	0.001
Cohort	5†	1.85 (1.15–2.98)	99.42	0.011
Publication year				
≤ 2013	13*	1.22 (1.17–1.27)	14.35	0.001
> 2013	6†	1.73 (1.08–2.75)	99.36	0.022
BMI cut-off				
> 29 kg/m^2	3*	1.17 (1.09–1.26)	0	0.001
> 30 kg/m^2	15†	1.42 (1.13–1.77)	98.46	0.002
Moderate obesity				
Overall	9†	1.15 (1.11–1.20)	47.69	0.001
Diabetes				
Excluded PDM and GDM	3*	1.12 (1.05–1.20)	39.61	0.001
Excluded only PDM	4*	1.17 (1.13–1.23)	0	0.001
Study location				
USA	5†	1.13 (1.03–1.23)	81.34	0.007
Europe	3*	1.18 (1.13–1.23)	0	0.001
Middle East	1	—	—	—
Study design				
Case–control	5†	1.16 (1.06–1.27)	76.12	0.002
Cohort	4*	1.15 (1.10–1.20)	14.24	0.001
Publication year				
≤ 2013	5*	1.15 (1.11–1.20)	35.32	0.001
> 2013	4†	1.16 (1.06–1.27)	76.12	0.001
Severe obesity				
Overall	9†	1.39 (1.27–1.53)	74.39	0.001
Diabetes				
Excluded PDM and GDM	3*	1.41 (1.23–1.62)	0	0.001
Excluded only PDM	4*	1.48 (1.39–1.57)	0	0.001
Study location				
USA	5†	1.28 (1.06–1.55)	90.92	0.008
Europe	3*	1.48 (1.39–1.57)	0	0.001
Middle East	1	—	—	—
Study design				
Case–control	5†	1.42 (1.02–2.12)	95.31	0.008
Cohort	4*	1.44 (1.34–1.54)	0	0.001
Publication year				
≤ 2013	5*	1.44 (1.34–1.54)	0	0.001
> 2013	4†	1.42 (1.10–1.84)	95.31	0.008

*Fixed-effects. †Random-effects. GDM, gestational diabetes mellitus; OR, odds ratio; PDM, pregestational diabetes mellitus.

Table 3 Subgroup analyses for maternal body mass index categories and risk of subtypes of congenital heart defect (CHD)

CHD	*Studies* (n)	*Cases* (n)	*Pooled OR (95% CI)*	I^2 *(%)*	P	*Publication bias*		*GRADE quality*
						Egger's	*Begg's*	
Severe CHD								
Overweight*	9	7607	1.27 (0.95–1.69)	95.31	0.10	0.254	0.251	Very low
Obesity*	8	6988	1.48 (1.03–2.13)	96.34	0.03	0.909	0.266	Very low
Moderate obesity†	5	6541	1.18 (1.10–1.27)	0	0.001	0.497	0.807	Low
Severe obesity*	5	5923	1.45 (1.25–1.68)	39.47	0.001	0.599	1.000	Low
Conotruncal								
All CTD								
Overweight*	9	3704	1.09 (1.01–1.17)	42.57	0.02	0.437	0.917	Low
Obesity*	8	3331	1.48 (1.01–2.16)	93.26	0.04	0.990	0.266	Very low
Moderate obesity†	5	3088	1.10 (1.00–1.23)	0	0.06	0.397	0.221	Low
Severe obesity†	5	2839	1.52 (1.31–1.77)	6.30	0.001	0.770	1.000	Low
TGA								
Overweight†	6	1679	1.04 (0.93–1.16)	8.78	0.46	0.436	1.000	Low
Obesity*	6	1474	1.35 (0.77–2.37)	92.26	0.30	0.528	1.0000	Very low
Moderate obesity†	4	1377	1.01 (0.86–1.20)	20.94	0.86	0.633	0.734	Very low
Severe obesity*	4	1291	1.39 (1.10–1.74)	65.33	0.01	0.264	1.000	Very low
TOF								
Overweight†	6	1417	1.10 (0.98–1.24)	16.70	0.11	0.924	1.000	Low
Obesity*	6	1281	1.48 (0.94–2.32)	88.22	0.09	0.733	0.707	Very low
Moderate obesity†	4	11173	1.08 (0.91–1.28)	0	0.36	0.185	0.089	Low
Severe obesity†	4	1100	1.72 (1.38–2.16)	5.20	0.001	0.633	0.308	Low
Left outflow								
All LVOTO								
Overweight*	6	1815	1.57 (1.04–2.37)	92.05	0.03	0.001	0.133	Very low
Obesity*	5	1677	1.77 (1.03–3.04)	94.34	0.04	0.497	0.691	Very low
Moderate obesity†	4	1582	1.38 (1.22–1.58)	0	0.001	0.734	0.448	Low
Severe obesity*	4	1369	1.27 (1.02–1.58)	57.78	0.03	0.089	0.194	Very low
HLHS								
Overweight†	4	490	1.31 (1.08–1.59)	0	0.01	0.301	0.089	Low
Obesity†	4	467	1.51 (1.23–1.86)	0	0.001	0.308	0.242	Low
Moderate obesity†	3	434	1.54 (1.21–1.94)	0	0.001	0.450	1.000	Low
Severe obesity†	3	374	1.56 (1.08–2.27)	0	0.02	0.297	1.000	Low
CoA								
Overweight†	4	575	1.17 (0.98–1.40)	29.80	0.09	0.040	0.089	Extremely low
Obesity†	4	534	1.24 (1.01–1.51)	0	0.04	0.389	0.734	Low
Moderate obesity†	4	507	1.29 (1.03–1.60)	0	0.03	0.815	1.000	Low
Severe obesity†	4	429	1.04 (0.69–1.56)	17.45	0.86	0.225	0.296	Very low
AS								
Overweight†	2	254	0.99 (0.75–1.30)	22.09	0.93	0.257	—‡	Very low
Obesity*	2	285	1.63 (0.43–6.12)	95.43	0.47	0.001	—‡	Extremely low
Moderate obesity*	2	243	1.48 (0.78–2.81)	75.53	0.23	0.043	—‡	Extremely low
Severe obesity*	2	194	1.02 (0.35–2.96)	66.33	0.97	0.014	—‡	Extremely low
Right outflow								
All RVOTO								
Overweight†	5	1894	1.25 (1.13–1.38)	21.71	0.001	0.076	0.221	Low
Obesity*	4	1706	2.03 (1.01–4.09)	96.66	0.049	0.689	0.308	Extremely low
Moderate obesity†	3	1582	1.37 (1.21–1.56)	0	0.001	0.552	0.296	Low
Severe obesity†	3	1393	1.63 (1.34–1.98)	0	0.001	0.304	0.296	Low
PVS								
Overweight†	2	957	1.26 (1.09–1.44)	23.04	0.001	0.254	—‡	Very low
Obesity†	2	896	1.44 (1.24–1.67)	0	0.001	0.729	—‡	Low
Moderate obesity†	2	821	1.33 (1.13–1.58)	3.79	0.001	0.308	—‡	Low
Severe obesity*	2	710	1.79 (1.39–2.30)	50.39	0.001	0.156	—‡	Very low
Septal								
All SD								
Overweight*	7	25 704	1.06 (0.99–1.12)	54.80	0.07	0.004	0.133	Very low
Obesity*	6	22 947	1.60 (1.06–2.40)	98.98	0.02	0.799	0.452	Very low
Moderate obesity†	5	21 754	1.14 (1.09–1.19)	9.45	0.001	0.708	0.807	Low
Severe obesity†	5	19 842	1.38 (1.30–1.47)	0	0.001	0.957	1.000	Low
VSD								
Overweight†	7	15 758	1.00 (0.96–1.03)	0	0.93	0.180	0.548	Low
Obesity*	6	13 955	1.48 (0.96–2.30)	98.43	0.08	0.851	0.452	Extremely low

Continued over.

Table 3 *Continued*

CHD	*Studies* (n)	*Cases* (n)	*Pooled OR (95% CI)*	I^2 *(%)*	P	*Publication bias*		*GRADE quality*
						Egger's	*Begg's*	
Moderate obesity*	5	13 347	1.05 (0.98–1.13)	36.75	0.19	0.604	0.882	Very low
Severe obesity†	5	12 195	1.16 (1.06–1.26)	0	0.001	0.314	0.462	Low
ASD								
Overweight*	6	9077	1.12 (1.04–1.21)	39.94	0.001	0.247	0.707	Low
Obesity*	6	8169	1.84 (1.11–3.03)	98.27	0.02	0.793	0.452	Extremely low
Moderate obesity†	5	7624	1.30 (1.23–1.39)	0	0.001	0.513	1.000	Low
Severe obesity*	5	6887	1.71 (1.48–1.97)	42.05	0.001	0.866	1.000	Low
AVSD								
Overweight†	4	1316	0.92 (0.80–1.05)	0	0.20	0.423	0.734	Low
Obesity*	4	1260	1.50 (0.73–3.09)	94.43	0.27	0.365	1.000	Extremely low
Moderate obesity†	4	1200	1.05 (0.89–1.25)	0	0.56	0.179	0.089	Low
Severe obesity†	4	1112	1.47 (1.13–1.91)	0	0.001	0.708	0.308	Low
Other								
SV								
Overweight†	2	400	1.04 (0.84–1.30)	0	0.71	0.434	—‡	Very low
Obesity*	2	357	2.25 (0.42–12.03)	97.41	0.35	0.001	—‡	Extremely low
Moderate obesity*	2	335	1.24 (0.76–2.04)	59.01	0.39	0.118	—‡	Extremely low
Severe obesity†	2	307	1.20 (0.78–1.86)	0	0.41	0.372	—‡	Very low
APVR								
Overweight†	3	195	1.25 (0.39–4.04)	89.00	0.71	0.048	1.000	Extremely low
Obesity*	2	193	1.11 (0.66–1.87)	56.27	0.69	0.313	—‡	Extremely low
Moderate obesity*	2	181	1.14 (0.78–1.66)	17.84	0.51	0.271	—‡	Very low
Severe obesity†	2	159	1.26 (0.68–2.32)	0	0.46	0.176	—‡	Very low

*Random effects. †Fixed effects. ‡Insufficient observations. APVR, anomalous pulmonary venous return; AS, aortic valve stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; CTD, conotruncal defect; HLHS, hypoplastic left heart syndrome; LVOTO, left ventricular outflow tract obstruction; OR, odds ratio; PVS, pulmonary valve stenosis; RVOTO, right ventricular outflow tract obstruction; SD, septal defect; SV, single ventricle; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

documented in women with obesity, which may lead to underdiagnosis[75]. BMI estimations in many included studies were based on self-reported retrospective data, which can be subject to recall bias. Variations in case ascertainment and classification methods across studies may also have influenced the results. Additionally, the sensitivity analyses excluding diabetes might not have completely accounted for glycemic variations in the original study populations, given that these studies did not specify levels of glycemic control. Further exploration of infertility and the use of assisted reproductive technologies could have provided additional insights into the association of obesity and CHD within specific study populations[76]. However, only one study[65] included in our analysis reported on the mode of conception, offering insufficient data for generating pooled estimates. A further limitation is the varied definition of CHD subtypes, a common issue due to the lack of a universally endorsed prenatal classification system[77]. We endeavored to adhere to the 11th revision of the International Classification of Diseases (ICD-11) criteria (https://icd.who.int/en). However, as older studies did not define the defects with the same level of detail, universally adopted classifications based upon severity and topography were chosen[33,34].

Conclusions

CHD is a significant and emerging global issue in child health[78]. This meta-analysis confirms the association between maternal obesity and CHD, underlining the importance of public health measures while calling for more research into the mechanisms behind this relationship. It is crucial for women of childbearing age to be aware of the adverse effects of elevated BMI. As obesity is a potentially modifiable risk factor, lifestyle interventions, such as weight management, increased physical activity and a healthy diet, can be suggested as a preventive strategy for CHD. Moreover, early CHD detection is crucial for proper management and planning[79]. This includes early identification and prompt referral to a tertiary center for optimal delivery and neonatal treatment[80,81], which is essential to enhance survival and the long-term outcome[82].

We recommend classifying obesity as a high-risk pregnancy, with the aim that fetal ultrasound cardiac monitoring and early referral for echocardiography may prompt CHD detection[79]. Regarding optimal timing, some experts recommend transvaginal cardiac screening for obese women between 13 and 16 weeks' gestation because of enhanced visualization[83,84]. This approach may improve early CHD diagnosis and management, although its performance and cost-effectiveness require further study. Additionally, in women with severe obesity and suboptimal cardiac views, fetal cardiovascular magnetic resonance imaging may be considered in later stages of pregnancy[85].

ACKNOWLEDGMENT

Open access funding was provided by BIBLIOSAN.

REFERENCES

1. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins–Obstetrics. Obesity in pregnancy: ACOG practice bulletin, number 230. *Obstet Gynecol*. 2021;137(6):e128-e144.
2. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:1-253.
3. Zeitlin J, Alexander S, Barros H, et al. Perinatal health monitoring through a European lens: eight lessons from the Euro-Peristat report on 2015 births. *BJOG*. 2019;126(13):1518-1522.
4. Driscoll AK, Gregory ECW. Increases in prepregnancy obesity: United States, 2016-2019. *NCHS Data Brief*. 2020;392:1-8.
5. Creanga AA, Catalano PM, Bateman BT. Obesity in pregnancy. *N Engl J Med*. 2022;387(3):248-259.
6. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril*. 2008;90(3):714-726.
7. Chu SY, Callaghan WM, Kim SY, et al. Maternal obesity and risk of gestational diabetes mellitus. *Diabetes Care*. 2007;30(8):2070-2076.
8. Wang Z, Wang P, Liu H, et al. Maternal adiposity as an independent risk factor for pre-eclampsia: a meta-analysis of prospective cohort studies. *Obes Rev*. 2013;14(6):508-521.
9. Vats H, Saxena R, Sachdeva MP, Walia GK, Gupta V. Impact of maternal pre-pregnancy body mass index on maternal, fetal and neonatal adverse outcomes in the worldwide populations: a systematic review and meta-analysis. *Obes Res Clin Pract*. 2021;15(6):536-545.
10. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet*. 2011;377(9774):1331-1340.
11. Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. *JAMA*. 2014;311(15):1536-1546.
12. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA*. 2009;301(6):636-650.
13. Rasmussen SA, Chu SY, Kim SY, Schmid CH, Lau J. Maternal obesity and risk of neural tube defects: a metaanalysis. *Am J Obstet Gynecol*. 2008;198(6):611-619.
14. Stott-Miller M, Heike CL, Kratz M, Starr JR. Increased risk of orofacial clefts associated with maternal obesity: case-control study and Monte Carlo-based bias analysis. *Paediatr Perinat Epidemiol*. 2010;24(5):502-512.
15. Cai GJ, Sun XX, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. *Am J Obstet Gynecol*. 2014;211(2):91-117.
16. Zheng Z, Yang T, Chen L, et al. Increased maternal Body Mass Index is associated with congenital heart defects: an updated meta-analysis of observational studies. *Int J Cardiol*. 2018;273:112-120.
17. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58(21):2241-2247.
18. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890-1900.
19. Lopez KN, Baker-Smith C, Flores G, et al. Addressing social determinants of health and mitigating health disparities across the lifespan in congenital heart disease: a scientific statement from the American Heart Association (published correction appears in J Am Heart Assoc. 2022;11(8):e020758). *J Am Heart Assoc*. 2022;11(8):e025358.
20. AIUM practice parameter for the performance of fetal echocardiography. *J Ultrasound Med*. 2020;39(1):E5-E16.
21. Carvalho JS, Axt-Fliedner R, Chaoui R, et al. ISUOG Practice Guidelines (updated): fetal cardiac screening. *Ultrasound Obstet Gynecol*. 2023;61(6):788-803.
22. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation*. 2014;129(21):2183-2242.
23. Helle E, Priest JR. Maternal obesity and diabetes mellitus as risk factors for congenital heart disease in the offspring. *J Am Heart Assoc*. 2020;9(8):e011541.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269. W64.
25. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012.
26. Giri A, Hartmann KE, Hellwege JN, Velez Edwards DR, Edwards TL. Obesity and pelvic organ prolapse: a systematic review and meta-analysis of observational studies. *Am J Obstet Gynecol*. 2017;217(1):11-26.e3.
27. Deeks JJ, Higgins JP, Altman DG, Cochrane Statistical Methods Group. In: Higgins JPT et al., eds. *Assessing Risk of Bias in a Non-Randomized Study in Cochrane Handbook for Systematic Reviews of Interventions Version 6.3*. The Cochrane Collaboration; 2022 Accessed April 27, 2023. https://training.cochrane.org/handbook/current/chapter-25
28. Higgins JP, ROBINS-E Development Group. Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E). Launch version, 1. 2022 Accessed April 27, 2023. https://www.riskofbias.info/welcome/robins-e-tool
29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
30. Salmeri N, Li Piani L, Cavoretto PI, Somigliana E, Viganò P, Candiani M. Endometriosis increases the risk of gestational diabetes: a meta-analysis stratified by mode of conception, disease localization and severity. *Sci Rep*. 2023;13(1):8099.
31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
32. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101.
33. Dolk H, Loane M, Garne E, European Surveillance of Congenital Anomalies (EUROCAT) Working Group. Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005. *Circulation*. 2011;123(8):841-849.
34. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A, National Birth Defects Prevention Study. Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. *Birth Defects Res A Clin Mol Teratol*. 2007;79(10):714-727.
35. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
36. Arias W, Viner-Brown S. Prepregnancy obesity and birth defects in Rhode Island. *Med Health R I*. 2010;93(10):325-326.
37. Baardman ME, Kerstjens-Frederikse WS, Corpeleijn E, et al. Combined adverse effects of maternal smoking and high body mass index on heart development in offspring: evidence for interaction? *Heart*. 2012;98(6):474-479.
38. Block SR, Watkins SM, Salemi JL, et al. Maternal pre-pregnancy body mass index and risk of selected birth defects: evidence of a dose-response relationship. *Paediatr Perinat Epidemiol*. 2013;27(6):521-531.
39. Blomberg MI, Källén B. Maternal obesity and morbid obesity: the risk for birth defects in the offspring. *Birth Defects Res A Clin Mol Teratol*. 2010;88(1):35-40.
40. Brite J, Laughon SK, Troendle J, Mills J. Maternal overweight and obesity and risk of congenital heart defects in offspring (published correction appears in Int J Obes (Lond). 2014;38(6):886). *Int J Obes (Lond)*. 2014;38(6):878-882.
41. Cedergren M, Selbing A, Källén B. Geographic variations in possible risk factors for severe cardiac malformations. *Acta Paediatr*. 2002;91(2):222-228.
42. Cedergren MI, Selbing AJ, Källén BA. Risk factors for cardiovascular malformation--a study based on prospectively collected data. *Scand J Work Environ Health*. 2002;28(1):12-17.
43. Cedergren MI, Källén BA. Maternal obesity and infant heart defects. *Obes Res*. 2003;11(9):1065-1071.
44. Cedergren MI, Källén BA. Obstetric outcome of 6346 pregnancies with infants affected by congenital heart defects. *Eur J Obstet Gynecol Reprod Biol*. 2006;125(2):211-216.
45. García-Patterson A, Erdozain L, Ginovart G, et al. In human gestational diabetes mellitus congenital malformations are related to pre-pregnancy body mass index and to severity of diabetes. *Diabetologia*. 2004;47(3):509-514.
46. Ghaderian M, Emami-Moghadam AR, Khalilian MR, Riahi K, Ghaedi F. Prepregnancy maternal weight and body mass index of children with and without congenital heart disease. *Iran J Pediatr*. 2014;24(3):313-318.
47. Gilboa SM, Correa A, Botto LD, et al. Association between prepregnancy body mass index and congenital heart defects. *Am J Obstet Gynecol*. 2010;202(1):51.e1-51.e10.
48. Khalil HS, Saleh AM, Subhani SN. Maternal obesity and neonatal congenital cardiovascular defects. *Int J Gynaecol Obstet*. 2008;102(3):232-236.
49. Madsen NL, Schwartz SM, Lewin MB, Mueller BA. Prepregnancy body mass index and congenital heart defects among offspring: a population-based study. *Congenit Heart Dis*. 2013;8(2):131-141.
50. Martínez-Frías ML, Frías JP, Bermejo E, Rodríguez-Pinilla E, Prieto L, Frías JL. Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. *Diabet Med*. 2005;22(6):775-781.
51. Mikhail LN, Walker CK, Mittendorf R. Association between maternal obesity and fetal cardiac malformations in African Americans. *J Natl Med Assoc*. 2002;94(8):695-700.
52. Mills JL, Troendle J, Conley MR, Carter T, Druschel CM. Maternal obesity and congenital heart defects: a population-based study. *Am J Clin Nutr*. 2010;91(6):1543-1549.
53. Moore LL, Singer MR, Bradlee ML, Rothman KJ, Milunsky A. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology*. 2000;11(6):689-694.
54. Oddy WH, De Klerk NH, Miller M, Payne J, Bower C. Association of maternal pre-pregnancy weight with birth defects: evidence from a case-control study in Western Australia. *Aust N Z J Obstet Gynaecol*. 2009;49(1):11-15.
55. Persson M, Cnattingius S, Villamor E, et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. *BMJ*. 2017;357:j2563.
56. Persson M, Razaz N, Edstedt Bonamy AK, Villamor E, Cnattingius S. Maternal overweight and obesity and risk of congenital heart defects. *J Am Coll Cardiol*. 2019;73(1):44-53.
57. Richards ID. Congenital malformations and environmental influences in pregnancy. *Br J Prev Soc Med*. 1969;23(4):218-225.
58. Rutkowski RE, Tanner JP, Anjohrin SB, Kirby RS, Salemi JL. Proportion of critical congenital heart defects attributable to unhealthy prepregnancy body mass index among women with live births in Florida, 2005-2016. *Birth Defects Res*. 2021;113(18):1285-1298.
59. Shaw GM, Todoroff K, Schaffer DM, Selvin S. Maternal height and prepregnancy body mass index as risk factors for selected congenital anomalies. *Paediatr Perinat Epidemiol*. 2000;14(3):234-239.
60. Shaw GM, Carmichael SL. Prepregnant obesity and risks of selected birth defects in offspring. *Epidemiology*. 2008;19(4):616-620.
61. Waller DK, Mills JL, Simpson JL, et al. Are obese women at higher risk for producing malformed offspring? *Am J Obstet Gynecol*. 1994;170(2):541-548.
62. Waller DK, Shaw GM, Rasmussen SA, et al. Prepregnancy obesity as a risk factor for structural birth defects. *Arch Pediatr Adolesc Med*. 2007;161(8):745-750.
63. Watkins ML, Botto LD. Maternal prepregnancy weight and congenital heart defects in offspring (published correction appears in Epidemiology. 2001;12(5):517). *Epidemiology*. 2001;12(4):439-446.
64. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. *Pediatrics*. 2003;111(5 Pt 2):1152-1158.

65. Wu XX, Ge RX, Huang L, et al. Pregestational diabetes mediates the association between maternal obesity and the risk of congenital heart defects. *J Diabetes Investig*. 2022;13(2):367-374.
66. Yuan X, Liu Z, Zhu J, et al. Association between prepregnancy body mass index and risk of congenital heart defects in offspring: an ambispective observational study in China. *BMC Pregnancy Childbirth*. 2020;20(1):444.
67. Ramsay JE, Ferrell WR, Crawford L, Wallace AM, Greer IA, Sattar N. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *J Clin Endocrinol Metab*. 2002;87(9):4231-4237.
68. Pou KM, Massaro JM, Hoffmann U, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. *Circulation*. 2007;116(11):1234-1241.
69. Mele J, Muralimanoharan S, Maloyan A, Myatt L. Impaired mitochondrial function in human placenta with increased maternal adiposity. *Am J Physiol Endocrinol Metab*. 2014;307(5):E419-E425.
70. Fowden AL, Camm EJ, Sferruzzi-Perri AN. Effects of maternal obesity on placental phenotype. *Curr Vasc Pharmacol*. 2021;19(2):113-131.
71. Holland O, Dekker Nitert M, Gallo LA, Vejzovic M, Fisher JJ, Perkins AV. Review: Placental mitochondrial function and structure in gestational disorders. *Placenta*. 2017;54:2-9.
72. Case AP, Ramadhani TA, Canfield MA, Beverly L, Wood R. Folic acid supplementation among diabetic, overweight, or obese women of childbearing age. *J Obstet Gynecol Neonatal Nurs*. 2007;36(4):335-341.
73. Jones HN, Jansson T, Powell TL. Full-length adiponectin attenuates insulin signaling and inhibits insulin-stimulated amino Acid transport in human primary trophoblast cells. *Diabetes*. 2010;59(5):1161-1170.
74. Acosta O, Ramirez VI, Lager S, et al. Increased glucose and placental GLUT-1 in large infants of obese nondiabetic mothers. *Am J Obstet Gynecol*. 2015;212(2):227.e1–7.
75. Hendler I, Blackwell SC, Bujold E, et al. The impact of maternal obesity on midtrimester sonographic visualization of fetal cardiac and craniospinal structures. *Int J Obes Relat Metab Disord*. 2004;28(12):1607-1611.
76. Giorgione V, Parazzini F, Fesslova V, et al. Congenital heart defects in IVF/ICSI pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2018;51(1):33-42.
77. Jacobs JP, Franklin RCG, Béland MJ, et al. Nomenclature for pediatric and congenital cardiac care: unification of clinical and administrative nomenclature - the 2021 International Paediatric and Congenital Cardiac Code (IPCCC) and the eleventh revision of the International Classification of Diseases (ICD-11). *Cardiol Young*. 2021;31(7):1057-1188.
78. GBD 2017 Congenital Heart Disease Collaborators. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017 (published correction appears in Lancet Child Adolesc Health. 2020). *Lancet Child Adolesc Health*. 2020;4(3):185-200.
79. Quaresima P, Fesslova V, Farina A, et al. How to do a fetal cardiac scan. *Arch Gynecol Obstet*. 2023;307(4):1269-1276.
80. Khoshnood B, Lelong N, Houyel L, et al. Impact of prenatal diagnosis on survival of newborns with four congenital heart defects: a prospective, population-based cohort study in France (the EPICARD Study). *BMJ Open*. 2017;7(11):e018285.
81. Giorgione V, Fesslova V, Boveri S, Candiani M, Khalil A, Cavoretto P. Adverse perinatal outcome and placental abnormalities in pregnancies with major fetal congenital heart defects: a retrospective case-control study. *Prenat Diagn*. 2020;40(11):1390-1397.
82. Inversetti A, Fesslova V, Deprest J, Candiani M, Giorgione V, Cavoretto P. Prenatal growth in fetuses with isolated cyanotic and non-cyanotic congenital heart defects. *Fetal Diagn Ther*. 2020;47(5):411-419.
83. Paladini D. Sonography in obese and overweight pregnant women: clinical, medicolegal and technical issues. *Ultrasound Obstet Gynecol*. 2009;33(6):720-729.
84. Majeed A, Abuhamad A, Romary L, Sinkovskaya E. Can ultrasound in early gestation improve visualization of fetal cardiac structures in obese pregnant women? *J Ultrasound Med*. 2019;38(8):2057-2063.
85. Moerdijk AS, Claessens NH, van Ooijen IM, et al. Fetal MRI of the heart and brain in congenital heart disease. *Lancet Child Adolesc Health*. 2023;7(1):59-68.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Search strategy

Figure S1 Risk of bias assessment for included studies.

Figure S2 Funnel plots showing risk of congenital heart defect (CHD) according to maternal body mass index category: (a) overweight; (b) obesity; (c) moderate obesity; and (d) severe obesity. Red vertical lines represent pooled effect estimate and gray lines indicate 95% CI for the effect size. OR, odds ratio; SE, standard error.

Figure S3 Forest plots of subgroup analyses of body mass index categories and risk of subtypes of congenital heart defect.

Table S1 Studies included in systematic review but excluded from meta-analysis and reason for exclusion

Table S2 GRADE evidence profile for quality assessment

Ultrasound Obstet Gynecol 2024; **64**: 294–307
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.27659.

El peso materno antes del embarazo como factor de riesgo independiente de cardiopatía congénita: revisión sistemática y metaanálisis estratificado por subtipo y gravedad de la cardiopatía

RESUMEN

Objetivo. Evaluar la asociación entre el aumento del índice de masa corporal (IMC) materno antes del embarazo y el riesgo de cardiopatías congénitas (CC) en la progenie.

Métodos. En esta revisión sistemática y metaanálisis se realizaron búsquedas en PubMed/MEDLINE, Web of Science y Scopus desde el inicio hasta el 20 de abril de 2023. Las estimaciones de riesgo se derivaron o calcularon para categorías de IMC más altas (sobrepeso, obesidad, obesidad moderada y obesidad grave) en comparación con el peso normal (referencia). Se utilizaron modelos de efectos fijos o aleatorios para combinar las estimaciones de riesgo de los estudios individuales en función del grado de heterogeneidad. Se realizaron análisis de sensibilidad para ponderar las estimaciones combinadas para los factores moderadores relevantes, en particular la diabetes previa y posterior al embarazo. Se realizaron análisis de subgrupos para subtipos específicos de CC cuando había al menos dos estudios con datos disponibles. Los resultados se presentaron segregados por grupo de cardiopatías, clasificados según criterios de gravedad y topográfico-funcionales, y para cada cardiopatía individual. La certeza de la evidencia para cada estimación del efecto se evaluó según las directrices de Clasificación de las Recomendaciones, Valoración, Desarrollo y Evaluación (GRADE, por sus siglas en inglés).

Resultados. En total, se incluyeron 31 estudios que comprendían 4 861 693 pacientes y 86 136 casos de CC. El riesgo de CC aumentó progresivamente de la obesidad moderada a la grave (razón de momios [RM] combinada 1,15 [IC 95%, 1,11–1,20] y 1,39 [IC 95%, 1,27–1,53], respectivamente). El análisis de sensibilidad indicó que este efecto persistía independientemente del estado de la diabetes materna previa o posterior al embarazo. En el análisis de subgrupos, la obesidad se asoció con un aumento de hasta 1,5 veces en el riesgo de CC grave (RM combinada 1,48 [IC 95%, 1,03–2,13]). La obesidad grave se asoció a un riesgo aún mayor, con probabilidades 1,8 veces superiores en comparación con el grupo de referencia para subtipos específicos de CC, como la tetralogía de Fallot (RM combinada 1,72 [IC 95%, 1,38–2,16]), la estenosis de la válvula pulmonar (RM combinada 1,79 [IC 95%, 1,39–2,30]) y la comunicación interauricular (RM combinada 1,71 [IC 95%, 1,48–1,97]).

Conclusiones. El peso materno es un factor de riesgo modificable crucial para la CC, en particular para las formas graves de las cardiopatías. Es necesario seguir investigando si el control del peso antes del embarazo podría servir como medida preventiva contra las CC. En las mujeres embarazadas obesas, la ecocardiografía fetal debería ser un procedimiento diagnóstico rutinario.

孕前体重作为先天性心脏缺陷的独立风险因素：按缺陷亚型和严重程度分层的系统综述和荟萃分析

摘要

目的 评估孕前体重指数（BMI）增长与后代先天性心脏缺陷（CHD）风险之间的关系。

方法 本系统综述和荟萃分析检索了从开始到 2023 年 4 月 20 日的 PubMed/MEDLINE、Web of Science 和 Scopus。与正常体重（参照）相比，对 BMI 增长类别（超重、肥胖、中度肥胖和重度肥胖）的风险估计值进行了摘录或计算。根据异质性程度，采用固定效应或随机效应模型合并单项研究的风险估计值。进行了敏感性分析，以对相关调节因子（尤其是孕前和孕期糖尿病）的集合估计值进行加权。如果至少有两项研究提供了数据，则对特定的 CHD 亚型进行分组分析。根据严重程度和局部功能标准对缺陷组进行分类，按组报告研究结果，并对单个缺陷报告研究结果。根据推荐分级的评估、制定与评价（GRADE）指南对每项效应估计值的证据确定性进行了评估。

结果 共纳入 31 项研究，包括 4,861,693 名患者和 86,136 例 CHD 病例。从中度肥胖到重度肥胖，罹患 CHD 的风险逐渐增加（汇总比值比（OR）分别为 1.15（95% CI，1.11-1.20）和 1.39（95% CI，1.27-1.53））。敏感性分析表明，这一影响不受孕前或孕期母体糖尿病状况的影响。在亚组分析中，肥胖与严重 CHD 风险增加高达 1.5 倍有关（汇总 OR，1.48（95% CI，1.03-2.13））。重度肥胖与更高的风险相关，与参照组相比，重度肥胖与特定 CHD 亚型几率高出 1.8 倍有关，包括法洛氏四联症（汇总 OR，1.72（95% Ci，1.38-2.16））、肺动脉瓣狭窄（汇总 OR，1.79（95% CI，1.39-2.30））和房间隔缺损（汇总 OR，1.71（95% CI，1.48-1.97））。

结论 孕妇体重是导致 CHD 的一个重要的可改变风险因素，尤其是对于严重形式的缺陷。孕前控制体重是否可作为预防 CHD 的措施还需进一步研究。对于肥胖孕妇，胎儿超声心动图检查应作为常规诊断程序。