

# 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<sup>1,2</sup> , A. SEIDENARI<sup>3,4</sup>, P. I. CAVORETTO<sup>1,2</sup> , M. PAPALE<sup>1,2</sup>, M. CANDIANI<sup>1,2</sup> and A. FARINA<sup>3,4</sup> 

<sup>1</sup>Gynecology and Obstetrics Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; <sup>2</sup>Vita-Salute University, Milan, Italy; <sup>3</sup>Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum-University of Bologna, Bologna, Italy; <sup>4</sup>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)

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## INTRODUCTION

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

Congenital heart defects (CHD) are the most prevalent congenital malformation among neonates, affecting up to 1% of all live births worldwide<sup>17,18</sup>. CHD has been identified as a significant cause of neonatal morbidity and mortality globally, thereby posing a major public health challenge<sup>19</sup>. 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<sup>20</sup>. 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<sup>21,22</sup>. 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)<sup>23</sup>. 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<sup>24,25</sup>. 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<sup>2</sup>; (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<sup>2</sup>: 18.5–24.9 kg/m<sup>2</sup> (reference group), 25.0–30.0 kg/m<sup>2</sup> (overweight) and > 30.0 kg/m<sup>2</sup> (obese). Moderate and severe obesity were defined as a BMI of 30.1–34.9 kg/m<sup>2</sup> and ≥ 35.0 kg/m<sup>2</sup>, 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<sup>26</sup>. 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<sup>27,28</sup>.

## 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<sup>29</sup>, which was interpreted as follows: 0–25%, insignificant; 26–50%, low; 51–75%, moderate; > 75%, high<sup>30</sup>. 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.*<sup>31</sup> and the adjusted rank correlation test proposed by Begg and Mazumdar<sup>32</sup>.

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 ( $\leq 2013$  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<sup>33</sup> and a topographic–functional criterion<sup>34</sup>, 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.*<sup>33</sup>; 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<sup>35</sup>. STATA version 17 software (Stata Corp., College Station, TX, USA) was used for statistical analysis.

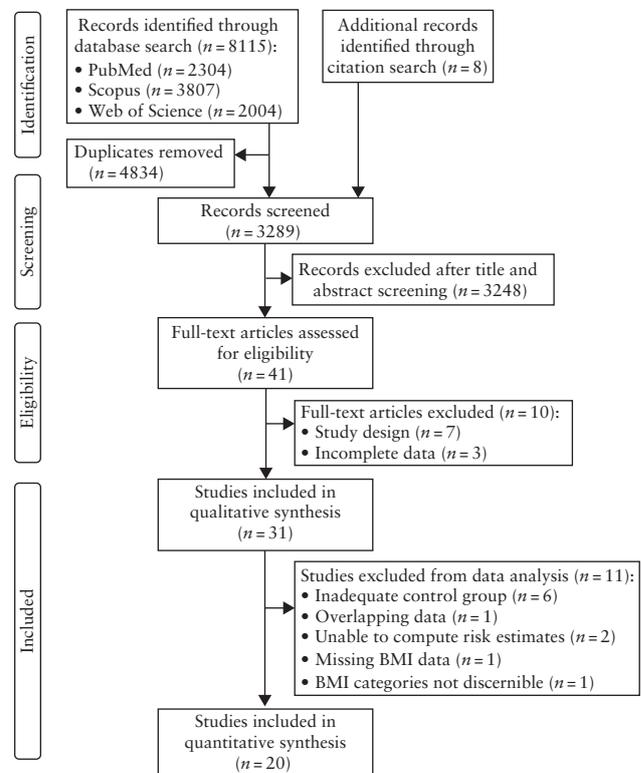
## RESULTS

### Study characteristics

After removal of duplicates, the literature search identified 3289 results, of which 31 publications were eligible for qualitative synthesis<sup>36–66</sup>. 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<sup>27,28</sup>. 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) <sup>36</sup>	Case-control	USA	Included PDM, excluded GDM	2007-2009	Obesity: $\geq 30.0$ kg/m <sup>2</sup>	—	SD, CTD, obstructive defects
Baardman (2012) <sup>37</sup>	Case-control	Europe	Excluded PDM, included GDM	1997-2008	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; obesity: $\geq 30.0$ kg/m <sup>2</sup>	Neonatal examination, prenatal/postnatal echocardiography	SD, CTD, OFTD§
Block (2013) <sup>38</sup>	Case-control	USA	Excluded PDM, included GDM	2004-2009	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; obesity class I: 30.0-34.9 kg/m <sup>2</sup> ; obesity class II: 35.0-39.9 kg/m <sup>2</sup> ; obesity class III: $\geq 40.0$ kg/m <sup>2</sup>	—	TOF, VSD, PVS, PA, TGA, HLHS, CoA, AS
Blomberg (2010) <sup>39</sup>	Case-control	Europe	Included PDM and GDM	1995-2007	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; moderate obesity: 30.0-39.9 kg/m <sup>2</sup> ; severe obesity: $\geq 40.0$ kg/m <sup>2</sup>	Neonatal examination, postnatal echocardiography	TOF, TGA, HLHS, common truncus
Brite (2014) <sup>40</sup>	Cohort	USA	Excluded PDM and GDM*	2002-2008	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; moderate obesity: 30.0-40.0 kg/m <sup>2</sup> ; severe obesity: $\geq 40.0$ kg/m <sup>2</sup>	—	CTD, ASD, VSD
Cedergren (2002) <sup>41</sup>	Case-control	Europe	—	1982-1996	Overweight: 26.0-28.9 kg/m <sup>2</sup> ; obesity: $\geq 29.0$ kg/m <sup>2</sup>	Neonatal examination	—§
Cedergren (2002) <sup>42</sup>	Case-control	Europe	—	1982-1996	Overweight: 26.0-28.9 kg/m <sup>2</sup> ; obesity: $\geq 29.0$ kg/m <sup>2</sup>	Neonatal examination	ASD, VSD, ECD, SV, TOF, common truncus, TGA, HLHS, PVS, CoA§
Cedergren (2003) <sup>43</sup>	Case-control	Europe	Excluded PDM, included GDM	1992-2001	Overweight: 26.1-29.0 kg/m <sup>2</sup> ; moderate obesity: 29.1-34.9 kg/m <sup>2</sup> ; severe obesity: $\geq 35.0$ kg/m <sup>2</sup>	Neonatal examination, postnatal echocardiography	HLHS, TOF, TGA, CoA, VSD, ASD, AVSD
Cedergren (2006) <sup>44</sup>	Cohort	Europe	—	1992-2001	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; obesity: $\geq 30.0$ kg/m <sup>2</sup>	Neonatal examination, postnatal echocardiography	—§
García-Patterson (2004) <sup>45</sup>	Cohort	Europe	All cases had GDM	1986-2002	First tertile: 15.43-21.91 kg/m <sup>2</sup> ; second tertile: 21.92-24.77 kg/m <sup>2</sup> ; third tertile: 24.78-47.07 kg/m <sup>2</sup>	Neonatal examination	—§
Ghaderian (2014) <sup>46</sup>	Case-control	Middle East	Excluded PDM and GDM	2011-2012	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; obesity: $\geq 30.0$ kg/m <sup>2</sup>	—	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) <sup>47</sup>	Case-control	USA	Excluded PDM, included GDM	1997-2004	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; moderate obesity: 30.0-34.9 kg/m <sup>2</sup> ; severe obesity: ≥ 35.0 kg/m <sup>2</sup>	Postnatal echocardiography, cardiac surgery	EBS, CTD, OFTD, HLHS, PA, SV, TOF, TGA, APVR, AS, PVS, AVSD, SD, CoA, VSD, ASD
Khalil (2008) <sup>48</sup>	Case-control	Middle East	Excluded PDM and GDM	1998-2005	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; moderate obesity: 30.0-34.9 kg/m <sup>2</sup> ; severe obesity: ≥ 35.0 kg/m <sup>2</sup> †	Neonatal examination, postnatal echocardiography	ASD, VSD, PA, PVA, AS, PVS, CoA, TOF, TGA, complete heart block, EBS, hypoplastic right heart§
Madsen (2013) <sup>49</sup>	Case-control	USA	Excluded PDM, included GDM	1992-2007	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; moderate obesity: 30.0-34.9 kg/m <sup>2</sup> ; severe obesity: ≥ 35.0 kg/m <sup>2</sup>	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) <sup>50</sup>	Case-control	Europe	Excluded PDM and GDM	1976-2001	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; obesity: ≥ 30.0 kg/m <sup>2</sup>	Neonatal examination	HLHS, TOF, TGA, DORV
Mikhail (2002) <sup>51</sup>	Cohort	USA	Excluded PDM and GDM	1981-1994	Obesity: ≥ 27.0 kg/m <sup>2</sup>	—	HLHS, CTD, TOF, TGA, CoA, DORV, PVS, OFTD, APVR, AS, SD, VSD, ASD, AVSD
Mills (2010) <sup>52</sup>	Case-control	USA	Excluded PDM and GDM	1993-2003	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; moderate obesity: 30.0-39.9 kg/m <sup>2</sup> ; severe obesity: ≥ 40.0 kg/m <sup>2</sup>	—	HLHS, SD
Moore (2000) <sup>53</sup>	Cohort	USA	Excluded PDM and GDM	1984-1987	Obesity: ≥ 28.0 kg/m <sup>2</sup>	—	—
Oddy (2009) <sup>54</sup>	Case-control	Australia	—	1997-2000	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; obesity: ≥ 30.0 kg/m <sup>2</sup>	Postnatal echocardiography	CTD
Persson (2017) <sup>55</sup>	Cohort	Europe	Included PDM and GDM	2001-2014	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; obesity class I: 30.0-34.9 kg/m <sup>2</sup> ; obesity class II: 35.0-39.9 kg/m <sup>2</sup> ; obesity class III: ≥ 40.0 kg/m <sup>2</sup>	Neonatal examination, prenatal and postnatal echocardiography	—§
Persson (2019) <sup>56</sup>	Cohort	Europe	Included PDM and GDM*	1992-2012	Overweight: 25.0-29.9 kg/m <sup>2</sup> ; obesity class I: 30.0-34.9 kg/m <sup>2</sup> ; obesity class II: 35.0-39.9 kg/m <sup>2</sup> ; obesity class III: ≥ 40.0 kg/m <sup>2</sup>	Neonatal examination, prenatal and postnatal echocardiography	TOF, TGA, AVSD, aortic arch defects, SV, ASD, VSD, PVA, valve defects, right ventricular defects
Richards (1969) <sup>57</sup>	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) <sup>58</sup>	Cohort	USA	Excluded PDM, included GDM	2005–2016	Overweight: 25.0–29.9 kg/m <sup>2</sup> ; obesity class I: 30.0–34.9 kg/m <sup>2</sup> ; obesity class II: 35.0–39.9 kg/m <sup>2</sup> ; obesity class III: ≥ 40.0 kg/m <sup>2</sup>	—	Truncus arteriosus, HLHS, TOF, PA, TGA, APVR, RVOTO, EBS, CoA, SV <sup>§</sup>
Shaw (2000) <sup>59</sup>	Cohort	USA	Included PDM and/or GDM	1987–1988	Obesity: ≥ 29.0 kg/m <sup>2</sup>	Neonatal examination	— <sup>§</sup>
Shaw (2008) <sup>60</sup>	Case-control	USA	Excluded PDM and GDM	1999–2004	Overweight: 25.0–29.9 kg/m <sup>2</sup> ; obesity: ≥ 30.0 kg/m <sup>2</sup>	Postnatal echocardiography	TGA, TOF
Waller (1994) <sup>61</sup>	Case-control	USA	Excluded PDM, included GDM	1985–1987	Overweight: 27.0–29.9 kg/m <sup>2</sup> ; obesity: ≥ 30.0 kg/m <sup>2</sup>	Prenatal ultrasonography	— <sup>§</sup>
Waller (2007) <sup>62</sup>	Case-control	USA	Excluded PDM, included GDM	1997–2002	Overweight: 25.0–29.9 kg/m <sup>2</sup> ; obesity: ≥ 30.0 kg/m <sup>2</sup>	Postnatal echocardiography	— <sup>§</sup>
Watkins (2001) <sup>63</sup>	Case-control	USA	Excluded PDM and GDM	1968–1980	Overweight: 26.1–28.9 kg/m <sup>2</sup> ; obesity: ≥ 29.0 kg/m <sup>2</sup>	Neonatal examination	OFTD, TGA, TOF, ASD, VSD <sup>§</sup>
Watkins (2003) <sup>64</sup>	Case-control	USA	Excluded PDM, GDM not specified	1993–1997	Overweight: 25.0–29.9 kg/m <sup>2</sup> ; obesity: ≥ 30.0 kg/m <sup>2</sup>	Neonatal examination	LVOTO, HLHS, CoA, RVOTO, ASD, VSD, TOF, TGA, OFTD
Wu (2022) <sup>65</sup>	Cohort	China	Included PDM and GDM	2017–2019	Overweight: 24.0–27.9 kg/m <sup>2</sup> ; obesity: ≥ 28.0 kg/m <sup>2</sup> †	Prenatal echocardiography, pediatric neonatal examination	Heterotaxia, CTD, AVSD, APVR, LVOTO, RVOTO, SD and complex CHD <sup>§</sup>
Yuan (2020) <sup>66</sup>	Case-control	China	Excluded PDM and GDM	2010–2015	Overweight: ≥ 24.0 kg/m <sup>2</sup> ‡	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 valve 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<sup>67</sup>. 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<sup>68</sup>. 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<sup>69</sup>. 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<sup>70</sup>. Women with obesity exhibit inefficient placental blood flow and

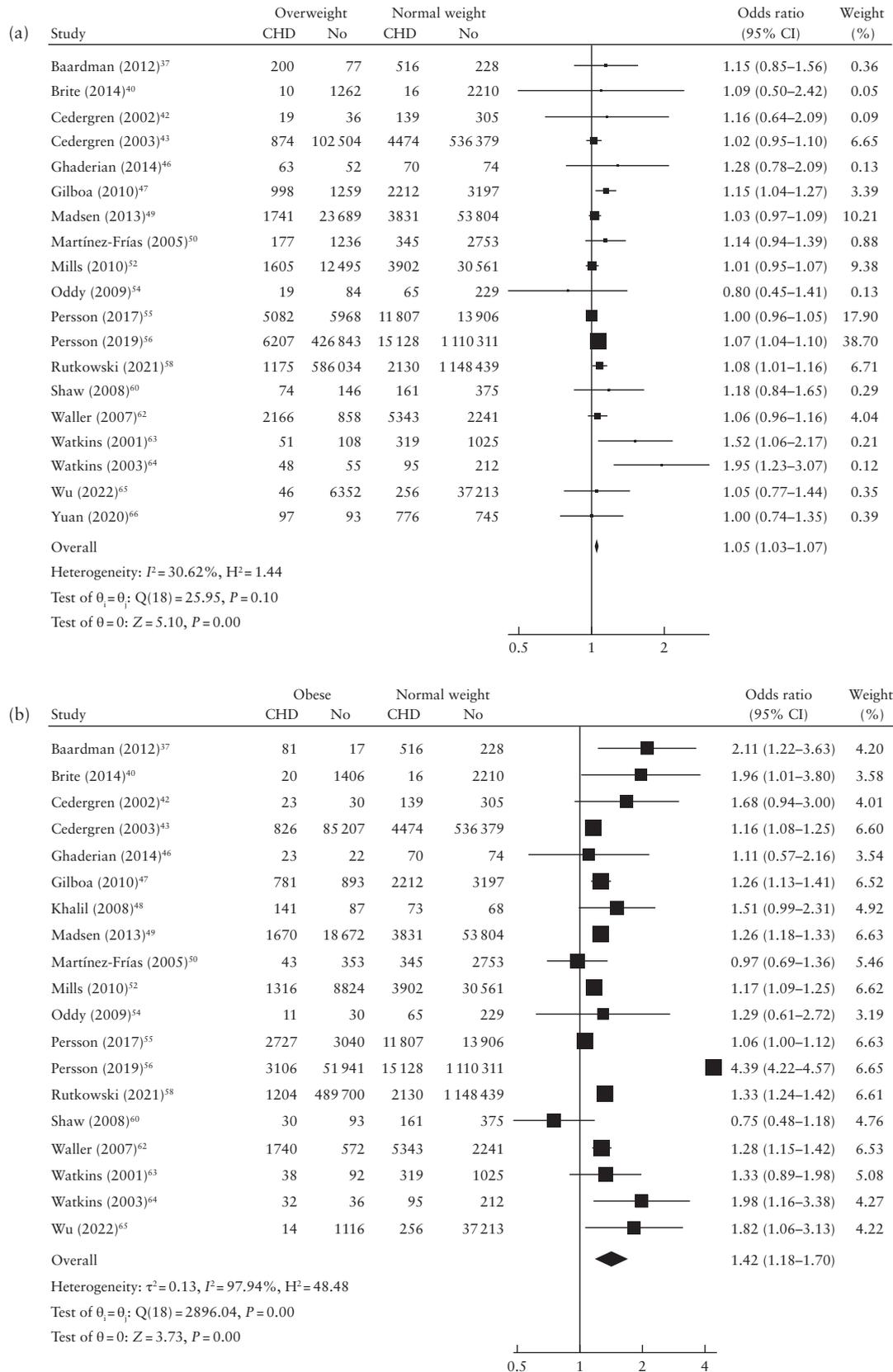
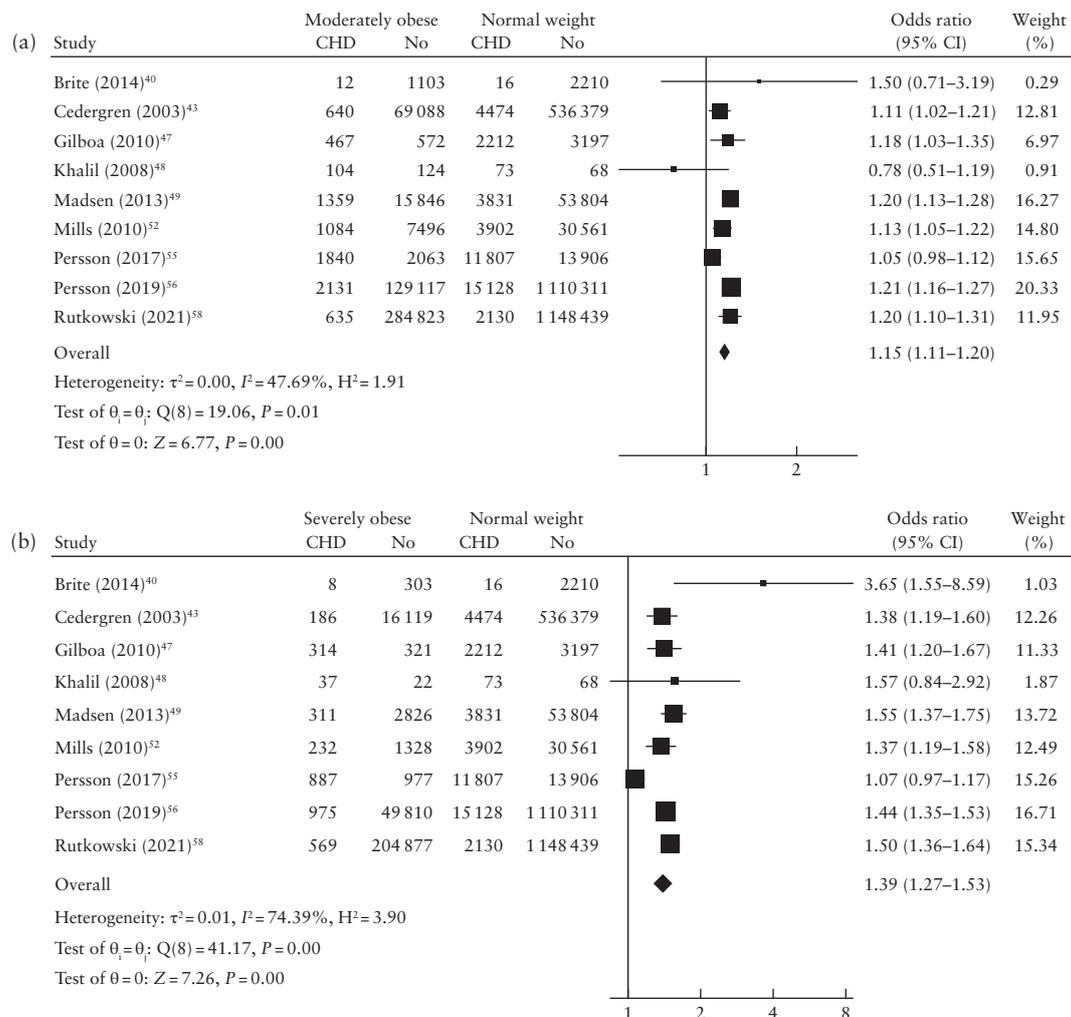


Figure 2 Forest plots showing risk of congenital heart defect (CHD) according to maternal body mass index category: (a) overweight; and (b) obesity. Only first author is given for each study.



**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<sup>71</sup>.

In addition, women with obesity frequently exhibit diminished levels of circulating adiponectin during pregnancy<sup>72</sup>, which has been linked to the development of placental insulin resistance<sup>73</sup> and increased placental nutrient transfer<sup>74</sup>. 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<sup>12,15</sup>. 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 <sup>2</sup> (%)	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 <sup>2</sup>	14*	1.05 (1.03–1.07)	19.89	0.001
> 26 kg/m <sup>2</sup>	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 <sup>2</sup>	3*	1.17 (1.09–1.26)	0	0.001
> 30 kg/m <sup>2</sup>	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 <sup>2</sup> (%)	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 <sup>2</sup> (%)	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<sup>75</sup>. 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<sup>76</sup>. However, only one study<sup>65</sup> 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<sup>77</sup>. We endeavored to adhere to the 11<sup>th</sup> 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<sup>33,34</sup>.

## Conclusions

CHD is a significant and emerging global issue in child health<sup>78</sup>. 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<sup>79</sup>. This includes early identification and prompt referral to a tertiary center for optimal delivery and neonatal treatment<sup>80,81</sup>, which is essential to enhance survival and the long-term outcome<sup>82</sup>.

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<sup>79</sup>. Regarding optimal timing, some experts recommend transvaginal cardiac screening for obese women between 13 and 16 weeks' gestation because of enhanced visualization<sup>83,84</sup>. 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<sup>85</sup>.

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## 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



## 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。