Association between maternal obesity and metabolic disorders and congenital heart defects in the offspring: a literature review

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Summary

Congenital heart defects (CHDs) are the most common congenital malformation and will, in severe cases, have a serious impact on neonatal mortality and morbidity. The aetiology of CHDs is complex. Large cohort studies have reported an association between increased risk of CHDs in the offspring and individual maternal metabolic disorders such as diabetes, hypertension, preeclampsia, and obesity. All conditions that can be related to insulin resistance and possibly metabolic syndrome (MetS). The aim of this review is to evaluate the existing evidence on the association between maternal metabolic disorders, defined as obesity, diabetes, hypertension, preeclampsia, dyslipidaemia, and MetS, or combinations thereof and CHDs in the offspring. A literature search was performed using PubMed and Embase databases. Of the 2,076 potentially relevant identified studies, 30 qualified for inclusion. Only one study dealt with the combination of more than one maternal metabolic condition as risk factor for CHDs in the offspring. All other studies investigated the individual metabolic disorders and their association with CHDs. Some disorders (chronic hypertension, gestational diabetes, and obesity) increased risk of CHDs marginally whereas pregestational diabetes and early-onset preeclampsia were highly associated with CHDs. Future studies on the combination of several metabolic disorders in the same pregnancy and their association with CHDs are needed.

Abbreviations:

CHDs, congenital heart defects; MetS, metabolic syndrome; PE, preeclampsia; BMI, body mass index; GDM, gestational diabetes; DM2, diabetes type 2; DM1, diabetes type 1; ICD-10, International Classification of Diseases, 10th revision; NOS, Newcastle-Ottawa Scale; OR, odds ratios; RR, relative risks; PR, prevalence ratios; CI, 95% confidence interval; aOR/aRR/aPR, adjusted; AVSD, atrioventricular septal defects; RVOTO, right ventricular outflow tract obstruction; VSD, ventricular septal defects; ASD, atrial septal defect; NBDPS, National Birth Defects Prevention Study; CoA, coarctation of the aorta.
1. Introduction

Congenital heart defects (CHDs) are structural malformations of the heart and/or the great intrathoracic vessels. They are the most frequent congenital malformation (1) and birth prevalence is estimated to be around 8-10 per 1,000 live births worldwide (1–3). The most critical and severe defects, major CHDs, (prevalence of 0.14% in Denmark) have a serious impact on neonatal mortality and morbidity, and frequently result in neonatal heart failure or circulatory collapse requiring acute surgery (3). Whereas, other types of CHDs like bicuspid aortic valve and transient septal heart defects are far more frequent but more often with limited clinical significance.

Population-based prevalence of CHDs are difficult to determine, but Denmark’s electronic registers are a useful resource for ascertaining the number of diagnosed cases as well as treatment complications and outcomes. Using such data, Lytzen et al. found that 75% of children with major CHDs, born in Denmark 1996-2013, underwent surgery. Furthermore, the 1-year mortality rate for this group was 19.6%, although the rate decreased during the study period (4). Improved infant treatment has led to a decrease in infant mortality and an increase in children and adults living with CHDs (5–7). Indeed, a Canadian study estimated that adults account for two thirds of patients with CHDs (8). The mortality rate is increased in adults with CHDs compared to the general population with the majority of patients with CHDs succumbing to cardiovascular causes such as arrhythmia and heart failure (9).

The aetiology of CHDs is complex and poorly understood. An identifiable underlying cause (genetic and/or environmental) is present in 20-30% of CHDs (10). For instance, 8-10% of CHDs can be attributed to chromosomal aberrations (e.g., DiGeorge syndrome, Down syndrome, Turner syndrome, etc.) (10,11); while 5-15% may be the result of single-nucleotide or pathogenic copy number variants (10,12). Additionally, viral infections in pregnancy (e.g., rubella), as well as exposure to certain teratogenic substances (e.g., alcohol or antiepileptic drugs) (13) may cause CHDs if the foetus is exposed at a critical point in development.

The normal pregnancy is an adaptation between the maternal metabolism and foetal development. Differentiation of cardiac tissues begins in the third week of gestation, and by week 8, the foetal heart has undergone major changes, and will resemble the postnatal heart in structure and function (14). Thus, the maternal-foetal interaction in first trimester is likely to be the most relevant for an association between maternal metabolism and CHDs. In first trimester, the foetus does not have the ability to secrete insulin which may result in foetal hyperglycaemia in the
event of relative maternal insulin resistance (15). The significance of foetal hyperglycaemia has not been
demonstrated in humans, however, animal models have shown that in embryos of chicks and rodents, exogenous
glucose may cause a variety of malformations (16,17). Furthermore, increasingly worse glycaemic control around
conception in women with diabetes type 1 (DM1) was associated with a progressively increased risk of CHDs in the
offspring (18).

Large cohort studies from Scandinavia and North America have reported an association between increased risk of
CHDs and maternal metabolic disorders such as diabetes (19–21), chronic hypertension (22,23), preeclampsia (PE)
(24,25), and obesity (26,27). All metabolic disorders that could be associated with an underlying insulin resistance and
possibly the metabolic syndrome (MetS) (28,29).

MetS comprises a cluster of metabolic disorders in combination, usually any three of the following: abdominal obesity,
insulin resistance, dyslipidaemia and hypertension (28,30). It is commonly described in a non-pregnant population as a
risk factor for diabetes type 2 (DM2) and cardiovascular disease. Only one study has assessed MetS in pregnant
women and reported an incidence of 12.3% at 15 weeks' gestation (31) using the International Diabetes Federation
criteria (30). Since MetS is more prevalent with increasing age (28), it seems plausible that obesity, diabetes,
hypertension, PE and dyslipidaemia as individual conditions, or more likely in combination, during pregnancy are
related to MetS (28,29). Furthermore, the same conditions have been associated with increased risk of CHDs in the
offspring (19–27). We hypothesize that the combination of several maternal metabolic disorders (defined as obesity,
diabetes, hypertension, PE and dyslipidaemia), all related to MetS, could be associated with cumulative risk of CHDs in
the offspring.

The aim of this review is to evaluate the literature of associations between maternal metabolic disorders (obesity,
diabetes, hypertension, PE, dyslipidaemia, or MetS) or combinations thereof and CHDs in the offspring. Furthermore,
to point out gaps in current knowledge and make recommendations for future research.

2. Methods

2.1 Search strategy
A literature search of papers published between January 1, 1990 and October 6, 2019 was conducted using PubMed and Embase. MetS was described by G.M. Reaven in 1988 as an “insulin resistance syndrome” (32), therefore the literature search was limited to publications thereafter. The search strategy used keywords that combined CHDs and pregnancies with different maternal metabolic disorders (overweight/obesity, hypertension, PE, diabetes, dyslipidaemia and/or MetS). More details about the literature search can be found in Appendix 1. Subsequently, reference lists were reviewed for additional relevant studies.

2.2 Exposures, outcomes and definitions

The exposures of interest were maternal overweight and obesity, hypertension, PE, diabetes (diabetes type 1 (DM1), DM2 or GDM), dyslipidaemia, and/or MetS during pregnancy. Maternal body mass index (BMI) (weight in kilograms divided by the square of the height in meters (kg/m²)) was defined as pre-pregnancy or early-pregnancy BMI measured in first trimester. The World Health Organization has defined BMI groups (BMI 18.5–24.9: normal weight; BMI 25.0–29.9: overweight; BMI 30.0–34.9: obesity class I; BMI 35.0–39.9: obesity class II; BMI ≥40: obesity class III) (33). The outcome of interest was CHDs defined as structural malformations of the heart chambers, heart valves, great arteries and septal defects, corresponding to DQ20-26 in the World Health Organization International Classification of Diseases (ICD-10) or diagnoses referable to these. The CHD diagnoses are described as “any CHD” for the whole group of diseases, “major CHDs” for a group of the most critical and severe CHD diagnoses (Table 1) or as specific CHD diagnoses. Studies could include terminated pregnancies, miscarriages, stillbirths and/or live births.

2.3 Eligibility criteria

Two different authors (GH, PLH and/or INT) screened all titles and abstracts individually. Studies were initially eligible if they met the following criteria: 1. Studies were published in English; 2. Studies were case-control or cohort studies; 3. The exposures of interest were maternal overweight or obesity, maternal hypertension or PE, maternal diabetes, maternal dyslipidaemia, and/or maternal MetS; and 4. The outcome of interest was CHDs in the offspring.
2.4 Quality assessment

One author (GH) conducted the study selection and quality assessment based on a full-text review. Any doubts were resolved by discussion with at least one co-author. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of eligible studies (34). Using this tool, each study was judged on eight items, arranged into three categories: selection of cohorts or cases and controls; comparability of cohorts or cases and controls; and ascertainment of outcome or exposure. Highest quality studies could be awarded nine stars. If a study received seven or more stars, it was considered of high methodological quality and included in the review (34).

Results are presented as odds ratios (OR), relative risks (RR) or prevalence ratios (PR) with 95% confidence interval (CI) unless otherwise stated.

3. Results

3.1 Study identification and selection

The selection of studies is described in Figure 1. In the event of multiple publications using the same data, we included the study that provided the most comprehensive information. A total of 30 publications were included in the review (Table 1). Among these, none was about maternal MetS (as a diagnostic category) and CHDs, seven publications dealt with maternal hypertension or PE and CHDs (22–25,35–37), 13 dealt with maternal overweight or obesity and CHDs (22,26,27,38–47), 16 dealt with maternal diabetes and CHDs (18–22,36,37,40,48–55), and none were about dyslipidaemia and CHDs. Three studies investigated more than one maternal metabolic disorder (but not in combination) (22,36,37), and only one study assessed a combination of two conditions and the risk of CHDs (40).

Figure 2 summarizes the content of the included studies.

3.2 Maternal chronic hypertension and CHDs in the offspring
Two large nationwide population-based cohort studies reported a significant association between maternal chronic hypertension and any CHDs: one was a Canadian study by Liu et al. including 2.3 million mother-infant pairs, among these 0.6% had chronic hypertension, and found an adjusted OR (aOR) 1.81; CI 1.61-2.03 (22). The other was a study from Taiwan that included 1.4 million pregnancies and reported an aOR 1.87; CI 1.69-2.07 (36). Furthermore, Liu et al. found a significant increased risk of five subtypes of CHDs when the mother had chronic hypertension: conotruncal defects (aOR 1.71; CI 1.20–2.47), atrioventricular septal defects (AVSD) (aOR 1.97; CI 1.07–3.64), right ventricular outflow tract obstruction (RVOTO) (aOR 3.17; CI 1.39–7.81), ventricular septal defects (VSD) (aOR 1.52; CI 1.11–2.09), and atrial septal defect (ASD) (aOR 3.12; CI 2.41–4.03), and were not able to find an association for other subtypes (heterotaxia and left ventricular outflow tract defects) (22). A Hungarian case-control study with 3,562 live-born cases with CHDs reported a significant association between chronic hypertension and three subtypes of CHDs: VSD (OR 1.31; CI 1.08–1.58), AVSD (OR 2.47; OR 1.19–4.60), and common truncus (OR 2.75; CI 1.04–6.06), but did not find an association for a number of other subtypes of CHDs (Table 1) (37). None of these studies reported potential antihypertensive use by the mothers. In an American multi-site, population-based case-control study with 21,762 participants (National Birth Defects Prevention Study, NBDPS), Fisher et el. found use of antihypertensive medication (centrally acting antiadrenergics, β-blockers, renin–angiotensin system blockers, calcium channel blockers, and diuretics) from one month before conception through the third month of pregnancy to be associated with an increased risk of both any CHD (OR 1.59; CI 1.23–2.05) and five subtypes of CHDs (23). Although, they observed statistically significant estimates for coarctation of the aorta (CoA), pulmonary valve stenosis, Ebstein’s anomaly, perimembranous VSD, and ASD secundum, ranging from OR 1.90 (CI 1.09–3.31) for VSD to OR 3.89 (CI 1.51–10.06) for Ebstein’s anomaly, they did not find an association for a multiple of other CHD subtypes (23). The study also found a significant association between untreated hypertension or late pregnancy antihypertensive medication initiation and the same subtypes of CHDs (with the exception of Ebstein’s anomaly) (23). Information on maternal use of antihypertensive medication in the NBDPS was from telephone interviews with the mother made between six weeks and 24 months after estimated due date (23).
Three studies investigated associations between preeclampsia (PE) and any CHDs or major CHDs, although the definition of PE varied among the studies. Auger et al. reported a PR 1.57 (CI 1.48-1.67) of any CHDs in pregnancies with PE, compared to pregnancies without PE in a Canadian population-based cohort study including 1.9 million deliveries (25). However, PE with onset before 34 weeks of gestation was associated with a highly increased risk of having an infant with any CHD in singleton pregnancies (PR 7.37; CI 6.61-8.21) (25). Boyd et al. reported a similar association between early-onset PE (delivery before 34 weeks’ gestation) and risk of any CHD in the offspring, in a cohort of almost two million singleton pregnancies (OR 7.00; CI 6.11-8.03) (24). Brodwall et al. reported an association between early-onset PE and major CHDs (Table 1) (aRR 2.7; CI 1.3-5.6), compared to normotensive pregnancies in 900,000 Norwegian singleton births (35). Similarly, Auger et al. found an association between early-onset PE and critical CHDs (Table 1) (aPR 2.78; CI 1.71-4.50) (25), and reported an increased risk when presenting with PE with intrauterine growth restriction (aPR 3.72, CI 2.45-5.64) (25).

Boyd et al. reported an association between any CHD and PE with delivery at 34 to 36 weeks (OR 2.82, CI 2.38-3.34). They found a weaker association between PE at term and any CHDs (OR 1.16; CI 1.06-1.27), and no association between gestational hypertension and any CHDs (24). Auger et al. found a weak association between any CHD and late-onset PE (>34 weeks) (aPR 1.14; CI 1.06-1.23) (25).

Two studies assessed PE and CHDs, and potential risks of both in subsequent pregnancies (24,35). Brodwall et al. did not find an association between PE and CHDs across pregnancies (35). However, Boyd et al. reported an increased risk of having a child with CHD in subsequent pregnancies after a pregnancy with PE and delivery before 34 weeks’ gestation (OR 7.91; CI 6.06-10.3). Also an association between a previous pregnancy with a child with CHDs and increased risk of PE with delivery before 34 weeks’ gestation in subsequent pregnancies (OR 2.37; CI 1.68-3.34) (24).

3.4 Maternal overweight or obesity and CHDs in the offspring

Several studies have investigated the association between maternal overweight or obesity and any CHD, but only some have specified how they defined “any CHD” (22,26,27,40,42,46). A large nationwide Swedish cohort study by Persson et al. with two million singleton infants reported increasing risk estimates for any CHD with increasing maternal BMI (overweight: RR 1.07; CI 1.04-1.10 to obesity class III: RR 1.60; CI 1.42-1.81) (26). Persson et al. made
their estimates from BMI measurements from the first antenatal visit. A similar American cohort study including 121,815 deliveries and maternal BMI from medical records also found increasing risk of any CHD with increasing maternal BMI (overweight: aOR 1.15; CI 1.01-1.32 to obesity class III: aOR 1.34; CI 1.02-1.76) (27), and so did Gilboa et al. in their case-control study including approximately 12,000 American deliveries from the NBDPS (40). Another large cohort study by Liu et al. found an association between maternal obesity diagnosed as ICD-10 codes and any CHD (aOR 1.48; CI 1.32-1.65) (22). Two studies failed to find a significant association between any CHD in the offspring and maternal overweight or obesity (42,46): one cohort study from Northern England by Rankin et al. including 41,000 singleton pregnancies (42), the other an American case-control study with 851 cases and 2,767 controls (46).

Most studies investigated specific CHD diagnoses in relation to maternal BMI (Table 1). While some studies found positive associations, other could not replicate these findings. A comparison between studies was impossible because of varying definitions of BMI groups and CHD subtypes (Table 2).

3.5 Maternal pregestational diabetes and CHDs in the offspring

Seven studies reported how they defined “any CHD” (Table 1) (18–22,36,52). All studies found a significant association, whether they reported association between any CHD and pregestational diabetes (PGDM) (19–21,52), DM1 (18,22,36), or DM2 (22,36). PGDM was defined as DM1 or DM2 in all studies. Risk estimates for any CHD and association with PGDM was reported by three large population-based cohort studies and one case-control study. One study from Texas including 4.2 million infants (aPR 3.24; CI 2.86-3.67) (20), a second from Denmark including two million infants (aRR 3.96; CI 3.48-4.49) (19), a third from Norway including 900,000 livebirths, stillbirths or terminated pregnancies (aRR 2.92; CI 2.54-3.36) (21) and last an American study (NBDPS) with approximately 18,000 infants, who reported risks for both isolated CHDs (aOR 4.65; CI 2.87–7.51) and CHD as part of multiple defects (aOR 10.77; CI 6.23–18.62) (52).

The association between any CHD and DM1 was reported by three large population-based studies, each of which included at least one million pregnancies, from Sweden (aRR 3.19; CI 2.69-3.80) (18), Taiwan (aOR 2.32; CI 1.66–3.25) (36), and Canada (OR 4.65; CI 4.13–5.24) (22). Two of the studies also reported a significant association between any CHD and DM2 (aOR 2.85; CI 2.60–3.12 (36), or aOR 4.12; CI 3.69–4.60 (22)).
Four studies evaluated subtypes of CHDs according to Botto et al.’s classification (56). All studies found positive associations for PGDM and selected subtypes listed in Table 1 (19–21,52), except for anomalous pulmonary venous return in two studies (19,21), RVOTO in one study (21), and heterotaxia in one study (52). Two studies presented associations between PGDM and major CHDs, but they defined major CHDs differently (Table 1): Leirgul et al. found an association between PGDM and major CHDs (aRR 3.34; CI 2.48–4.49) (21), Chou et al. only found an association between DM2 and major CHDs (aOR 2.80; CI 2.04–3.85), but not for DM1 and major CHDs (36).

Several studies have investigated the relationship between PGDM and specific CHD diagnoses (37,48,50–54) and in most cases found a significant association (Table 3).

3.6 Maternal gestational diabetes and CHDs in the offspring

Five studies reported how they defined “any CHD” (Table 1) (19–21,52,55). Three studies found a significant association between any CHD and GDM (aPR 1.49; CI 1.39–1.60 (20), aRR 1.47; CI 1.26–1.71 (21), and aOR 1.59; CI 1.27–1.99 for isolated CHDs (52)). These studies also reported on GDM and subtypes of CHDs (Table 4). Øyen et al. found an association between any CHD and GDM diagnosed in the third trimester (aRR 1.36; CI 1.07–1.69), but could not find a significant association between any CHD and GDM diagnosed in the second trimester (19). A Chinese study reported the prevalence of any CHD from postnatal population-based screening of approximately 90,000 infants to be 33.7/1,000 in pregnant women with GDM vs. 19.8/1000 in pregnant women without GDM (55).

3.7 Combination of maternal obesity and gestational diabetes and CHDs in the offspring

Only one study comprised an assessment of the combined risk of two maternal metabolic conditions. Gilboa et al. reported an accumulating effect of the combination of maternal obesity (BMI ≥ 30 kg/m²) and GDM and the risk of any CHD (aOR 1.82; CI 1.36–2.44) (40). The relation between the combination of maternal obesity and GDM and subtypes of CHDs are reported in Table 5.

4. Discussion
No studies assessing the association between CHDs in the offspring and maternal MetS were identified. Only one study dealt with the combination of more than one maternal metabolic condition as risk factor for CHDs in the offspring (40). All other studies investigated the individual metabolic disorders and their association with CHDs, and here were no eligible studies on dyslipidaemia.

The associations between maternal metabolic disorders related to MetS and CHDs fall in three groups: A. chronic hypertension, GDM, and obesity with ORs or RRs of 1.3-1.8; B. PGDM with ORs or RRs around 3-4; and C. early-onset PE with ORs or PRs of 7. Thus, for the most prevalent maternal conditions, the relative risks of CHDs are only marginally elevated. However, most of these conditions co-occur in pregnant women, which is why it is important to study the relative risks associated with combinations of metabolic disorders. Furthermore, it is important to examine whether a modification of a pre-existing condition influences risks for CHDs.

The aetiology of CHD is complex and the large population- and register based studies cannot distinguish subgroups with markedly elevated risks from the larger group presumably without specific aetiologies, such specific chromosomal aberrations or Mendelian inherited CHDs to establish evidence-based information for use in a clinical setting. Furthermore, these studies do not address the combination of several maternal metabolic disorders related to MetS, and they are hampered due to diverging definitions, classifications, and methodology.

The number of high-quality studies is surprisingly small, particularly in view of the high and increasing prevalence of obesity, diabetes, and MetS. Furthermore, no studies from countries with high prevalence of PE, i.e. Sub-Saharan Africa, were eligible, very few publications addressed this issue in high prevalence countries and those that did, unfortunately, did not fulfil the inclusion criteria. This skewness may result in the findings being irrelevant for large parts of the global population.

There is a clear pathophysiological connection between maternal insulin resistance and foetal CHDs, with glucose-mediated mechanisms of CHD involving multiple developmental pathways (57). The association between PE, a condition occurring by definition after gestational week 20, and CHDs developed much earlier may be explained by the changes in maternal adipocytokine levels in first trimester of PE pregnancies (58,59).

PE is considered a disease of multiple aetiologies and may present with signs ranging from mild hypertension with a normal foetus to a condition with severe intrauterine growth retardation and a maternal hypertensive syndrome (60).
As the mild hypertension may reflect a physiological response to the placental hypo-perfusion whereas the maternal syndrome is caused by widespread endothelial damage, it is important to study the association between CHDs and PE in cohorts of well-characterized patients. In two large studies, the association between CHDs and PE is much stronger in PE with early-onset (24,25). This is compatible with an interference with foetal glucose regulation in first trimester.

Furthermore, one study also report a strong relation between CHD and PE with intrauterine growth retardation (25).

Women with chronic hypertension will most likely be undergoing treatment with antihypertensive drugs. It is thus important to distinguish between the effects of antihypertensive drugs and the hypertension proper. A meta-analysis by Ramakrishnan et al. observed an association between untreated hypertension and CHDs, which suggests that the association between hypertension and CHDs is not simply due to teratogenic effects of medication alone (61). But the effect is larger for treated hypertension. Thus, antihypertensive medications may lead to an additional increase in risk.

Treated hypertension might also indicate more severe disease in the mother.

Our findings regarding maternal obesity are compatible with findings from recent meta-analyses which included studies not eligible for this review: Zhu et al. (17 studies) reported an OR 1.17 (CI 1.15-1.20) for maternal BMI ≥ 30 kg/m² (62), and Zheng et al. (29 studies) reported an OR 1.32 (CI 1.21-1.43) for BMI > 30 kg/m² and OR 1.42 (1.33-1.51) for BMI ≥ 40 kg/m² (63). Two meta-analyses reported a dose-response effect on risk of CHDs with increasing BMI (63,64). It is very well-established that maternal obesity is associated with marginally increased risk of CHDs. However, an increase of 20-40% of a very small risk may not be clinically significant. Particularly as it has not been shown that weight reduction normalizes the risk.

No articles on dyslipidaemia fulfilled the inclusion criteria for the review. However, one small case-control study from China found significantly increased levels of low-density lipoprotein cholesterol and apolipoprotein B at 24 to 28 weeks’ gestation in the pregnancies with a foetus with CHD compared to uncomplicated pregnancies (65). The mean BMI was normal in both groups (p=0.83) (65).

Our analysis shows a remarkable lack of knowledge on the link between MetS, a major global health problem, and CHDs in the offspring. There is a need for large population-based studies of the risk for foetal CHDs and combinations of various maternal metabolic disorders. Furthermore, such studies should be ethnically inclusive and include women of different socio-economic status. There is also a need for more detailed studies of the molecular mechanisms of...
CHDs. A combination of large NGS-based genome and exome sequencing studies and the use of electronic health records in a population-wide biobank setting could bring relevant knowledge on molecular mechanisms that might support preventive approaches to CHDs as well as information of possible use in development of evidence-based personalized medical advice.

The strength of this review is that we have selected only high-quality, original research studies. However, we have limited our selection of studies to those published in English, which may have excluded a number of high-quality studies which were published in another language.

### 5. Conclusion

The aetiology of CHDs is complex; furthermore, they are the most common malformations and a major cause of morbidity and mortality in childhood. It is thus important to identify risk factors. Our review shows that there is a well-established association, albeit to a varying extent, between obesity, hypertension, diabetes and PE with increased risk of CHDs in the child. Frequently, these disorders occur clustered in the same pregnancy. Unfortunately, no studies had been conducted into the risk of CHDs in children born by mothers with combination of several metabolic disorders related to MetS. This hampers the clinical usefulness of the risk assessments. Since occurrence of MetS is rapidly increasing, there is a need for such studies. Secondly, there is also a need for studies covering populations other than those of European and Asian descent, particularly as the prevalence of MetS and its different manifestations vary widely globally. Finally, despite the growing knowledge on the molecular aetiology of individual CHDs no studies have, as of yet, studied the relation between the combination of maternal metabolic disorders and CHDs. Such studies may result in the identification of subgroups of women where MetS might be of particularly importance as a risk factor. The shortage, found in this study, of high-quality studies on the combination of metabolic disorders as a risk factor for CHDs in the child makes it difficult to define treatment and preventive strategies.
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**Table and Figure Legends**

**Figure 1.** Flow diagram. The process of selection of studies to be included in the review. Literature search included studies published from January 1, 1990 to October 6, 2019.

- CHDs, congenital heart defects; ICD, International Classification of Disease; NOS, Newcastle-Ottawa Scale
Figure 2. Content of the included studies. A. Number of different maternal metabolic disorders assessed in the studies. Metabolic disorders were defined as obesity, diabetes, hypertension, preeclampsia, dyslipidaemia or metabolic syndrome. B. Number of different congenital heart defect diagnoses assessed in the studies. C. Number of patients with congenital heart defects included in the studies.
| Author/publication year | Country of study population | Study design | Sample source (size of population) | Included study population | Plurality | Reported CHDs | Adjusted for confounders or matched | Maternal exposure | Sources of maternal exposure |
|-------------------------|-----------------------------|--------------|-----------------------------------|---------------------------|-----------|--------------|-----------------------------------|-----------------|-------------------------------|
| Agopian 2012            | USA (Texas)                 | Cohort       | Population-based (n=3,806,299)     | Livebirths, stillbirths, terminated | All       | AVSD (BPA: 745.620) | Unadjusted?                        | Any DM, PGDM, GDM | Registers                      |
| Auger 2015              | Canada (Quebec)             | Cohort       | Population-based (n=1,942,072)     | Livebirths                | All       | Any CHD (ICD-9: 745-747.4; ICD-10: Q20-26.4 + Q26.8-26.9); critical CHDs (ToF, TGA, truncus arteriosus, hypoplastic left heart, UVH, CoA); non-critical CHDs (endocardial cushion, VSD, ASD, valve, aorta, pulmonary artery, heterotaxia) | Adjusted | Early-onset PE, late-onset PE, PE with growth restriction, severity of PE | Register |
| Block 2013              | USA (Florida)               | Case-control | Population-based (2,767 CHD cases/1,079,746 controls) | Livebirths                | Singletons | Aortic valve stenosis; CoA; AVSD; pulmonary valve atresia and stenosis; ToF; TGA; VSD | Adjusted | Overweight/obesity | Medical records |
| Blomberg 2010           | Sweden                      | Cohort       | Population-based, nationwide (n=1,049,582) | Livebirths, stillbirths | Not stated | ToF, TGA, HLHS, common truncus (pooled as "serious CHDs" or separate) | Adjusted | Overweight/obesity | Registers |
| Boyd 2017               | Denmark                     | Cohort       | Population-based, nationwide (n=1,972,857) | Live births               | Singletons | Any CHD (ICD-8: 746.00-747.49, 759.00, 759.01, 759.09; ICD10: Q20-26 + Q893); Heterotaxia; Conotruncal defects; AVSD; APVR; LVOTO; RVOTO; different septal defects; other subtypes of CHDs | Adjusted | Early preterm PE, late preterm PE, term PE, gestational hypertension | Register |
| Brite 2014              | USA                         | Cohort       | Population-based, multi-site, CSL (n=121,815) | Livebirths                | Singletons | Any CHD (ICD-9: 745-747.4); Conotruncal defects; VSD; ASD | Adjusted | Overweight/obesity | Medical records |
| Brodwall 2016           | Norway                      | Cohort       | Population-based, nationwide (n=914,703) | Livebirths, stillbirths, terminated | Singletons | Major CHDs also incl. VSD corrected age < 1y, UVH, cc-TGA, DOLV | Adjusted | Early-onset PE+severe/mild/unspecified, late-onset PE+severe/mild/unspecified, pregnancy-induced hypertension | Register |
| Cedergren 2003          | Sweden                      | Case-control | Population-based, nationwide (7,379 CHD cases/812,457 controls) | Livebirths, stillbirths | Not stated | HLHS; d-TGA; Endocardial cushion defects; ToF; VSD; ASD; CoA; Severe CHDs (11 subtypes of CHDs grouped together) | Adjusted | Overweight/obesity | Registers |
| Study | Country | Study Design | Population | Livebirths | CHD Diagnosis | Adjustment/Stratification | Data Collection |
|-------|---------|--------------|-------------|------------|---------------|---------------------------|----------------|
| Chou 2016 | Taiwan | Cohort | Population-based, nationwide (n=1,387,650) | Livebirths | All | Any CHD (ICD-9-CM: 745-747.4); severe CHDs (ToF, TGA, DORV, APVR, tricuspid atresia, cCTGA, common truncus, UVH) | Adjusted DM1, DM2, chronic hypertension | Register |
| Correa 2008 | USA | Case-control | Population-based, multisite, NBDPS (13,030 CM cases/4,895 controls) | Livebirths | Not stated | Any CHD (described in NBDPS); 16 subtypes of CHDs | Adjusted PGDM (DM1 or DM2), GDM | Interviews |
| Erickson 1991 | USA | Case-control | Population-based, ABDCCS (4,900 CM cases/3,000 controls) | Livebirths, stillbirths | Not stated | 13 subtypes of CHDs | Matched DM | Interviews |
| Fisher 2017 | USA | Case-control | Population-based, multisite, NBDPS (10,625 CHD cases/11,137 controls) | Livebirths, stillbirths, terminated | Singletons | Any CHD (described in NBDPS); Heterotaxia; Conotruncal defects; AVSD; APVR; LVOT defects; RVOT defects; Ebstein’s anomaly; Septal defects; UVH | Adjusted Hypertension incl. antihypertensive medications | Interviews/self-reported |
| Gilboa 2010 | USA | Case-control | Population-based, multisite, NBDPS (6,440 CHD cases/5,673 controls) | Livebirths, stillbirths | Not stated | Any CHD (described in NBDPS); Heterotaxia; UVH; Conotruncal defects; AVSD; APVR; LVOTO; RVOTO; Ebstein’s anomaly; Septal defects; CoA+VSD; VSD+ASD; pulmonary valve stenosis+ASD | Adjusted Overweight/obesity, overweight/obesity+GDM | Interviews |
| Hoang 2016 | USA (Texas) | Cohort | Population-based (n=4,207,898) | Livebirths | All | Any CHD (ICD-10: Q20-Q269, Q893); Heterotaxia; Conotruncal defects; AVSD; LVOTO; RVOTO; UVH; AVPR; VSD | Adjusted Any DM, PGDM, GDM | Self-reported / medical records |
| Kovalenko 2018 | Russia (Murmansk) | Cohort | Population-based (n=52,253) | Livebirths | Singletons | VSD (ICD-10: Q21.0) | Adjusted PGDM (DM1 or DM2), overweight/obesity | Registers |
| Leirgul 2016 | Norway | Cohort | Population-based, nationwide (n=914,427) | Livebirths, stillbirths, terminated | Singletons | Any CHD (45 CHD diagnoses listed in paper); major CHDs also incl. cCTGA, UVH, double inlet left ventricle, absent pulmonary valve and except valvular pulmonary stenosis; other subtypes of CHDs | Adjusted DM1, DM2, GDM or unspecified DM | Registers |
| Liu 2013 | Canada (excl. Quebec) | Cohort | Population-based, nationwide (n=2,278,838) | Livebirths | All | Any CHD (ICD-10-CA: Q200-269, Q893); Heterotaxia; Conotruncal defects; AVSD; LVOTO; RVOTO; VSD; ASD; Multiple defects | Adjusted PGDM (DM1, DM2), chronic hypertension, obesity | Register |
| Study          | Country         | Type         | Population | Livebirths | CHD Diagnosis                                                                 | Adjusted | Study Design/Methodology |
|---------------|-----------------|--------------|-------------|------------|-------------------------------------------------------------------------------|----------|-------------------------|
| Liu 2015      | China (Tianjin) | Cohort       | Population-based (n=90,796) | Livebirths | Any CHD (ASD, VSD, PDA, PS, ToF, AVSD, AS, UVH, Ebstein's anomaly, compound and others) | ??       | Self-reported / medical records |
| Ludvigsson 2018 | Sweden         | Cohort       | Population-based, nationwide (n=1,162,323) | Livebirths | Singletons Any CHD (Q20-Q25, Q260, Q262-Q269) | Adjusted | DM1                     |
| Mills 2010    | USA (New York State) | Case-control (nested) | Population-based (7392 CHD cases/56,304 controls) | Livebirths and stillbirths? | Singletons Conotruncal defects; TGA; DORV; ToF; All septal defects; ASD; VSD; LVOTO; HLHS; CoA; Aortic valve stenosis; RVOTO; Pulmonic valve stenosis; APVR; Total APVR; AVSD | Adjusted | Overweight/obesity                   |
| Persson 2019  | Sweden         | Cohort       | Population-based, nationwide (n=2,050,491) | Livebirths | Singletons Any CHD (ICD-10: Q20-25, Q260, Q262-269); ToF; TGA; AVSD; Aortic arch defect; UVH (complex CHDs) and 7 subtypes of CHD | Adjusted | Overweight/obesity                   |
| Rankin 2010   | England        | Cohort       | Population-based (n=41,013) | Livebirths and stillbirths, terminated | Singletons Any CHD (ICD-10: Q20-26); TGA; VSD; ASD; ToF; Ebstein's anomaly; Pulmonary valve stenosis; Aortic valve atresia/stenosis, CoA | Adjusted | Overweight/obesity                   |
| Sharpe 2005   | Australia      | Cohort       | Population-based (n=282,260) | Livebirths and stillbirths | Singletons TGA | Adjusted | PGDM, GDM                   |
| Shaw 2000     | USA (California)| Case-control | Population-based (1,299 CM cases/734 controls) | Livebirths and stillbirths | Not stated Conotruncal defects (ToF, d-TGA, TA, DORV, pulmonary valve atresia with VSD, subaortic VSD type I and aortico-pulmonary window); d-TGA; ToF | Adjusted | Overweight/obesity                   |
| Shaw 2001     | USA (California)| Case-control | Population-based (301 CHD cases/1,390 controls) | Livebirths and stillbirths, terminated | Not stated ToF; d-TGA | Adjusted | Overweight/obesity                   |
| Verczekkey 2014 | Hungary       | Case-control | Population-based (3,562 CHD cases/38,151 controls) | Livebirths | All | Adjusted | DM, chronic hypertension       |
| Vinceti 2014  | Italy          | Cohort       | Population-based (n=479,720) | Livebirths and stillbirths | All TGA; ToF; VSD; ASD | Matched | PGDM (DM1 or DM2)             |
| Watkins 2001  | USA            | Case-control | Population-based, ABDCCS (1049 CHD cases/2,767 controls) | Livebirths and stillbirths | Not stated Any CHD (ICD-9: 745.00—747.49, isolated or multiple); outflow tract defects (ToF, DORV, TA, TGA); ToF; TGA; Septal defects (VSD, ASD); VSD; ASD; Right-sided defects (PA without VSD, pulmonic stenosis, pulmonic atresia) | Matched and adjusted | Overweight/obesity                   |
| Study          | Country | Design      | Population        | Outcomes                          | Adjusted | Risk Factor | Notes                                                                 |
|---------------|---------|-------------|-------------------|-----------------------------------|----------|--------------|-----------------------------------------------------------------------|
| Watkins 2003  | USA     | Case-control| Population-based, Atlanta BDRFSS (640 CM cases/330 controls) | Livebirths, stillbirths, terminated | Not stated | LVOTO; RVOTO; ASD; VSD; ASD or VSD; outflow tract defects            | Adjusted Overweight/obesity Interviews                                  |
| Øyen 2016     | Denmark | Cohort      | Population-based, nationwide (n=2,025,727)                     | Livebirths Singletons               | Any CHD (ICD-8: 740-759; ICD-10: Q20-26); Heterotaxia; Conotruncal defects; AVSD; APVR; LVOTO; RVOTO; Septal defects; other subtypes of CHDs | Adjusted DM1, DM2, GDM Registers                                      |

Note: The CHD diagnoses are described as “any CHD” for the whole group of diseases, “major CHDs” for a group of the most critical and severe CHD diagnoses, or as specific CHD diagnoses. Major CHDs are defined as (unless other stated): heterotaxia, conotruncal defects, atrioventricular septal defects, anomalous pulmonary venous return, left ventricular outflow tract obstruction, right ventricular outflow tract obstruction.

Abbreviations: ABDDCS, Atlanta Birth Defect Case-Control Study; APVR, anomalous pulmonary venous return; ASD, atrial septum defect; AVSD, atrioventricular septal defect; BDRFSS, Birth Defects Risk Factor Surveillance Study; BMI, body mass index (pre-pregnancy or early-pregnancy unless other stated); BPA, British Pediatric Association (codes); BWIS, Baltimore Washington Infant Study; CHDs, congenital heart defects; CM, congenital malformations; CSL, The Consortium of Safe Labor; CVM, cardiovascular malformations; DM, diabetes mellitus; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; DOLV, double outlet left ventricle; d-TGA, dextro-transposition of the great arteries; ECM, early cardiovascular malformations; EUROCAT, European network of population-based registries for the epidemiological surveillance of congenital anomalies; GA, gestational age in weeks; GDM, gestational diabetes mellitus; HbA1C, glycated haemoglobin; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; ICD-10, International Classification of Diseases, 10th revision; ICD-10-CA, International Classification of Diseases, 10th Revision, Canada; ICD-8, International Classification of Diseases, 8th revision; ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; LVOTO, left ventricular outflow tract obstruction; NBDPS, National Birth Defects Prevention Study; PA, pulmonary atresia; PE, preeclampsia; PGDM, pregestational diabetes; RVOTO, right ventricular outflow tract obstruction; TA, truncus arteriosus; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; UVH, univentricular heart; VSD, ventricular septal defect.
## Table 2. Studies on maternal overweight/obesity and subtypes of congenital heart defects

| Publication | Agopian 2012 | Block 2013 | Blomberg 2010 | Brite 2014 | Cedergren 2003 | Gilboa 2010 | Liu 2013 | Mills 2010 | Persson 2019 | Rankin 2010 | Shaw 2000 | Shaw 2008 | Watkins 2001 | Watkins 2003 |
|-------------|--------------|------------|--------------|------------|----------------|--------------|----------|------------|-------------|-------------|-----------|-----------|-------------|-------------|
| Risk estimate | aPR (CI) | aOR (CI) | OR (CI) | aOR (CI) | aOR (CI) | aOR (CI) | aOR (CI) | aPR (CI) | aOR (CI) | aOR (CI) | aOR (CI) | aOR (CI) | OR (CI) | aOR (CI) | OR (CI) |
| UVH | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA |
| Common truncus | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA |
| TGA | I: 1.32 (1.01–1.73); II: 1.54 (1.08–2.20); III: 1.80 (1.19–2.72) | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA |
| ToF | I: 1.35 (1.02–1.79); II: 1.93 (1.38–2.71); III: 2.11 (1.42–3.12) | NSA | NSA | BMI ≥25: 1.24 (1.01–1.53) | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA |
| DORV | | | | | | | | | | | | | | | |
| Aortic arch defects | | | | | | | | | | | | | | | |
| AVSD | BMI≥30: 1.7 (1.2–2.3) | BMI≥30: 1.55 (1.09–2.22) | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA | NSA |
| TAPVR | | | | | | | | | | | | | | | |
| Ebstein’s anomaly | | | | | | | | | | | | | | | |

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| CHD Type                  | I: 1.34 (1.03–1.73) | NSA | I+II: 1.51 (1.24–1.83); III: 1.52 (1.01–2.29); BMI≥30: 1.51 (1.25–1.82) | NSA | Overweight: 3.3 (1.6–6.7) | NSA |
|--------------------------|---------------------|-----|--------------------------------------------------------------------------------|-----|---------------------------|-----|
| LVOTO                    | CoA                 | NSA | NSA                                                                 | NSA | Overweight: 3.9 (1.1–13.8) | NSA |
|                          | Aortic valve stenosis| I: 1.93 (1.09–3.43) | NSA                                                                 | I+II: 2.03 (1.41–2.92); BMI≥30: 2.04 (1.44–2.88) | NSA |
| RVOTO                    | I: 1.51 (1.03–2.22); BMI≥25: 1.32 (1.02–1.72) | NSA | I+II: 1.66 (1.13–2.45); BMI ≥30: 1.71 (1.19–2.46) | NSA |
|                         | II: 1.45 (1.13–1.87); III: 1.83 (1.39–2.40)* | NSA | Overweight: 1.40 (1.11–1.75); BMI ≥35: 1.76 (1.24–2.48); BMI ≥25: 1.36 (1.12–1.66) | NSA |
| HLHS                     | NSA                 | BMI≥30: 1.67 (1.13–2.46) | I+II: 1.30 (1.06–1.59); BMI ≥30: 1.29 (1.07–1.56) | NSA |
|                         | II: 1.45 (1.13–1.87); III: 1.83 (1.39–2.40)* | NSA | Overweight: 1.16 (1.01–1.34); BMI≥35: 1.35 (1.07–1.70); BMI≥25: 1.15 (1.02–1.30) | NSA |
| Pulmonary valve stenosis | I+II: 1.66 (1.13–2.45); BMI ≥30: 1.71 (1.19–2.46) | NSA | Overweight: 1.40 (1.11–1.75); BMI ≥35: 1.76 (1.24–2.48); BMI ≥25: 1.36 (1.12–1.66) | NSA |
| Septal defects           | I+II: 1.30 (1.06–1.59); BMI ≥30: 1.29 (1.07–1.56) | NSA | Overweight: 1.16 (1.01–1.34); BMI≥35: 1.35 (1.07–1.70); BMI≥25: 1.15 (1.02–1.30) | NSA |
| CHD Type | BMI Range | Adjusted PR/Adjusted OR | NSA | NSA | NSA | NSA | NSA |
|----------|-----------|-------------------------|-----|-----|-----|-----|-----|
| VSD      | I: 1.10 (1.01–1.20); II: 1.17 (1.04–1.32); III: 1.32 (1.15–1.52) | I+II: 1.39 (1.05–1.83); BMI≥30: 1.38 (1.06–1.79) | BMI>29: 1.14 (1.01–1.28) | NSA | NSA | BMI≥30: 1.38 (1.06–1.79) | NSA |
| ASD      | BMI 30–39.9: 1.19 (1.01–1.42), BMI≥30: 1.22 (1.04–1.43) | BMI≥29: 1.37 (1.09–1.72) | Overweight: 1.28 (1.03–1.59); BMI≥35: 1.51 (1.09–2.11); BMI≥25: 1.29 (1.07–1.55) | BMI≥25: 1.74 (1.32–2.31) | NSA | NSA |

Note: * Pulmonary valve stenosis and atresia; NSA = no significant association; overweight = BMI 25.0–29.9; I = obesity class I (BMI 30.0–34.9); II = obesity class II (BMI 35.0–39.9); III = obesity class III (BMI ≥40)

Abbreviations: aPR/aOR, adjusted; AVSD, atrioventricular septal defect; BMI, body mass index (kg/m²); CI, 95% confidence interval; CoA, coarctation of the aorta; DORV, double outlet right ventricle; LVOTO, left ventricular outflow tract obstruction; OR, odds ratio; PR, prevalence ratio; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; UVH, univentricular heart
### Table 3. Studies on pre-gestational diabetes and subtypes of congenital heart defects

| Publication | Agopian 2012 | Correa 2008 | Erickson 1991 | Hoang 2016 | Kovalenko 2018 | Leigui 2016 | Sharpe 2005 | Vereczkey 2014 | Vinceti 2014 |
|-------------|--------------|-------------|---------------|------------|----------------|-------------|-------------|----------------|-------------|
| Risk estimate | aPR (CI) | aOR (CI) | OR (CI) | aPR (CI) | aOR (CI) | aRR (CI) | RR (CI) | OR (CI) | aPR (CI) |
| UVH | | | | | | | | | |
| | | | | | | | | | |
| Conotruncal | | | | | | | | | |
| Common truncus | | | | | | | | | |
| | NSA | | | NSA | | NSA | | NSA | |
| TGA | 3.34 (1.11–10.07)**, 71.97 (7.43–696.81)** | 5.30 (2.2–15.8) | | NSA | NSA | NSA | NSA | NSA | NSA |
| ToF | 4.89 (2.18–10.95)*, 6.60 (1.67–21.58)** | NSA | 2.47 (1.10–5.55) | | | | | |
| DORV | | | | | | | | | |
| Aortic arch defects | | | | | | | | | |
| AVSD | 12.36 (3.68–41.49)*, 25.28 (4.20–152.11)** | 5.33 (2.81–10.11) | 8.72 (3.16–24.07) | 6.38 (3.15–12.94) | NSA | NSA | NSA | NSA | NSA |
| TAPVR | 6.7 (3.7–12.4) | 7.12 (1.99–25.42)* | 3.40 (1.95–5.93) | NSA | | NSA | | NSA | NSA |
| Ebstein’s anomaly | | | 6.28 (1.06–37.27) | NSA | | NSA | | NSA | NSA |
| LVOTO | 4.58 (1.30–16.10)* | 4.55 (2.93–7.05) | 2.21 (1.14–4.26) | NSA | | NSA | | NSA | NSA |
| CoA | NSA | NSA | 4.27 (2.41–7.57) | NSA | | NSA | | NSA | NSA |
| Aortic stenosis | 5.01 (1.09–22.90)* | NSA | 4.95 (2.46–9.97) | NSA | | NSA | | NSA | NSA |
| RVOTO | 9.61 (3.53–26.15)*, 9.83 (1.05–91.85)** | 4.08 (2.93–5.70) | NSA | NSA | NSA | NSA | NSA | NSA |
| HLHS | NSA | NSA | 4.14 (1.55–11.02) | NSA | | NSA | | NSA | NSA |
| Pulmonary valve stenosis | 1.44 (0.41–5.06)* | 3.81 (2.68–5.50) | NSA | NSA | NSA | NSA | NSA | NSA | NSA |

### Septal defects

| Publication | Agopian 2012 | Correa 2008 | Erickson 1991 | Hoang 2016 | Kovalenko 2018 | Leigui 2016 | Sharpe 2005 | Vereczkey 2014 | Vinceti 2014 |
|-------------|--------------|-------------|---------------|------------|----------------|-------------|-------------|----------------|-------------|
| Risk estimate | aPR (CI) | aOR (CI) | OR (CI) | aPR (CI) | aOR (CI) | aRR (CI) | RR (CI) | OR (CI) | aPR (CI) |
| VSD | 2.89 (1.27–6.56)*, 7.0 | 2.65 (1.3–5.3) | 3.49 (2.99–4.08) | NSA | NSA | NSA | NSA | NSA | NSA |
| ASD | 8.47 (4.37–16.42)*, 13.46 (5.23–34.60)** | NSA | 2.89 (2.49–3.36) | NSA | NSA | NSA | NSA | NSA | NSA |

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Note: Risks are for PGDM if nothing else is stated. PGDM is defined as diabetes type 1 or type 2; * = isolated defects; ** = multiple defects, NSA = no significant association

Abbreviations: aPR/aOR/aRR, adjusted; AVSD, atrioventricular septal defect; CI, 95% confidence interval; CoA, coarctation of the aorta; DORV, double outlet right ventricle; LVOTO, left ventricular outflow tract obstruction; PGDM, pregestational diabetes; OR, odds ratio; PR, prevalence ratio; pregestational diabetes; RR, relative risk; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; UVH, univentricular heart
### Table 4. Studies on gestational diabetes and subtypes of congenital heart defects

| Publication | Correa 2008 | Hoang 2016 | Leirgui 2016 |
|-------------|-------------|------------|--------------|
| Risk estimate | aOR (CI) | aPR (CI) | aRR (CI) |

**UVH**

| Condition | Risk Estimate |
|-----------|---------------|
| NSA       | NSA           |

**Conotruncal**

| Condition        | Risk Estimate |
|------------------|---------------|
| Common truncus   | 2.78 (1.17–6.60) |
| TGA              | NSA           |
| ToF              | 1.80 (1.12–2.87)* |
| DORV             | NSA           |

**Aortic arch defects**

| Condition | Risk Estimate |
|-----------|---------------|
| AVSD      | NSA           |
| 1.54 (1.03–2.31) |
| TAPVR     | NSA           |
| 2.31 (1.53–3.49) |
| Ebstein's anomaly | NSA |

**LVOTO**

| Condition | Risk Estimate |
|-----------|---------------|
| CoA       | NSA           |
| 2.23 (1.79–2.77) |
| Aortic stenosis | NSA |
| 1.76 (1.18–2.62) |

**RVOTO**

| Condition             | Risk Estimate |
|-----------------------|---------------|
| HLHS                  | NSA           |
| 2.41 (1.59–3.64)*,   | 5.96 (1.86–19.11)** |
| Pulmonary valve stenosis | NSA |

**Septal defects**

| Condition | Risk Estimate |
|-----------|---------------|
| VSD       | NSA           |
| 1.33 (1.20–1.48) |
| ASD       | 2.16 (1.46–3.21)*, 2.40 (1.19–4.82)** |

**Note:** *, isolated defects; ** multiple defects; NSA = no significant association
Abbreviations: aPR/aOR/aRR, adjusted; AVSD, atrioventricular septal defect; CI, 95% confidence interval; CoA, coarctation of the aorta; DORV, double outlet right ventricle; LVOTO, left ventricular outflow tract obstruction; OR, odds ratio; PR, prevalence ratio; RR, relative risk; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; UVH, univentricular heart
Table 5. Study on the combination of gestational diabetes and maternal overweight/obesity and subtypes of congenital heart defects

| Publication   | Risk estimate |
|---------------|---------------|
| Gilboa 2010   | aOR (CI)      |

| UVH | NSA |
|-----|-----|
| Conotruncal | NSA |
| Common truncus | NSA |
| TGA | NSA |
| ToF | BMI≥30: 2.38 (1.37-4.14) |
| DORV | |
| Aortic arch defects | |
| AVSD | NSA |
| TAPVR | NSA |
| Ebstein's anomaly | NSA |
| LVOTO | BMI≥30: 1.87 (1.15-3.05) |
| CoA | Overweight: 1.98 (1.01-3.87) |
| Aortic valve stenosis | NSA |
| RVOTO | Overweight: 2.06 (1.17-3.63); BMI ≥30: 1.82 (1.09-3.03) |
| HLHS | Overweight: 2.48 (1.03-5.97); BMI ≥30: 2.81 (1.40-5.64) |
| Pulmonary valve stenosis | BMI≥30: 2.21 (1.30-3.76) |
| Septal defects | BMI≥30: 1.91 (1.35-2.70) |
| VSD | NSA |
| ASD | BMI≥30: 2.74 (1.82-4.14) |

Note: NSA = no significant association; overweight = BMI 25.0–29.9
Abbreviations: AVSD, atrioventricular septal defect; aOR, adjusted odds ratio; BMI, body mass index (kg/m²); CI, 95% confidence interval; CoA, coarctation of the aorta; DORV, double outlet right ventricle; LVOTO, left ventricular outflow tract obstruction; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; UVH, univentricular heart