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Association between maternal body mass index and congenital heart defects in infants: A meta-analysis

Yu Zhu MM[1*] | Yong Chen MM[1*] | Yu Feng PhD[2] | Di Yu PhD[1] | Xuming Mo MD[1]

[1]Department of Cardiothoracic Surgery, Children's Hospital of Nanjing Medical University, Nanjing, China

[2]Department of Thoracic Surgery, The First Affiliated Hospital of Soochow University, Soochow, China

Correspondence
Xuming Mo, Department of Cardiothoracic Surgery, Children's Hospital of Nanjing Medical University, 72 Guangzhou Road, Nanjing, 210008, China.
Email: mohsuming15@sina.com

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Abstract

We conducted this meta-analysis to address the open question of a possible association between maternal body mass index (BMI) and congenital heart defects (CHDs) in infants. We conducted a comprehensive computerized search of PubMed, Web of Science, Medline, and Embase databased (January 1980 through August 2017). We assessed the association between maternal BMI and the risk for congenital heart defects in their offspring. Study-specific relative risk estimates were polled according to random-effect or fixed-effect models. From 2567 citations, a total of 13 case-control studies and 4 cohort studies were selected for a meta-analysis, including more than 1 150 000 cases. The pooled odds radio (OR) of 1.065 (95% confidence interval [CI], 1.021-1.100; $P = .001$; $I^2 = 60.1\%$) indicated a positive effect of maternal overweight status (BMI 25.0–29.9 kg/m^2) on the risk for congenital heart defects in infants. Moreover, we observed a significant association between maternal obesity (BMI $\geq$ 30 kg/m^2) and congenital heart defects in their offspring (OR: 1.174; 95% CI, 1.146–1.203, $P = 0.161$; $I^2 = 25.5\%$). However, there was little significant evidence of an association between maternal underweight status (BMI $<$ 18.5 kg/m^2) and offspring with congenital heart defects, and the pooled OR was 1.015 (95% CI, 0.980–1.052; $P = 0.085$; $I^2 = 34.0\%$). Our meta-analysis provides robust evidence of the positive association between maternal BMI and the risk for fetal congenital heart defects.

KEYWORDS

congenital heart defects, maternal body mass index, meta-analysis

1 | INTRODUCTION

Congenital heart defects (CHDs) are the most common birth defects in newborns worldwide. The prevalence of CHDs varies widely among studies. It is reported that the highest CHDs prevalence was 9.3 per 1000 live births in Asia, while the lowest is 1.9 per 1000 live birth in Africa.[1] The various reports of prevalence of CHDs may be due to different levels of diagnostic knowledge and treatment. On the whole, the prevalence of CHDs over time forms as an "s" shaped curve, increasing substantially from 0.6 per 1000 live births in 1930s to 9.1 per 1000 live births currently.[1]

Until now, the exact causes of CHDs have remained elusive, although several causes have been identified, such as genetic factors, infections, phenylketonuria, rubella, retinoic acid, and various therapeutic drug exposures.[2] Other potential factors such as maternal

Abbreviations: APVR, anomalous pulmonary venous retum; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defects; BAV, bicus-pid aortic valve; CTD, conotruncal defects; DORV, doubt outlet right ventricle; EBS, Ebstein's anomaly; ECD, endocardial cushion defect; ECMC, Spanish Collaborative Study of Congenital Malformations; HLHS, hypoplastic left heart syndrome; LVOTA, left ventricular outflow tract anomaly; LVOTD, left ventricular outflow tract defect; MVD, mitral valve defect; NBDPS, National Birth Defects Prevention Study; OTD, outflow tract defect; PA, pulmonary atresia; PAA, pulmonary artery anomaly; PDA, patent ductus arteriosus; PVA, pulmonary valve anormaly; RVOTD, right ventricular outflow tract defect; SD, septal defect; SV, single ventricle; TGA, transposition of the great arteries; TA, tricuspid atresia; TOF, tetralogy of Fallot; VSD, ventricular septal defect; UMCG, the University Medical Center Groningen.

*These authors equally contributed to the work.

overweight status and obesity have not got sufficient evidence to be determined as risks until now.

The prevalence of overweight and obese people, as assessed with body mass index (BMI), has become a global problem. BMI is calculated as weight (kg) divided by height (m^2). It is expected that there will be 2.3 billion overweight adults and no less than 700 million obese adults worldwide by 2015.[3] Block et al.[4] and Madsen et al.,[5] suggested that CHDs links to maternal obesity and elevated BMI increase the risk for fetal/infant CHDs. Reducing maternal prepregnancy obesity may reduce the occurrence of infant CHDs.[4] Conversely, Khalil et al.[6] and Ghaderian et al.[7] cast doubt on the relationship between maternal BMI and CHDs in offspring. Another inconsistency in studies involves the classification of BMI. Without the unification of BMI, a generalization of results has become complicated. We conducted this meta-analysis to assess and to confirm the association between maternal BMI and infant CHDs.

2 | METHODS

2.1 | Search strategy

We conducted a comprehensive computerized search of PubMed, Web of Science, Medline, Embase databases (January 1980 through August 2017) using the following search strategy: (congenital heart defect OR malformation of heart OR heart abnormality OR CHD) AND (body mass index OR BMI).

Potentially eligible articles were identified by the following inclusion criteria: (1) The search was restricted to original research papers written in the English language; (2) The study design was limited to case-control or cohort studies; (3) The outcome was defined as CHDs or one of the CHD subtypes; (4) BMI criteria were reported based on the definitions that were established by the Centers for Disease Control; (5) Additional articles were identified by reviewing reference lists of articles. If articles assessed the same link based on data of the same participants, we used those articles with a greater number of participants. Results reported from more than one population were considered as separate studies.

2.2 | Data extraction

A standardized data extraction form was used to retrieve information of interest, which included study characteristics, BMI distribution, the subtypes of congenital heart defects and conducted analyses (Table 1). Two reviewers Yu Zhu and Yong Chen retrieved the articles independently. Crude estimates were extracted when no adjusted estimates were available. No discrepancies existed among the reviewers in terms of the extracted data. The Newcastle-Ottawa Scale[8] was used to assess the quality of the studies. The highest score was 9, and the score of a high-quality study should be ≥ 7.

2.3 | Meta-analysis

After searching the literature in accordance with the inclusion criteria, eligible articles were divided into subgroups. Stata 10.0 was used to perform statistical analyses. The Metan, metabias, metatrim and other macros were used for the meta-analytic procedures. P values of < 0.05 were considered to be of statistical significance. Odds radio (OR) and 95% confidence interval (CI) were calculated with sufficient data to compare over-weight and obese mothers with mothers with a normal BMI (18.5–24.9 kg/m^2). In most of the articles, the BMI categories were in line with the World Health Organization guidelines[9] (underweight, < 18.5 kg/m^2; normal weight, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obesity, ≥ 30 kg/m^2). Taking into account different races, other articles similar to the international standards were deemed acceptable.

Weight was calculated to determine the contribution of each study to the pooled ORs using the inverse of the variance. Heterogeneity was tested using the Cochrane Q test and qualified with the I^2 statistic.[10] An appropriate pooling method was selected using the value of the I^2 statistic. If I^2 was less than 50%, a fixed-effects analysis was used. Conversely, random-effects models were used for I^2 greater than 50%. The trim and fill method and the Egger regression asymmetry test as well as Begg's rank correlation methods were applied to identify the presence of bias. The trim and fill method was used to stimulate studies because of publication bias and estimate the pooled OR.

3 | RESULT

3.1 | Study characteristics

A total of 2567 citations were generated according to the search strategy, and 2387 were excluded after screening titles or abstracts. About 148 papers were excluded by reviewing the articles further. 33 articles met our inclusion criteria. Among the articles that met our inclusion criteria, 5 references did not include BMI, while another 5 articles had no underweight cases according to the defined BMI category. Additionally, 1 paper lacked a control group, 1 was duplicated in another study and 2 were reviews. Finally, 17 publications[5,7,11–25] were selected for this meta-analysis (Figure 1). Of these, 11 articles were from the United States[5,7,12–15,17,18,21,22,25], 2 were from Sweden,[19,20] 1 from Spain,[16] 1 from The Netherlands,[24] 1 from Australia[11] and 1 from England.[23] A total of 8 articles were published before 2010,[11,14–20] and 9 articles were published since 2010.[5,7,12,13,21–25] Nine articles had less than 10 000 cases and controls,[7,11,14–16,18,19,24,25] and eight articles had over 10 000.[5,12,13,17,20–23] There were 13 articles reported the results of case-control studies,[5,7,11–19,24,25] and 4 were cohort studies.[20–23]

3.2 | BMI distribution

There was little significant evidence of an association between maternal underweight status and offspring with CHDs; the pooled OR was 1.015 (0.980–1.052) (Figure 2), and the P value was 0.085. The I^2 statistic was 34.0%, indicating little heterogeneity. We used Begg's test and Egger's test to examine the presence of publication bias. Funnel plot was created with Begg's test and Egger's test. The P value of Begg's test was 0.502 and of Egger's test was 0.595, suggesting that there was no publication bias (Figure 3).

TABLE 1 Characteristics of studies

Author & Year	Study period	Country	Source of cases	Study design	BMI distribution					Types of CHDs
					Underweight	Normal weight	Overweight	Obesity	Total	
Brite et al. (2014)[22]	–	The United States	From the Eunice Kennedy Shriver National Institute of Child Health and Human Development	Cohort study	72/6196	651/62162	352/28519	313/23550	1388/120427	CTD (n=399); VSD (n=360); ASD (n=1060)
Wijers et al. (2014)[24]	1990–2012	The Netherlands	From the Departments of Pediatric Surgery, or UMCG	Case-control	18/23	228/487	72/127	34/42	371/714	All types
Gilboa et al. (2010)[12]	1998–2003	The United States	From NBDPS, a population-based study	Case-control	371/324	3333/3194	1527/1259	1209/893	6440/5673	Heterotaxia (n=169); SV (n=174); CTD (n=894); AVSD (n=81); APVR (n=142); LVOTDs (n=687); RVOTDs (n=669); EBS (n=56); SDs (n=1728)
Mills et al. (2010)[13]	1993–2003	The United States	From the New York State	Case-control	569/4424	3902/30561	1605/12495	1316/8824	7392/56304	All types
Madsen et al. (2012)[5]	1992–2007	The United States	From Comprehensive Hospital Abstract Reporting System in Washington state	Case-control	305/4189	3831/53804	1741/23689	1670/18672	7547/100354	ASD (n=1690); VSD (n=2915); LVOTA (n=247); CoA (n=350); HLHS (n=174); PVA (n=621); PAA (n=626); DORV (n=85); TGA (n=177); TOF (n=377); MVD (n=66); SV (n=30)
Cedergren et al. (2002)[19]	1982–1996	Sweden	From Swedish medical health registers	Case-control	50/75	139/305	19/36	23/30	231/446	ASD (n=157); VSD (n=667); ECD (n=29); SV (n=32); TOF (n=55); TGA (n=65); HLHS (n=33); CoA (n=95)
Cedergren et al. (2006)[20]	1992–2001	Sweden	From Swedish medical health registers	Cohort study	726/91921	3578/438334	1444/171994	598/61760	6346/764009	All heart defects
Martínez-Frías et al. (2005)[16]	–	Spain	From the ECEMC	Case-control	205/1627	361/2857	191/1293	56/383	813/6160	All heart defects
Ghaderian et al.	2011–2012	The United States	From Golestan Medical,	Case-	8/10	70/74	63/52	23/22	164/158	VSD (n=64); ASD

(Continues)

TABLE 1 (Continued)

Author & Year	Study period	Country	Source of cases	Study design	BMI distribution					Types of CHDs
					Underweight	Normal weight	Overweight	Obesity	Total	
(2013)[7]			Educational, and Research Center, Jundishapur University of Medical Sciences, Ahvaz, Iran	control						(n=14); PDA (n=18); AS (n=15); CoA (n=4); ASD (n=16); TOF (n=10); TGA (n=2); TA (n=2); PA (n=2); SV (n=2); others (n=14)
Rankin et al. (2010)[23]	2003–2005	England	From five maternityunits in the northest of England	Cohort study	30/1060	274/16214	113/7975	105/4932	522/30181	TGA (n=31); VSD (n=164); ASD (n=111); AVSD (n=6); TGA (n=12); PS (n=51); AS/AP (n=15); CoA (n=17)
Shaw and Carmichael (2008)[18]	1999–2004	The United States	From the California counties of Los Angeles, San Francisco, and Santa Clara	Case-control	13/72	161/750	74/292	30/186	278/1300	TGA:128/650; TOF:150/650
Waller et al. (2007)[17]	1997–2002	The United States	From the NBDPS	Case-control	620/233	5343/2241	2166/858	1740/572	9869/3904	All heart defects
Warrick et al. (2015)[21]	2005–2011	The United States	From the Colorado Multiple Institutional Review Board.	Cohort	4/823	70/8764	21/4174	22/3074	117/16835	BAV (n=17); CoA (n=10); Left-to-right shunt (n=47); TA (n=3); TOF (n=13); PVA (n=9); TGA (n=7); EBS (n=3); other (n=8)
Watkins and Botto (2001)[15]	1982–1983	The United States	From the Atlanta Birth Defects Case-Control Study	Case-control	311/1067	451/1500	51/108	38/92	851/2767	Not mentioned
Watkins et al. (2003)[14]	1993–1997	The United States	From Metropolitan Atlanta Congenital Defects Program	Case-control	20/27	95/212	48/55	32/36	195/330	LVOTD (n=42); RVOTD (n=25); ASD (n=12); VSD (n=43); OTDs (n=50)
Oddy et al. (2009)[11]	1997–2000	Australia	From the Western Australian Birth Defects Regi-stry	Case-control	16/75	65/229	19/85	11/30	111/418	All types
Tang et al. (2015)[25]	1997–2008	The United States	From the University of Arkansas for Medical Sciences' IRB and the NBDPS	Case-control	14/74	261/878	148/361	130/281	553/1594	All types

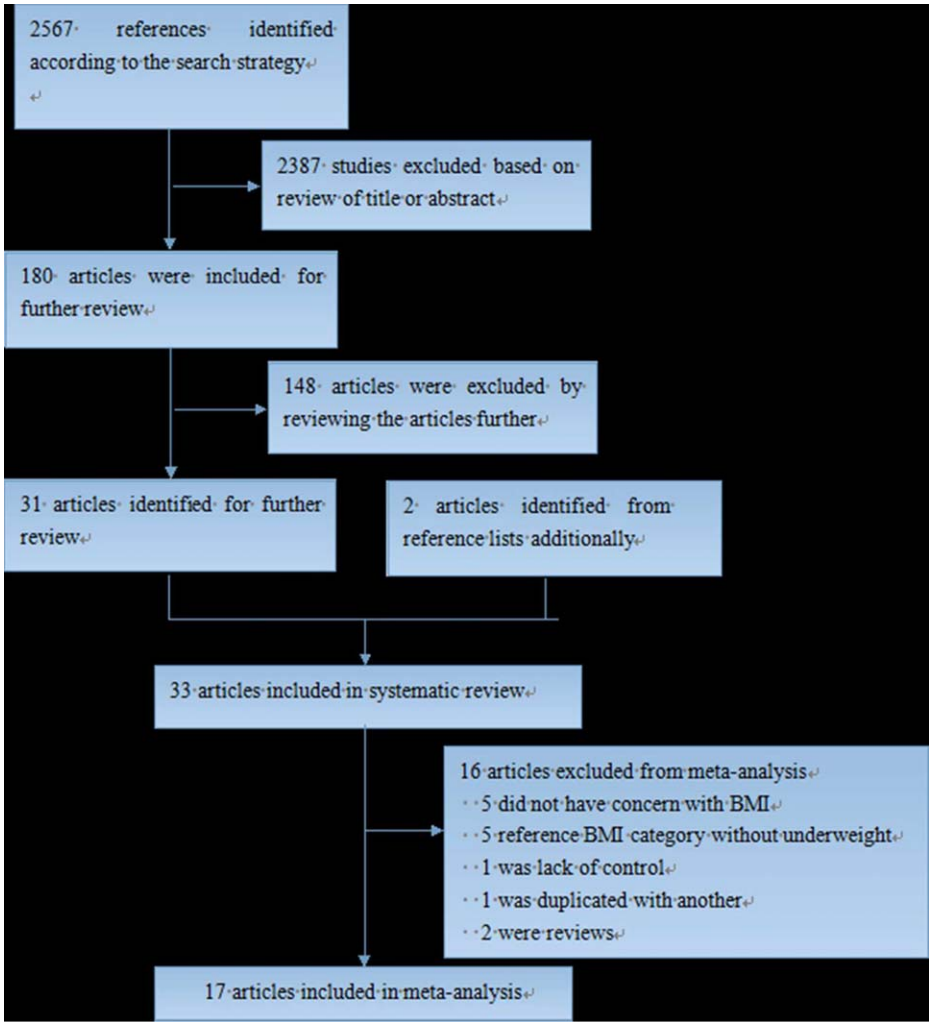

FIGURE 1 Review and selection of articles

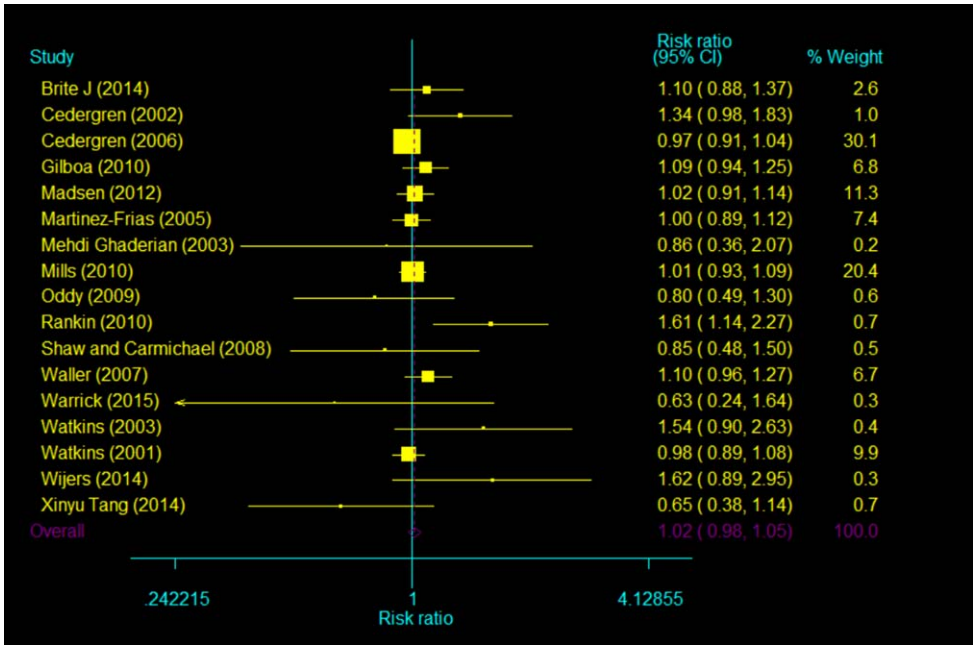

FIGURE 2 Forest plot for the subgroup of underweight

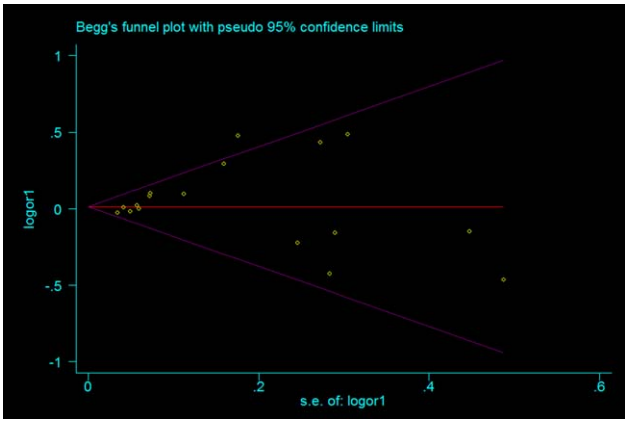

FIGURE 3 Begg's funnel plot for the subgroup of underweight

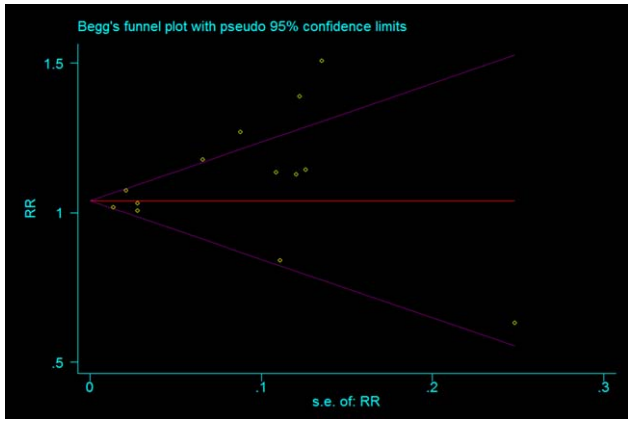

FIGURE 5 Begg's funnel plot for the subgroup of overweight

There was a positive association between maternal overweight status and infant CHDs (OR: 1.065; 95%CI: 1.021-1.100; $P = 0.001$) (Figure 4). The I^2 statistic was 60.1%, which indicated that there was heterogeneity. In subgroups, the pooled OR of articles from the USA was 1.087 (1.029–1.148) and the I^2 statistic was 68.8%, while articles from areas except the USA demonstrated an OR of 1.021 (0.982–1.062) and I^2 statistic of 27.1%, indicating that heterogeneity was resulted from American articles. Meanwhile, the I^2 statistic of articles with less than 10 000 patients was 19.6%, while articles with more than 10 000 patients had an I^2 statistic of 61.2%, indicating that heterogeneity was reported in articles whose case numbers were more than 10 000. In the sensitivity analysis, we excluded one study at a time sequentially and reanalyzed each study. If we dropped two articles from Watkins,[14,15] the I^2 statistic declined from 60.1% to 49.1%. The P value of Begg's test was 0.537 and of Egger's test was 0.143, which suggested that there was no publication bias (Figure 5).

Obese pregnant women were at significantly increased odds of having a fetus that suffered from a CHD compared with mothers within the recommended BMI (OR: 1.174; 95%CI, 1.146–1.203, $P = 0.161$) (Figure 6). The I^2 statistic was 25.5%, indicating that there was no heterogeneity. The P value of Begg's test was 0.537 and of Egger's test was 0.345, indicating no publication bias (Figure 7).

4 | DISCUSSION

Previous literature has been largely inconsistent in the association between maternal BMI and infant CHDs. Our meta-analysis shows that there is an established relationship between maternal BMI and congenital heart anomaly. In addition, little statistically significant heterogeneity was detected and no publication bias was indicated from Begg's test (Table 2).

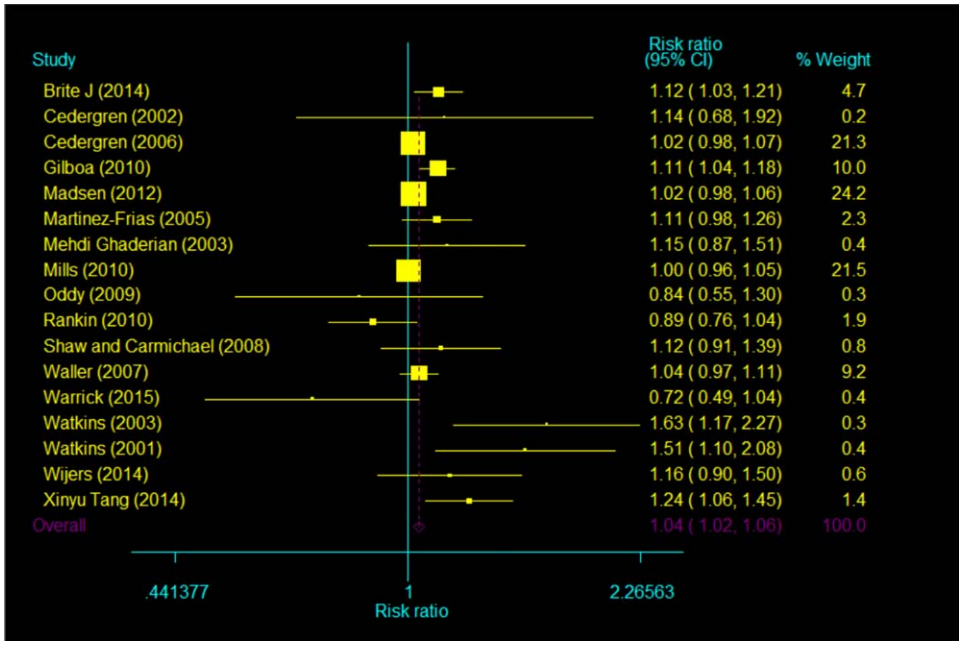

FIGURE 4 Forest plot for the subgroup of overweight

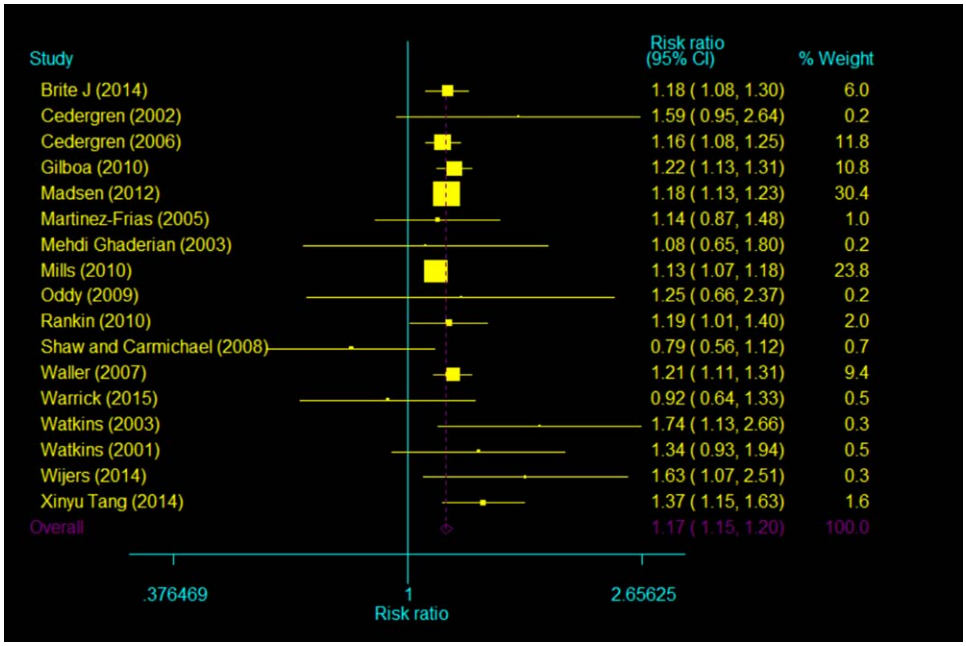

FIGURE 6 Forest plot for the subgroup of obesity

Previously, some studies on the association between maternal BMI and congenital heart defects have been conducted. Madsen et al.[5] suggested that increasing obesity had increasing risk of CHDs. Maternal obesity could lead to a greater risk of CHDs among offspring. Ghaderian et al.[7] claimed that overweight and obese women were not more likely to have offspring with CHDs. Similarly, we found that there was a positive association between maternal overweight as well as obese status and infant CHDs.

In most of the researches, they all agree with that maternal BMI is associated with CHDs, however, many of them have different opinions when it comes to the subtypes of CHDs. Rankin et al.[23] found that maternal obesity had increased risk of ventricular septal defects (VSDs) while maternal underweight was associated with significantly increased risks of atrial septal defects (ASDs). Cai et al.[26] reported that overweight and obese women are at risk of tetralogy of Fallot (TOF), but there was no statistically significant association between transposition of the great arteries (TGA) and any single maternal BMI category. Madsen et al.[5] declared that the strength of association increased with increasing BMI, and the association was greatest for left and right ventricular outflow tract defects, hypoplastic left heart syndrome was markedly associated. Besides, there was no association with conotruncal defects (CTDs). By contrast, Brite et al.[22] described significantly increased odds for CTDs, VSDs and ASDs in obese pregnant women. There was no association between underweight or overweight status for any specific type of CHDs. In our research, we intended to carry out the subtypes of CHDs, but due to the different criteria of each research and lack of raw data, no analysis had been conducted. We expect that the authors provide raw data to us so that we can analysis the relationship between subtypes of CHDs and maternal BMI.

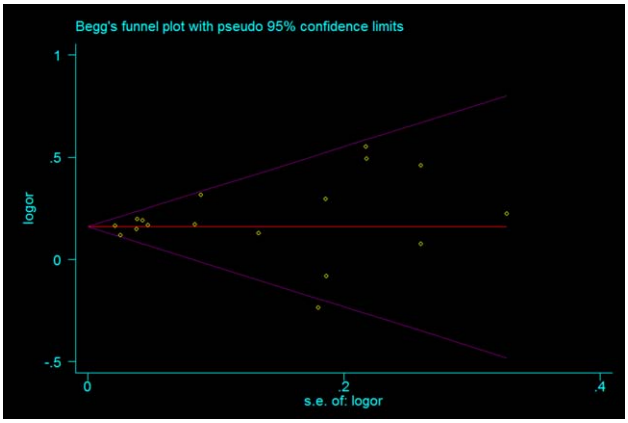

FIGURE 7 Begg's funnel plot for the subgroup of obesity

Moreover, other maternal lifestyle factors may have different effects on CHDs. Boyd et al.[27] stated that CHDs were strongly associated with early and late preterm preeclampsia in the same pregnancy and weakly associated with term preeclampsia. However, gestational hypertension had little link with CHDs. Feng[28] described that although they conducted a brief overview of maternal lifestyle factors, including smoking, caffeine, alcohol, BMI and psychological factors, women who smoke and have an excessive BMI during pregnancy are more likely to be associated with CHDs in offspring. Sullivan et al.[29] agreed with that, their research reported that maternal smoking in the first trimester of pregnancy were more likely to have offspring with CHDs, and most associated with PVA, PAA, and isolated ASD. In the factor of infection, a research[30] showed that CHD was related to maternal exposure to influenza infection. Besides, Dong[31] believed maternal exposure to Chlamydia was weakly associated with a higher risk of cyanotic CHDs in offspring. However, maternal hyperlipidemia has not been reported so far. Based on these researches, a question was raised that whether these factors lead to CHDs by changing the maternal BMI, which requires our further studies.

TABLE 2 Summary results of the subgroup analysis

Subgroup analysis	Studies number	OR (95%CI)	*P* value	I^2 heterogeneity index,%	Bias test *P* value (Begg's test/ Egger's test)	Pooling method
Underweight						
Overall	17	1.015 (0.980,1.052)	.085	34.0%	.502/.595	Fixed
Country						
The United States	11	1.025 (0.978,1.074)	.502	0.00%	.755/.698	Fixed
Not the United States	6	1.102 (0.950,1.279)	.012	65.9%	.452/.137	Random
Year						
Before 2010 and 2010	9	1.000 (0.955,1.047)	.284	17.9%	.466/.397	Fixed
After 2010	8	1.036 (0.979,1.096)	.064	47.6%	.711/.614	Fixed
Case Number						
Less than 10000	9	1.024 (0.909,1.152)	.151	33.3%	.917/.684	Fixed
More than 10000	8	1.019 (0.977,1.062)	.097	42.2%	.174/.176	Fixed
Design						
Case-control	13	1.028 (0.976,1.083)	.284	15.9%	.502/.595	Fixed
Cohort study	4	1.103 (0.878,1.386)	.023	68.6%	.743/.765	Random
Score						
<7	5	0.997 (0.943,1.054)	.109	47.1%	.806/.365	Fixed
≥7	12	1.029 (0.982,1.078)	.136	31.9%	.732/.694	Fixed
Overweight						
Overall	17	1.065 (1.021,1.10)	.001	60.1%	.360/.093	Random
Country						
The United States	11	1.087 (1.029,1.148)	.00	68.8%	.161/.071	Random
Not the United States	6	1.021 (0.982,1.062)	.231	27.1%	1.000/.985	Fixed
Year						
Before 2010 and 2010	9	1.095 (1.017,1.178)	.039	50.7%	.466/.061	Random
After 2010	8	1.051 (0.992,1.114)	.001	70.5%	.536/.835	Random
Case Number						
Less than 10000	9	1.182 (1.098,1.273)	.268	19.6%	.466/.634	Fixed
More than 10000	8	1.033 (0.995,1.073)	.012	61.2%	.536/.556	Random
Design						
Case-control	13	1.088 (1.035,1.144)	.005	57.9%	.300/.017	Random
Cohort study	4	0.995 (0.896,1.106)	.013	72.3%	.734/.452	Random
Score						
<7	5	1.023 (0.993,1.053)	.023	64.7%	1.000/.726	Random
≥7	12	1.081 (1.024,1.140)	.006	58.1%	.837/.224	Random
Obesity						
Overall	17	1.174 (1.146,1.203)	.161	25.5%	.537/.345	Fixed
Country						
The United States	11	1.173 (1.143,1.205)	.062	43.2%	.876/.793	Fixed
Not the United States	6	1.179 (1.105,1.257)	.571	0.0%	.260/.107	Fixed
Year						
Before 2010 and 2010	9	1.180 (1.121,1.244)	.223	24.8%	.466/.720	Fixed
After 2010	8	1.172 (1.141,1.205)	.150	34.9%	.711/.372	Fixed
Case Number						
Less than 10000	9	1.268 (1.137,1.414)	.111	38.6%	1.000/.994	Fixed
More than 10000	8	1.169 (1.141,1.199)	.561	0.00%	.711/.789	Fixed
Design						
Case-control	13	1.177 (1.146,1.210)	.075	38.7%	.669/.226	Fixed
Cohort study	4	1.162 (1.101,1.227)	.625	0.00%	.734/.315	Fixed
Score						
<7	5	1.176 (1.134,1.219)	.171	37.5%	.806/.575	Fixed
≥7	12	1.173 (1.136,1.212)	.180	26.9%	.837/.499	Fixed

4.1 | Potential mechanism

CHDs are due to modifiable risk factors between genetic susceptibilities and environmental factors involving a complex interplay.[2] It is currently known that genetic alterations contribute to CHDs,[32] but clinical data have suggested that nongenetic factors also play an important role in induction of CHDs.[2,28] One possible mechanism is the interplay between the alterations in folate and glutathione metabolism and genetic variants in folate and glutathione -related pathways. The maternal metabolic environment is important relative to both short and long term fetal developments.[33] BMI correlates positively with increased intake of trans-fatty acids, while homo-cysteine levels decreased as the folate increased.[34] Maternal obesity could result to decreased folate[35] and glutathione[36,37] intake and increased homo-cysteine intake,[38,39] which compromise the in-utero environment and ultimately lead to impaired fetal development. One alternative hypothesis is that maternal and fetal

genetic variants which encode critical enzymes in folate, homo-cysteine and glutathione metabolism impact on the developing heart. According to a recent study,[40] the risk of delivering infants with CTDs among obese mothers carrying AC genotype for a variant in the glutamate-cysteine ligase, catalytic subunit (*GCLC*) gene (rs6458939) was 2.00 times among those carrying CC genotype, while the fetal genotypes of the variants in the glutathione S-transferase alpha 3 (GSTA3) gene were related to an increased risk of CTDs among obese mothers.

In addition, overweight and obese women are more likely to have pregestational diabetes mellitus (PGDM). Maternal diabetes significantly increases the risk of infant CHDs.[41] Those pregnant women are 3 times (9.1% compared to 3.1%) more likely to have infants with CHDs than healthy women.[42] Apoptosis signal-regulating kinase 1 (ASK1) possibly plays a role in diabetes-induced heart defects. ASK1 activates the c-Jun NH2-terminal kinase 1/2 (JNK1/2)—endoplasmic reticulum (-ER) stress pathway, inhibits cell cycle progression and mediates the teratogenicity of diabetes. Diabetic embryopathy induced activation of ASK1 impedes the infant cardiogenesis, ventricular septation, and outflow tract. Deleting *Ask1* gene significantly reduced the risk for infant heart defects.[43] Another study[44] indicates that maternal type 2 diabetes mellitus causes heart defects in the developing embryo manifested with oxidative stress, excessive apoptosis, and endoplasmic reticulum stress in heart cells, which is similar to type 1 diabetic embryopathy. Phosphorylated-IRE1a, phosphorylated-PERK, phosphorylated-eIF2a, C/EBP homologous protein, and binding immunoglobulin protein, all of which are endoplasmic reticulum stress markers, are found elevated in diabetic embryonic hearts. Additionally, type 2 diabetes mellitus during pregnancy triggered excessive apoptosis in the outflow tract, ventricular myocardium and endocardial cushion of the embryonic heart.

4.2 | Study strengths and limitations

Our study strictly assessed 17 large population-based studies, which was a strength and added power to our conclusion. Several types of measurement error and bias, especially recall bias, were minimized by collecting medical records. Additionally, in our meta-analysis, weight categories were identical across the articles, because articles were pooled due to their internal definitions of underweight, overweight and obesity. The World Health Organization guidelines[9] recommended that underweight status was less than 18.5 kg/m^2, normal weight ranged from 18.5 to 24.9 kg/m^2, overweight ranged from 25.0 to 29.9 kg/m^2, and obesity was more than 30 kg/m^2. Most articles were in line with the World Health Organization guidelines, and the rest were broadly similar to it.

However, most data were extracted from case-control studies, which had several inevitable limitations. Case-control studies may be more prone to information bias than cohort studies. Also, self-report of maternal weight and height may lead to recall bias. Over-weight and obese women tended to report lower weight, and bias increases with the magnitude of weight.[45] Identification bias is highly unlikely. Another limitation is that we only assessed English publications, which means we may have missed relevant studies performed in other languages. Besides, we have not conducted comprehensive analyses of CHD subtypes because we have not included enough studies, whereas different CHD subtypes may have various etiologies. Subsequently, we did not take potential teratogens such as smoking, infections and hypertension, during pregnancy into account. Last but not least, cases with CHDs terminated prenatally were not available for our meta-analysis.

5 | CONCLUSIONS

Our finding has important implications for future investigations. There was little significant evidence of an association between maternal underweight status (BMI $<$ 18.5 kg/m^2) and offspring with CHDs, and a positive effect of maternal overweight status (BMI 25.0–29.9 kg/m^2) on the risk for CHDs in infants. Moreover, we observed a significant association between maternal obesity (BMI $\geq$ 30 kg/m^2) and CHDs in their offspring. However, the findings from our study need to be confirmed in future research in well-designed cohort or intervention studies.

Obesity has become a global problem and the growth of the obesity rate in the general adult population in the period of 2000–2005 and 2005–2012 was 0.4% per year.[46] Obese women are at risk of giving birth to a child with CHD and weight reduction may decrease the risk. These findings suggest that obese and underweight women should be aware of the risks and keep a healthy weight before they plan to conceive. Further, mechanistic analyses are also critical for developing clinical interventions, which is especially helpful for those women who are unable to optimize their weight before pregnancy.

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CONFLICT OF INTEREST

The authors declare that they have no competing interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript.
Data analysis/meta analysis: Zhu, Feng, Yu
Manuscript drafting: Zhu, Feng
Study design: Chen, Yu
Statistical analysis: Chen
Data coordination: Yu
Technical support: Mo
Manuscript presentation: Mo

AVAILABILITY OF DATA AND MATERIALS

The data sets generated during and/or analyzed during the current study are available in the [PubMed] repository, [www.ncbi.nlm.nih.gov]

ORCID

Yu Zhu MM http://orcid.org/0000-0002-6946-1716

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