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Prepregnancy obesity and the risk of birth defects: an update

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Abstract

The growing number of obese women worldwide has many implications for the reproductive health outcomes of mothers and their children. Specifically, prepregnancy obesity has been associated with certain major birth defects. Provided here is a summary of the most recent and comprehensive meta-analysis of reports of associations between prepregnancy obesity and birth defects, along with an update that includes a brief overview of reports of similar associations published since that meta-analysis. The possible reasons for the observed association between prepregnancy obesity and birth defects are explored, and knowledge gaps that suggest possible avenues for future research are highlighted.

Keywords

adverse pregnancy outcomes; birth defects; prepregnancy obesity

INTRODUCTION

In 2009–2010, the prevalence of obesity (defined as a body mass index [BMI] >30 kg/m²) was 35.8% among US women over the age of 20 years (31.9% among women aged 20–39 years).^{1,2} The increased prevalence of obesity among women of childbearing age (20–44 years) has also become common in many other parts of the world³ (Table 1), particularly in populations with a greater availability and consumption of more processed, affordable, and marketed food items.^{4–8} The rising prevalence of obesity is of concern to clinical and public health systems because obesity is associated with cardiometabolic risk factors (i.e., hypertension, lipid disorders, hyperglycemia, insulin resistance, inflammation), which in turn are associated with increased morbidity and mortality due to cardiovascular diseases.^{9–13} In recent years, the trend in the prevalence of obesity has also become a matter of concern to preconception healthcare programs because prepregnancy obesity is associated with an increased risk of adverse reproductive health outcomes, including subfertility, miscarriage, gestational diabetes, gestational hypertension, preeclampsia, macrosomia,

preterm birth, and fetal death.^{14,15} Furthermore, one meta-analysis on maternal obesity and birth defects published in 2008¹⁶ reported that maternal prepregnancy obesity was associated with an increased risk of neural tube defects. A second meta-analysis published in 2009 also concluded that maternal prepregnancy obesity was associated with neural tube defects and, possibly, congenital heart defects.¹⁷

Major structural birth defects (i.e., abnormalities of structure or function present at birth that are fatal or can result in significant physical or mental disabilities) are of public health concern because they are common, affecting one in 33 newborns,¹⁸ are a leading cause of infant mortality,^{19,20} and often result in increased use and costs of health services among affected individuals.^{21,22} In recent decades, notable progress has been made in the identification of important modifiable risk and health factors for some birth defects, including rubella infections, preconception use and consumption of folic acid, use of certain medications during pregnancy (e.g., certain anticonvulsants), and maternal pregestational diabetes.²³ Nevertheless, such identified risk factors are estimated to account for no more than 35% of major birth defects, indicating that the causes of most major birth defects remain unknown. Accordingly, when assessing reports of a possible novel risk factor for birth defects amenable to intervention and for which modification could potentially result in an appreciable reduction of affected infants in the population, it is useful to consider the parameters that determine the fraction of birth defects in the population that can be attributed to a causal factor, namely, the relative risk associated with that causal factor and the prevalence of exposure to that causal factor.²⁴

The relationship between the population attributable fraction and the relative risk for a given causal factor as a function of the prevalence of exposure in the population is such that, for a given prevalence of exposure, the attributable fraction increases as the relative risk increases (Figure 1). Similarly, for a given relative risk, the population attributable fraction increases as the prevalence of exposure increases. Therefore, greater public health value is likely to be derived from research strategies that give high priority to the identification of causal factors that are associated with a high relative risk, have a high prevalence of exposure in the population, and are potentially modifiable. Because prepregnancy obesity has been associated with certain major birth defects and has reached a high prevalence in many communities, it is useful to review the current literature on such associations and ask whether the available evidence is supportive of a causal association, and, if not, to consider possible research avenues that may help elucidate the causal and modifiable factors that may underlie the observed associations between obesity and birth defects.

This report summarizes the most recent and comprehensive meta-analysis of reports of associations between prepregnancy obesity and birth defects published in 2009¹⁷ and updates this summary with a brief overview of reports of similar associations published in the English literature since 2009 and through March 2013. The review focuses on associations with at least three published reports to allow for evaluation of consistency among reports and to de-emphasize associations based on fewer reports that may well reflect publication bias and/or chance. Because different types of birth defects are known to have different risk factors, associations between obesity and specific types of birth defects are highlighted to the greatest extent possible to minimize the potential for dilution of effects in

groupings with heterogeneity in risk factors. Findings of associations between obesity and broad categories or groups of birth defects (e.g., all neural tube defects and all congenital heart defects) are not considered because the composition of such broad groups is not provided in most reports and is likely to vary between studies, making meaningful comparisons of associations across studies difficult. Possible reasons for the observed associations of prepregnancy obesity with birth defects are discussed, as are knowledge gaps that suggest possible avenues for future research.

SUMMARY OF META-ANALYSIS OF PREPREGNANCY OBESITY AND BIRTH DEFECTS PUBLISHED IN 2009

In 2009, Stothard et al.¹⁷ published findings from their systematic review and meta-analysis of maternal overweight and obesity and risks of 13 types of birth defects: neural tube defects, cardiovascular anomalies, orofacial clefts, anorectal atresia, craniosynostosis, diaphragmatic hernia, gastroschisis, hydrocephaly, hypospadias, limb reduction anomalies, microcephaly, microtia and anotia, and esophageal atresia. Because some of these types of birth defects (i.e., neural tube defects, cardiovascular anomalies, and orofacial clefts) comprise several subtypes known to exhibit etiologic heterogeneity, findings of associations with obesity were also reported for subtypes for which sample sizes of cases were adequate (i.e., anencephaly and spina bifida in the case of neural tube defects; all septal defects, tetralogy of Fallot, and transposition of the great arteries in the case of cardiovascular anomalies; and cleft lip, cleft palate, and concomitant cleft lip and palate in the case of orofacial clefts). The definitions of reference BMI, overweight, and obesity varied between the studies, with the reference group inclusive of BMIs in the range of 18.5–29.0 kg/m², overweight status including BMIs in the range of 18.5–30.0 kg/m², and the lowest cutoff point of BMI for defining obesity status including BMIs in the range of 24.0–30.0 kg/m² (with several included in either recommended or obese categories or both). Based on analyses of types/subtypes of birth defects with three or more studies available, maternal obesity was found to be associated with the following birth defects (Table 2): 1) a 39% increased risk of anencephaly; 2) a twofold increase in the risk of spina bifida; 3) a 20% increased risk of all septal anomalies; 4) a 20% increased risk of cleft palate; 5) a 23% increased risk of cleft lip and palate; and 6) a 68% increased risk of hydrocephaly. No significant associations were noted for three types of birth defects for which there were at least three studies available for analysis (i.e., tetralogy of Fallot, transposition of the great arteries, and diaphragmatic hernia). Maternal overweight status was not associated with any of the birth defects examined, and there was no evidence of a dose-response relationship between BMI and risk of birth defects.

REPORTS OF ASSOCIATIONS BETWEEN PREPREGNANCY OBESITY AND BIRTH DEFECTS PUBLISHED SINCE 2009

A PubMed search for additional reports in the English literature on maternal obesity and birth defects (key words: obesity, birth defects, congenital anomalies) for the years 2009–2013 identified four additional population-based case-control studies: one published in 2009 that examined various types of birth defects,²⁵ two published in 2010 that focused on

congenital heart defects,^{26,27} and one published in 2012 that examined broad categories of types of birth defects.²⁸ One cohort study of pregnant glucose-tolerant women published in 2012 was also found; this study examined various pregnancy outcomes, including all congenital malformations as a group.²⁹ No reports of associations between prepregnancy obesity and birth defects published in 2011 or 2013 were found.

The one study published in 2009 was conducted in Western Australia between September 1997 and March 2000 and was based on a total sample of 111 cases of various groupings of birth defects.²⁵ In this study, the reference group was defined as a BMI of $<20 \text{ kg/m}^2$, and prepregnancy obesity was defined as a BMI of $\geq 30 \text{ kg/m}^2$. Analyses were adjusted for maternal age, education, marital status, and periconceptional use of supplements containing 200 μg of folic acid. Prepregnancy obesity was reported to be associated with a twofold or greater odds of neural tube defects, conotruncal heart defects, orofacial clefts, and limb reduction defects, as well as a 41% increased odds of urinary tract defects. None of the estimates for the various groupings of birth defects achieved statistical significance, reflecting in part the imprecision of the point estimates due to small sample sizes of the case groups as well as the possible heterogeneity of phenotypes and risks within such birth defects groupings.

Table 3 lists findings from the two studies on congenital heart defects published in 2012 that focused on cardiac defects or groups of cardiac defects for which at least one association with prepregnancy obesity – excluding the null value – was reported by at least one of these studies. The first study was based on a large population-based multicenter case-control study conducted between 1997 and 2004 in the United States with a total sample size of 6,440 cases of congenital heart defects classified into 19 specific phenotypes and additional groupings of some of the specific phenotypes.²⁷ The reference group was defined as a BMI of $18.5\text{--}24.9 \text{ kg/m}^2$, overweight status as a BMI of $25.0\text{--}29.9 \text{ kg/m}^2$, moderate obesity as a BMI of $30.0\text{--}34.9 \text{ kg/m}^2$, and severe obesity as a BMI of $\geq 35.0 \text{ kg/m}^2$. Analyses were adjusted for maternal age, race/ethnicity, education, hypertension, and periconceptional smoking and folic acid supplement use.²⁷ Prepregnancy moderate obesity was associated with two cardiac defects: 1) a 34% increased odds of having an infant with left ventricular outflow tract defects, specifically hypoplastic left heart syndrome; and 2) a twofold increased odds of total anomalous pulmonary venous return. Maternal severe obesity was associated with three cardiac defects: 1) a 36% increased odds of conotruncal defects, specifically tetralogy of Fallot; 2) a 35% increased odds of septal defects, specifically secundum atrial septal defects; and 3) a 61% increased odds of right ventricular outflow tract defects, specifically pulmonary valve stenosis. There were no associations of overweight status with any specific cardiac defects. However, analysis of the combination of categories of overweight and obesity identified one more association with Ebstein's anomaly (28 cases, odds ratio [OR] 1.78, 95% confidence interval [CI] 1.02–3.13). There was no consistent evidence of a dose-response relationship between BMI and risk of specific cardiac defects.

The second study on congenital heart defects and published in 2010 was conducted in the state of New York (excluding births in New York City) between 1993 and 2003 and was based on a total sample of 7,392 cases of congenital heart defects classified into 11 specific phenotypes and additional groupings of some of the specific phenotypes.²⁶ In this study, the

reference group was defined as a BMI of 19.0–24.99 kg/m², overweight status as a BMI of 25.0–29.99 kg/m², obesity as a BMI of 30.0–39.99 kg/m², and morbid obesity as a BMI of 40.0 kg/m². Analyses were adjusted for race-ethnicity, payment method, and maternal education, smoking, alcohol use, age, and parity. Maternal obesity was associated with the following cardiac defects: 1) an 18% increased odds of atrial septal defects; 2) a 51% increased odds of left ventricular outflow tract obstruction, specifically hypoplastic left heart syndrome and aortic valve stenosis; and 3) a 32% increased odds of right ventricular outflow tract obstruction, specifically pulmonic valve stenosis. Morbid obesity was associated with the following cardiac defects: 1) a 70% increased odds of conotruncal defects, specifically tetralogy of Fallot and double outlet right ventricle; 2) a 27% increased odds of all septal defects; and 3) a 52% increased odds of left ventricular outflow tract defects. Analysis of the combined categories of obesity did not identify any additional associations. There was no evidence of associations between maternal prepregnancy overweight and any specific type of cardiac defect. Furthermore, there was no consistent evidence of a dose-response relationship between BMI and risk of specific cardiac defects.

Despite the differences in definitions of obesity between the two 2010 publications by Gilboa et al.²⁷ and Mills et al.,²⁶ there was evidence of consistent associations between measures of maternal obesity and four types of congenital heart defects, namely, tetralogy of Fallot, atrial septal defects, one left ventricular outflow tract obstruction defect (hypoplastic left heart syndrome), and one right ventricular outflow tract obstruction defect (pulmonary valve stenosis). Because these findings on tetralogy of Fallot, hypoplastic left heart syndrome, and pulmonary valve stenosis differ from those reported in the meta-analysis conducted by Stothard et al.¹⁷ but are based on only two studies, further corroboration is warranted. Further comparisons of the findings from the two 2010 publications with those of earlier reports are not possible because of differences in case groupings between studies, not to mention differences in the definitions of obesity.

The one case-control study published in 2012 was conducted in a cohort of all live births ($n = 37,168$) delivered from April 2006 through December 2010 in one hospital in the Eastern Province of Saudi Arabia and was based on all 318 cases classified into various groupings of birth defects and 1,768 live birth controls. Cases were identified during the first week of life and excluded infants with multiple malformations. In this study, the reference group was defined as a BMI of 18.5 kg/m² and <25 kg/m², overweight as a BMI of 25 kg/m² and <30 kg/m², and obesity as a BMI of 30 kg/m². Analyses were adjusted for socioeconomic status and consanguinity. Prepregnancy obesity was reported to be associated with neural tube defects (88 cases, OR 7.8, 95%CI 3.9–15.4), facial defects (61 cases, OR 5.9, 95%CI 2.8–12.4), cardiac and lung defects combined (51 cases, OR 2.7, 95%CI 1.3–5.7), and genitourinary defects (42 cases, OR 4.6, 95%CI 1.9–11.1). There was no information provided on possible associations with more specific types of birth defects, the status of prepregnancy diabetes of case and control mothers, or efforts to adjust the results for maternal prepregnancy diabetes.

The one cohort study of glucose-tolerant pregnant women ($n = 3,656$) focused on women attending antenatal obstetric clinics in the setting of glucose tolerance testing (Atlantic Diabetes in Pregnancy cohort) and recruited between 2006 and 2009 in Ireland.²⁹ The

reference group was defined as a BMI of ≥ 18.5 kg/m² and <25 kg/m² ($n = 1,582$), overweight as a BMI of ≥ 25 kg/m² and <30 kg/m² ($n = 1,369$), and obesity as a BMI of ≥ 30 kg/m² ($n = 695$). This study evaluated the associations of increased BMI with a range of pregnancy outcomes, including all congenital malformations ascertained within 1 week of delivery and categorized into one broad group, adjusted for maternal age, parity, cigarette smoking, and ethnicity. It reported an increased prevalence of congenital malformations among infants born to obese mothers compared with infants born to mothers in the reference group (2% versus 0.8%, respectively), as well as a dose-response effect between increased levels of BMI and adjusted ORs for congenital malformations: overweight, OR 1.82 (95%CI 0.85–3.92); obese, OR 2.45 (95%CI 1.04–5.76). However, there were no findings reported for more specific categories or types of birth defects.

POSSIBLE REASONS FOR OBSERVED ASSOCIATIONS BETWEEN PREPREGNANCY OBESITY AND BIRTH DEFECTS

Birth defects are multifactorial in origin, involving complex interplays between genetic and environmental factors, and it is common for infants affected with the same phenotype (e.g., hypoplastic left heart syndrome) to exhibit different risk factor profiles. Therefore, in assessments of whether observed associations between an environmental factor such as maternal obesity and birth defects are likely to be causal, it is useful to consider the extent to which such associations meet the Bradford-Hill criteria for causality,³⁰ particularly in comparison with a well-known teratogen such as prepregnancy diabetes (Table 4). The reported associations between maternal prepregnancy diabetes and neural tube defects and congenital heart defects are known to meet six of the seven criteria for causality, namely, temporality, consistency of the association across studies, strength of the association, plausibility/coherence, biological gradient, and experimental evidence. In contrast, for maternal prepregnancy obesity, the reported associations with neural tube defects meet only three criteria (i.e., temporality, consistency, and strength of the association), while associations with congenital heart defects meet possibly two criteria (temporality and maybe consistency, if one is willing to accept evidence from two observational studies as adequate for consistency). Thus, the level of uncertainty regarding a causal relationship between prepregnancy obesity and birth defects could be considered as moderate for neural tube defects and strong for congenital heart defects. This level of uncertainty raises the question of whether some of the methodologic issues inherent to observational studies (i.e., chance, bias, and confounding) could account for the generally weak and/or inconsistent associations between prepregnancy obesity and birth defects.

Since most studies of birth defects and obesity involve multiple comparisons of various groupings of birth defects and categories of overweight and obesity, there is a good possibility that some of the observed associations might reflect chance (i.e., type I error). In addition, given that studies with positive findings are more likely to be submitted and published than studies with negative findings, it is possible that some of the observed associations could reflect bias in publication of positive findings due to chance. Because obesity in pregnancy can interfere with adequate prenatal diagnosis of birth defects, reducing the likelihood of pregnancy terminations, it is possible that some of the

associations between prepregnancy obesity and birth defects reflect differential rates of termination of pregnancies affected by birth defects due to differences in the sensitivity of prenatal diagnosis by obesity status.³¹

Two known risk factors for birth defects that may confound some of the observed associations between obesity and birth defects include blood folate status and prepregnancy diabetes. Although the analyses in the study by Gilboa et al.²⁷ adjusted for the intake of folic acid, given the uncertainties in estimating folic acid intake retrospectively and the potential misclassification of folic acid intake, residual confounding by low levels of blood folate remains a possible explanation for some of the observed associations. In case-control studies of prepregnancy diabetes and birth defects, the assessment of diabetes has been based on maternal self-reports, which are subject to recall error. This source of misclassification bias combined with the possibility that some case and control mothers may have had undiagnosed diabetes could have resulted in residual confounding in analyses that controlled or adjusted for diabetes. Of interest is a recent cross-sectional analysis of the prevalence of maternal obesity and birth defects, which used a perinatal database and in which the definition of diabetes was based on information in the perinatal database rather than on maternal self-report.³² These cross-sectional analyses showed an increase in the prevalence of birth defects as the prevalence of prepregnancy obesity increased. However, once diabetes was taken into account in a multivariate analysis, there was no evidence of an association between prepregnancy obesity and the prevalence of birth defects. Another potential confounder in studies of birth defects and obesity that warrants some consideration is prepregnancy impaired fasting glucose levels that do not reach the cutoff point for a diagnosis of diabetes. Since the threshold of hyperglycemia and other similar metabolic disturbances associated with birth defects has yet to be determined and obesity is likely to be associated with insulin resistance and hyperglycemia, impaired fasting glucose levels below the diagnostic cutoff point for diabetes have not been well accounted for in most studies of birth defects and obesity and thus remain a potential explanation for some of the observed associations.

The classification and grouping of cases of congenital heart defects has varied across epidemiologic studies up until recent years because there was no convention or widely used standard system for classification of heart defects. Standard approaches for classification of heart defects have been developed and implemented in some studies in recent years.^{33,34} Their wider use in new studies of obesity and heart defects will enable more meaningful comparisons of associations between obesity and specific heart defects across future studies. However, with such use, comparisons of associations with specific types of congenital heart defects are likely to remain a challenge because of the limited sample size that can be obtained for specific phenotypes of interest in a study from a single population-based surveillance system.

Obesity is a condition with varied anthropometric and pathophysiologic manifestations. Some individuals who are classified as obese on the basis of BMI may be metabolically normal, and some individuals who are classified as having an average BMI may actually be metabolically obese.^{35,36} This lack of correlation may also account in part for some of the inconsistent and weak associations observed between prepregnancy obesity and birth

defects. An interesting observation that suggests some new research approaches is that regional distribution of adiposity (i.e., visceral versus subcutaneous) is a better predictor of metabolic risk associated with adiposity than BMI.³⁶ Accordingly, future studies of the associations between prepregnancy obesity and birth defects might consider using some measures of regional distribution of adiposity, such as prepregnancy or postpartum waist circumference and/or waist:hip ratios. Because physical activity can be an important modifier of the metabolic effects of obesity, future studies of obesity and birth defects may need to account for maternal periconceptional levels of physical activity. Lastly, although the BMI cutoff point used to define obesity has proven useful for studies of cardiovascular risk, future studies may need to consider the possibility that the metabolic disorders associated with birth defects may occur at a different threshold and that such a threshold might differ by certain maternal characteristics (e.g., age, race/ethnicity, duration of obesity).

CONCLUSION

The prevalence of obesity has increased in many parts of the world and across most age groups, including women of childbearing age. Prepregnancy obesity is associated with a wide range of adverse pregnancy outcomes, including birth defects. Because birth defects are of public health concern, it is important to identify highly prevalent, potentially modifiable environmental risk factors such as pregravid obesity. The results of epidemiologic studies to date, however, have been limited by weak and inconsistent associations. Further research is warranted to elucidate the nature of the observed associations using innovative approaches that are effective in accounting for the heterogeneity of obesity manifestations and effects as well as for the types of birth defects.

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Figure 1.
Population attributable fraction in relation to relative risk and prevalence of exposure (Pe).

Table 1

Estimates of prevalence of overweight and obesity in women of childbearing age.

Country	Year of data collection	National/regional survey	Size of survey sample (males and females)	Age category (in years)	Overweight prevalence in females (%)	Obesity prevalence in females (%)
Europe region						
Albania	2008–2009	National (DHS)	10,302	15–49	29.6	9.7
Armenia	2005	National (DHS)	6,016	15–49	26.9	15.5
Austria	2005–2006	National (not necessarily a representative sample)	1,054	30–74	32.4	20.8
Azerbaijan	2006	National (DHS)	9,881	15–49	29.5	17.9
Belgium	2002–2004	National	5,170	18–75	29.8	10.2
Bosnia & Herzegovina	2002	National	2,750	25–64	NA	25
Bulgaria	2004	National	1,031	20+	32.2	19.2
Croatia	2003	National	9,040	18+	38.7	22.7
Cyprus	1999–2000	National	1,019	25–64	34.3	23.7
Czech Republic	2008	National	1,942	20+	29.2	22.3
Denmark (self-report)	2005	National	13,593	16+	25.6	11.8
England	2010	National	6,987	16+	31.7	26.1
Estonia (self-report)	2004	National	3,033	16–64	25.7	14.9
Finland (self-report)	2005	National	3,287	15+	26.7	13.5
France	2006	National	3,115	18–74	23.8	17.6
Germany	2008–2011	National	7,116	18–79	29	23.9
Greece	2001–2003	Regional	915	18–79	29.3	25.6
Hungary (self-report)	2004	National	1,179	18+	31.3	18.2
Iceland	1991–1996	Not specified	6,178	18+	35.2	18.3
Israel	1999–2001	National (DHS)	2,782	25–64	33.1	25.7
Ireland	2008–2010	National	1,500	18–64	30.9	21.3
Ireland (Northern)	2005–2006	National	3,378	16+	30	23
Italy (self-report)	2005	National	NA	NA	26.1	9.1
Italy (self-report)	1998	National (not verified)	NA	35–74	NA	22
Kazakhstan	1999	National (DHS)	2,235	15–49	19.9	12.6
Kyrgyzstan	1993	National (DHS)	4,053	18–59	24.3	10.7

Country	Year of data collection	National/regional survey	Size of survey sample (males and females)	Age category (in years)	Overweight prevalence in females (%)	Obesity prevalence in females (%)
Latvia (self-report)	2006	National	1,538	15–64	27.5	18.1
Lithuania (self-report)	2006	National	1,707	20–64	29.7	19.2
Luxembourg	2007	National (OECD)	NA	15+	44	19
Malta (self-report)	2003	National (DHS)	NA	15+	34.3	16.9
Moldova	2005	National (DHS)	7,062	15–49	23.3	18.2
Netherlands	1998–2002	National	3,691	20–59	28.5	10.1
Norway	1995–1997	Regional	66,140	NA	40	21
Poland	2003–2007	National	14,403	20+	28.4	23.8
Portugal	2003–2005	National	8,116	18–64	34.4	13.4
Romania (self-report)	2000	National (DHS)	21,000	15+	28.6	9.5
Russia	2000	National	9,006	19–55	27.4	21.6
Scotland	2011	National	6,103	16+	32	27.6
Serbia (Republic of)	2000	National	4,458	20+	31	20
Slovak Republic	2007	National	NA	15+	24.4	15.9
Slovenia (self-report)	2001	National	9,034	25–64	30.9	13.8
Spain	2008–2010	National	12,036	18+	32.5	21.4
Sweden (Gothenburg)	2002	Regional	1,032	25–64	26.6	11
Switzerland (self-report)	2007	National (OECD)	NA	15+	20.9	7.7
Turkey (urban)	2001–2002	Regional	5,016	20+	28.6	29.4
Turkmenistan	2000	National (DHS)	2,117	15–49	16	7.8
Uzbekistan	2002	National (DHS)	1,657	18–49	20.6	7.1
Wales (self-report)	2011	National	16,058	16+	31	22
Africa region						
Algeria	2003	Regional	4,112	25–64	32	21.4
Burundi	2010	National (DHS)	4,015	15–49	5.9	1.6
Benin	2006	National (DHS)	2,874	15–49	13.2	5.8
Burkina Faso	2003	National (DHS)	10,604	15–49	6.9	2.4
Cameroon	2004	National (DHS)	4,419	15–49	20.6	8.2
Central African Republic	1994–1995	National (DHS)	2,025	15–49	5.5	1.1
Chad	2004	National (DHS)	3,720	15–49	6.1	1.5

Country	Year of data collection	National/regional survey	Size of survey sample (males and females)	Age category (in years)	Overweight prevalence in females (%)	Obesity prevalence in females (%)
Comoros	1996	National (DHS)	773	15–49	15.9	4.4
Congo (The)	2004	Regional	2,100	25+	21.8	14.6
Cote d'Ivoire	1998–1999	National (DHS)	1,299	15–49	14.5	4.7
Democratic Republic of the Congo	2007	National (DHS)	4,097	15–49	8.9	2.4
Eritrea	2004	National	2,352	15–64	13.7	3.7
Ethiopia	2011	National (DHS)	14,381	15–49	4.7	1
Gabon	2000	National (DHS)	2,190	15–49	21.3	8.2
Ghana	2008	National (DHS)	4,380	15–49	20.7	9.3
Guinea	2005	National (DHS)	3,451	15–49	11.6	3.2
Kenya	2009	National (DHS)	7,548	15–49	17.9	7.2
Liberia	2007	National (DHS)	6,057	15–49	14.8	5.7
Lesotho	2009	National (DHS)	3,682	20–49	27.2	23.7
Madagascar	2008–2009	National (DHS)	7,520	15–49	5.1	1.2
Malawi	2010	National (DHS)	6,684	15–49	13.1	2.4
Maldives	2009	National (DHS)	5,173	15–49	32.4	13.1
Mali	2006	National (DHS)	12,010	15–49	12.4	5.2
Mauritania	2000–2001	National (DHS)	5,259	15–49	23.5	19.2
Mauritius	1998	National	6,291	25–74	34	20
Mozambique	2003	National (DHS)	10,239	15–49	10.3	3.9
Namibia	2006–2007	National (DHS)	8,803	15–49	16.4	11.7
Niger	2006	National (DHS)	3,765	15–49	9.8	3.2
Nigeria	2008	National (DHS)	28,200	15–49	16.1	6
Rwanda	2010	National (DHS)	12,034	15–49	14.1	2.2
Sao Tome & Principe	2008–2009	National (DHS)	2,004	15–49	21.5	12.2
Senegal	2010–2011	National (DHS)	9,183	15–49	15.5	5.8
Seychelles	2004	National	1,255	25–64	33	34.2
Sierra Leone	2008	National (DHS)	3,104	15–49	20.4	9.3
South Africa	2003	National	7,756	15+	27.5	27.4
Tanzania	2010	National (DHS)	8,789	15–49	NA	6.2
Togo	1998	National (DHS)	3,029	15–49	9	2.4

Country	Year of data collection	National/regional survey	Size of survey sample (males and females)	Age category (in years)	Overweight prevalence in females (%)	Obesity prevalence in females (%)
Uganda	2011	National (DHS)	4,572	15–49	14.6	4.2
Zambia	2001–2002	National (DHS)	3,629	15–49	7.9	2.4
Zimbabwe	2010–2011	National	14,669	15–49	20.7	10.6
Southeast Asia region						
Bangladesh	2007	National (DHS)	10,021	15–49	10.1	1.7
India	2005–2006	National (DHS)	177,523	15–49	9.8	2.8
Indonesia	2000–2001	National	20,593	20+	17.4	4.5
Nepal	2011	National (DHS)	5,800	15–49	11.2	2.2
Thailand	2004	National	39,290	18+	25.2	9.1
Western Pacific region						
Australia	2007–2008	National	16,601	25+	30.9	24
Brunei Darussalam	1997–1999	National (DHS)		Adults	45	13.9
Cambodia	2010	National (DHS)	8,757	15–49	9.6	1.3
China	2009	National	8,315	18+	25.5	4.4
Cook Island	1998	Regional	132	20+	NA	NA
Fiji	1993	National	2,573	18+	29	21
French Polynesia	1995	National	1,273	16+	28.2	44.3
Hong Kong	1995–1996	National	2,875	25–74	27	7
Japan	2000	National	15,000	20+	17.8	3.4
Korea (South)	1998	National	8,816	15–79	23.4	3
Malaysia	2007–2008	National	4,428	18+	33.1	22.5
Marshall Islands	2003 (year of publication)	National	1,582	18+	29	31
Mongolia	2005	National	3,411	15–64	25.5	12.5
Nauru	2004	National	2,254	15–64	21.8	60.5
New Zealand	2006–2007	National	12,488	15+	29.4	26
Niue	1987	Regional	740	20+	38	46
Philippines	1998	National	9,299	20+	18.9	4.4
Samoa	1995	Regional	588	29+	NA	63
Singapore	2010	National		18–69	NA	9.5

Country	Year of data collection	National/regional survey	Size of survey sample (males and females)	Age category (in years)	Overweight prevalence in females (%)	Obesity prevalence in females (%)
Tonga	1998–2000	National	1,024	15–85	22.7	70.3
Timor Leste	2009–2010	National (DHS)	11,698	15–49	4.3	0.8
Vanuatu	1998	National	1,614	20+	32.2	19.6
Vietnam	2001–2002	National	NA	19+	6.6 (obesity & overweight combined)	
Eastern Mediterranean region						
Bahrain	1998–1999	National	2,301	19+	28.3	34.1
Egypt	2008	National (DHS)	11,258	15–49	28.3	39.5
Iran	2005	National	89,404	15–64	29.3	19.2
Jordan	2009	National (DHS)	6,666	15–49	27.8	28.7
Kuwait	2006	National	2,280	20–64	29.5	47.9
Morocco	2003–2004	National (DHS)	15,818	15–49	25.7	11
Oman	2000	National	6,400	20+	29.8	21.7
Pakistan	1990–2004	National	8,972	15+	11.3	7.3
Palestine		National (DHS)	936	30–65	NA	42.5
Qatar	2003	Regional	1,208	25–65	33	45.3
Saudi Arabia	1995–2000	National	17,223	30+	31.8	44
Tunisia	1997	National	2,760	20–60	28.2	22.7
United Arab Emirates	2000	National	1,286	20–79	28.4	31.4
Yemen	1997	National (DHS)	5,479	15–49	11.1	4
Americas region						
Argentina (urban)	2003	Regional	1,100	18–65	10.8	17.5
Bahamas	1988–1989	National	1,771	15–64	25.6	28
Barbados	1991	National (DHS)		15–49	25.6	28
Bolivia	2008	National (DHS)	15,325	15–49	32.3	17.4
Brazil	2003	National	93,329	20+	26.9	13.1
Canada	2007–2009	National	3,072	20–69	23.7	23.5
Chile	2003	National	3,619	17+	32.7	29.3
Colombia	2010	National (DHS)	43,723	15–49	31.1	15.2
Cuba	1998	National	4,197	20–64	26.7	10.2

Country	Year of data collection	National/regional survey	Size of survey sample (males and females)	Age category (in years)	Overweight prevalence in females (%)	Obesity prevalence in females (%)
Dominican Republic	2002	National (DHS)	7,866	15–49	38 (obesity & overweight combined)	
Guatemala	1998–1999	National (DHS)	2,318	15–49	33.4	14
Guyana	2000	National	1,315	20+	30.7	26.9
Haiti	2005–2006	National (DHS)	4,897	15–49	14.9	6.3
Honduras	2005–2006	National (DHS)	17,856	15–49	27.8	18.8
Jamaica	1999	National	1,935	15+	30.3	23.9
Mexico	2006	National	33,624	20+	37.4	34.5
Nicaragua	2001	National	11,838	15–49	30.2	18
Panama	2000	National	875	15–93	33.4	36.1
Paraguay	1991–1992	National (DHS)	1,606	20–74	36.1	35.7
Peru (urban)	2007–2008	National (DHS)	20,192	15–49	34.3	14.6
St. Lucia	1991–1994	National	1,084	25–74	NA	28.7
Trinidad & Tobago	1999	National	803	20+	32.6	21.1
United States	2009–2010	National	5,926	20–39	55.8	31.9
Uruguay (urban, self-report)	1998	National	900	18+	30	18
Venezuela	1999–2001	National	3,159	20+	33.9	26.4

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Abbreviations: DHS, Demographic Health Surveys; OECD, Organization for Economic Cooperation and Development.

Summary estimates of odds ratios for associations between maternal prepregnancy obesity and birth defects on the basis of at least three studies, from the meta-analysis by Stothard et al. (2009).¹⁷

Type of birth defect	Overweight			Obesity		
	No. of studies	No. of cases	Overweight summary OR (95%CI)	No. of studies	No. of cases	Obesity summary OR (95%CI)
Anencephaly	3	233	1.12 (0.83–1.50)	4	373	1.39 (1.03–1.87)
Spina bifida	4	621	1.12 (0.92–1.37)	5	863	2.24 (1.86–2.69)
All cardiac septal anomalies	2	3,355	1.15 (0.71–1.85)	4	3,483	1.20 (1.09–1.31)
Tetralogy of Fallot	2	183	0.82 (0.53–1.25)	3	211	1.10 (0.76–1.61)
Transposition of the great arteries	0			3	182	1.41 (0.97–2.06)
Cleft lip and palate	3	1,237	1.00 (0.87–1.15)	3	1,188	1.20 (1.03–1.40)
Cleft palate	3	890	1.02 (0.86–1.20)	3	865	1.23 (1.03–1.47)
Diaphragmatic hernia	4	272	0.95 (0.72–1.26)	4	272	1.28 (0.95–1.71)
Hydrocephaly	3	198	1.28 (0.93–1.75)	3	188	1.68 (1.19–2.36)

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3

Odds ratios for associations between maternal prepregnancy obesity and congenital heart defects that exclude the null value in at least one of the two studies published in 2010.

Study	Location	Type of congenital heart defect	Overweight		Obesity – 1 ^a		Obesity – 1 ^b	
			No. of cases	OR (95%CI)	No. of cases	OR (95%CI)	No. of cases	OR (95%CI)
Gilboa et al. (2010) ²⁷	New York, USA	Conotruncal defects	202	1.09 (0.91–1.49)	100	1.20 (0.95–1.53)	66	1.36 (1.01–1.83)
		Transposition of great vessels	64	0.92 (0.68–1.25)	36	1.20 (0.82–1.76)	13	0.82 (0.46–1.47)
		Tetralogy of Fallot	106	1.17 (0.91–1.49)	49	1.18 (0.85–1.65)	42	1.68 (1.16–2.43)
		All septal defects	409	1.16 (1.01–1.34)	181	1.02 (0.84–1.24)	135	1.35 (1.07–1.70)
		Atrial septal defects ^c	153	1.28 (1.03–1.59)	76	1.16 (0.87–1.55)	55	1.51 (1.09–2.11)
		Ventricular septal defects	175	1.13 (0.93–1.37)	64	0.85 (0.64–1.13)	56	1.23 (0.89–1.71)
		Left ventricular outflow tract obstruction defects	163	1.14 (0.94–1.73)	88	1.34 (1.03–1.73)	33	0.85 (0.58–1.26)
		Hypoplastic left heart syndrome	66	1.27 (0.94–1.73)	38	1.51 (1.03–2.22)	18	1.21 (0.72–2.06)
		Aortic stenosis	30	0.87 (0.56–1.34)	17	1.06 (0.62–1.82)	4	0.34 (0.11–1.10)
		Right ventricular outflow tract obstruction defects	175	1.35 (1.11–1.65)	74	1.20 (0.91–1.58)	61	1.61 (1.17–2.20)
		Pulmonary valve stenosis	134	1.40 (1.11–1.75)	51	1.08 (0.78–1.49)	51	1.76 (1.24–2.48)
		Atrioventricular septal defects (nonsyndromic)	18	0.96 (0.55–1.69)	5	0.58 (0.23–1.49)	7	1.42 (0.62–3.23)
		Total anomalous pulmonary venous return	25	1.25 (0.76–2.00)	18	1.99 (1.14–3.47)	10	1.90 (0.92–3.93)
		Conotruncal defects	200	1.08 (0.91–1.28)	121	1.08 (0.88–1.32)	34	1.70 (1.19–2.43)
Mills et al. (2010) ²⁶	New York, USA	Transposition of great vessels	58	0.89 (0.66–1.21)	31	0.79 (0.54–1.17)	9	1.30 (0.66–2.55)
		Tetralogy of Fallot	105	1.28 (1.01–1.62)	60	1.20 (0.89–1.60)	18	2.02 (1.24–3.29)
		All septal defects	1,014	0.96 (0.89–1.04)	661	1.04 (0.95–1.14)	144	1.27 (1.07–1.52)
		Atrial septal defects ^c	365	0.95 (0.84–1.08)	275	1.18 (1.03–1.35)	56	1.32 (1.00–1.74)
		Ventricular septal defects	757	0.96 (0.88–1.05)	457	0.97 (0.87–1.08)	103	1.23 (1.00–1.52)
		Left ventricular outflow tract obstruction defects	177	1.15 (0.96–1.38)	139	1.51 (1.24–1.83)	25	1.52 (1.01–2.29)
		Hypoplastic left heart syndrome	48	1.31 (0.92–1.86)	37	1.66 (1.13–2.45)	8	2.01 (0.97–4.16)
		Aortic stenosis	42	1.16 (0.80–1.67)	44	2.03 (1.41–2.92)	8	2.08 (1.00–4.31)
		Right ventricular outflow tract obstruction defects	232	1.16 (0.99–1.36)	164	1.32 (1.10–1.58)	28	1.21 (0.82–1.79)
		Pulmonary valve stenosis	188	1.13 (0.95–1.35)	135	1.30 (1.06–1.59)	24	1.24 (0.81–1.88)
		Atrioventricular septal defects (nonsyndromic)	17	0.64 (0.37–1.10)	14	0.88 (0.49–1.57)	5	1.79 (0.71–4.48)

Study	Location	Type of congenital heart defect	Overweight		Obesity – I ^a		Obesity – II ^b	
			No. of cases	OR (95%CI)	No. of cases	OR (95%CI)	No. of cases	OR (95%CI)
		Total anomalous pulmonary venous return	12	0.48 (0.26–0.90)	13	0.85 (0.47–1.56)	1	0.33 (0.05–2.39)

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

^aObesity I category was defined as a BMI of 30.0–35.0 kg/m² in the Gilboa et al.²⁷ study and as a BMI of 35.0–39.0 kg/m² in the Mills et al.²⁶ study.

^bObesity II category was defined as a BMI of 35.0 kg/m² in the Gilboa et al.²⁷ study and as a BMI of 40 kg/m² in the Mills et al.²⁶ study.

^cThis category refers to secundum-type atrial septal defects in the Gilboa et al.²⁷ study but is not included in the Mills et al.²⁶ study.

Table 4

Evidence for causality between maternal prepregnancy conditions (diabetes and obesity) and selected birth defects (neural tube defects and congenital heart defects).

Criteria for causality	Evidence for diabetes and neural tube defects	Evidence for obesity and neural tube defects	Evidence for diabetes and congenital heart defects	Evidence for obesity and congenital heart defects
Temporality	+++	+++	+++	+++
Consistency	+++	+++	+++	+
Strength of association	++	++	+++	+
Plausibility, coherence	++	–	++	–
Biological gradient	++	–	++	–
Experimental evidence	+++	–	+++	–
Specificity	–	–	–	–

Symbols: +++, strong; ++, moderate; +, weak; –, none.