

Maternal Overweight and Obesity and the Risk of Congenital Anomalies

A Systematic Review and Meta-analysis

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OBESITY IS A MAJOR PUBLIC health and economic concern. Worldwide, an estimated 1.6 billion adults (aged 15 years and older) were overweight (body mass index [BMI] 25-30, calculated as weight in kilograms divided by height in meters squared), and 400 million were obese (BMI > 30) in 2005.¹ By 2015, it is expected there will be 2.3 billion overweight and more than 700 million obese adults worldwide. In the United States, a third of women aged 15 years and older were obese in 2004.² There are significant health implications of prepregnancy maternal obesity for both mother and child. For the mother, these may include gestational diabetes, hypertensive disorders, thromboembolic disorders, increased cesarean delivery rates, and wound infection.³⁻⁸ Infants of obese mothers are at increased risk of birth difficulties, macrosomia, and perinatal death.⁹⁻¹² Maternal obesity may also be associated with the development of congenital anomalies. Congenital anomalies are a leading cause of stillbirth and infant mortality, accounting for 1 in 5 infant deaths in the United States,¹³ and are important contributors to preterm birth and childhood

Context Evidence suggests an association between maternal obesity and some congenital anomalies.

Objective To assess current evidence of the association between maternal overweight, maternal obesity, and congenital anomaly.

Data Sources MEDLINE, EMBASE, CINAHL, and Scopus (January 1966 through May 2008) were searched for English-language studies using a list of keywords. Reference lists from relevant review articles were also searched.

Study Selection Observational studies with an estimate of prepregnancy or early pregnancy weight or body mass index (BMI) and data on congenital anomalies were considered. Of 1944 potential articles, 39 were included in the systematic review and 18 in the meta-analysis.

Data Extraction and Synthesis Information was extracted on study design, quality, participants, congenital anomaly groups and subtypes, and risk estimates. Pooled odds ratios (ORs) comparing risk among overweight, obese, and recommended-weight mothers (defined by BMI) were determined for congenital anomaly groups and subtypes for which at least 150 cases had been reported in the literature.

Results Pooled ORs for overweight and obesity were calculated for 16 and 15 anomaly groups or subtypes, respectively. Compared with mothers of recommended BMI, obese mothers were at increased odds of pregnancies affected by neural tube defects (OR, 1.87; 95% confidence interval [CI], 1.62-2.15), spina bifida (OR, 2.24; 95% CI, 1.86-2.69), cardiovascular anomalies (OR, 1.30; 95% CI, 1.12-1.51), septal anomalies (OR, 1.20; 95% CI, 1.09-1.31), cleft palate (OR, 1.23; 95% CI, 1.03-1.47), cleft lip and palate (OR, 1.20; 95% CI, 1.03-1.40), anorectal atresia (OR, 1.48; 95% CI, 1.12-1.97), hydrocephaly (OR, 1.68; 95% CI, 1.19-2.36), and limb reduction anomalies (OR, 1.34; 95% CI, 1.03-1.73). The risk of gastroschisis among obese mothers was significantly reduced (OR, 0.17; 95% CI, 0.10-0.30).

Conclusions Maternal obesity is associated with an increased risk of a range of structural anomalies, although the absolute increase is likely to be small. Further studies are needed to confirm whether maternal overweight is also implicated.

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morbidity. We conducted a systematic review and meta-analysis of observational studies to assess and quantify the relationship between maternal overweight and obesity and the risk of congenital anomaly in the offspring.

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METHODS

Study Selection

We conducted a comprehensive literature search of MEDLINE, EMBASE, CINAHL, and Scopus (January 1966 through May 2008) using terms for mother (eg, *mother**, *matern**, *wom*n*), weight (eg, *weight*, *body mass index*, *BMI*), and congenital anomaly (eg, *anomal**, *malform**, *birth defect*). The full list of terms is available from the authors. Additional articles were identified by reviewing reference lists. Articles were included if the participants were pregnant women, a measure or estimate of prepregnancy or early pregnancy weight was reported, and the outcome was a congenital anomaly. Searches were restricted to English-language articles. Articles were excluded from the meta-analysis if they did not report BMI, report the number of cases with a recommended BMI, or specify a congenital anomaly group or subtype. The database searches elicited 1944 articles. A title and abstract review resulted in 102 original articles and 18 review articles. The abstracts and, where necessary, full articles were reviewed in detail. Reference lists were searched and produced 3 additional studies. Thirty-nine articles were included in the systematic review, and 18 of these articles were included in the meta-analysis (FIGURE 1).

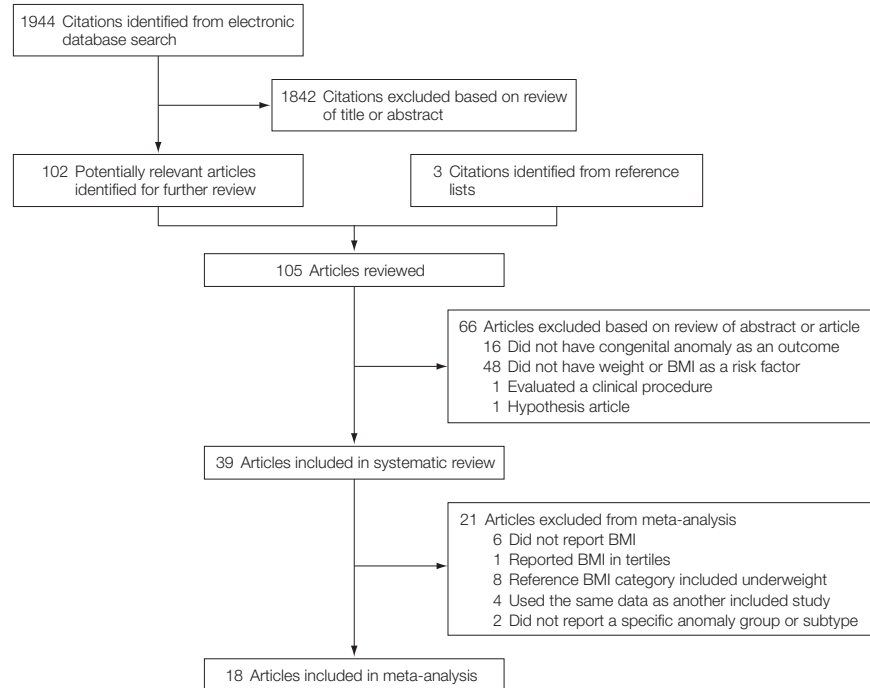
Data Extraction

A standardized, piloted data extraction form was used to retrieve information of interest, including study characteristics, participant information, measure for maternal weight estimation, congenital anomaly group or subtype, and analyses conducted. Data extraction was completed by 4 reviewers, each study being independently reviewed by 2 individuals. There were no discrepancies between reviewers in terms of data extracted or choice of articles meriting inclusion.

Meta-analysis

We followed published guidelines for the meta-analysis of observational studies.¹⁴ We calculated odds ratios (ORs)

Figure 1. Review and Selection of Articles



BMI indicates body mass index.

and 95% confidence intervals (CIs) for all articles with sufficient data to compare obese or overweight mothers with maternal recommended BMI (reference category). Recommended and risk BMI categories were selected to best match the World Health Organization guidelines¹⁵ (TABLE 1 and TABLE 2). Where direct calculation was not possible, reported ORs and CIs were used. Where data were duplicated between articles, only the largest or oldest article was included. Few articles presented adjusted ORs, so crude ORs were entered into the primary analysis, although, when reported, adjusted ORs and CIs were obtained for sensitivity analysis.

We calculated pooled ORs as the weighted average of the ORs for all congenital anomaly groups and subtypes where the total number of cases included across the risk and comparison groups, throughout the included articles, was greater than 150. The number of cases was chosen so that inclusion was determined by statistical

power (150 cases would provide adequate power [0.81] to detect a medium effect [$\delta=0.5$] in a typical study with a risk group prevalence of $\geq 10\%$ and control-case ratio of $\geq 2:1$). Weighting was assigned according to the inverse of the variance. Heterogeneity was tested using the Cochrane Q test and quantified with the I^2 statistic.⁵⁵ The value of the I^2 statistic was used to select the appropriate pooling method: fixed-effects models were used for I^2 less than 50% and random-effects models for I^2 greater than 50%. The presence of bias was examined using a combination of the Egger regression asymmetry test⁵⁶ and the trim and fill method.⁵⁷ The trim and fill method simulates studies that may be missing from the literature, for example, due to publication bias, and the trim and fill OR estimates the pooled OR if these “missing” studies were present. Agreement between the standard OR and the trim and fill OR provides confidence that the results are robust to bias.⁵⁸ Trim and fill ORs are reported where they

Table 1. Overview of Case-Control Studies Included in the Systematic Review

Study (Location)	Study Period	Risk Factor	Measurement of Maternal Weight	Pregnancy Outcomes Included	Definition of RBMI, Overweight, and Obese ^a	Congenital Anomaly Groups and Subtypes, No. of Cases (No. Used in Meta-analysis)
Richards, ¹⁶ 1969 (South Wales, UK)	1964-1966	Weight	Retrospectively self-reported by mother and confirmed in mother's records	"Births"	NA ^b	All nervous system anomalies, 279; neural tube defects, 247; anencephaly, 107; spina bifida, 140; all cardiovascular anomalies, 100; septal anomalies, 21; patent ductus arteriosus, 16; aortic anomalies, 29; all orofacial clefts, 66; pyloric stenosis, 39; limb reduction anomalies, 11; hip dislocation and/or dysplasia, 15; talipes, 92; eye and/or ear anomalies, 16; urinary and/or genital anomalies, 15; skin anomalies, 46 ^c
Wald et al, ¹⁷ 1981 (Oxford, UK)	1972-1980	Weight	Measured at antenatal visit	NA (performed during pregnancy)	NA ^b	Neural tube defects, 56; anencephaly, 30; spina bifida, 26 ^c
Haddow et al, ¹⁸ 1982 (US)	NS	Weight	Measured during second trimester	NA (performed during pregnancy)	NA ^b	Anencephaly, 27; spina bifida, 21 ^c
Johnson et al, ¹⁹ 1990 (US)	NS	Weight	NS	NA (performed during pregnancy)	NA ^b	Spina bifida, 143 ^c
Waller et al, ²⁰ 1994 (California, Illinois)	1985-1987	BMI	Retrospectively self-reported by mother	Congenital anomaly diagnosed prenatally or postnatally	Recommended: 19-27; overweight: 28-30; obese: ≥ 31 ^d	Neural tube defects, 499 (408); anencephaly, 156 (156); encephalocele, 39; spina bifida, 199 (199); all cardiovascular anomalies, 81 (81); septal anomalies, 33 (33); all respiratory anomalies, 7; diaphragmatic hernia, 7 (7); pyloric stenosis, 10; upper alimentary anomalies, 13; other intestinal anomalies, 14; all abdominal wall anomalies, 50; renal agenesis, 12; other urinary anomalies, 20; all genital anomalies, 8; limb reduction anomalies, 7; multiple anomalies, 8; other anomalies, 24 ^{e,f,g}
Shaw et al, ²¹ 1996 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 19-27; overweight: 28-30; obese: ≥ 31 ^d	Neural tube defects, 538 (443); anencephaly, 217; spina bifida, 296; other neural tube defects, 25 ^e
Watkins et al, ²² 1996 (Georgia)	1968-1980	BMI	Retrospectively self-reported by mother	Stillbirths, livebirths	Recommended: 19.8-26; overweight: >26-29; obese: >29 ^h	Neural tube defects, 307 (201)
Werler et al, ²³ 1996 (US, Canada)	1988-1994	Weight (1988-1994); BMI (1992-1994)	Retrospectively self-reported by mother	Terminations (from 1990), stillbirths, livebirths	Recommended: 19-23.9; overweight: 24-27.9; obese: ≥ 28 ^d	Neural tube defects, 604 (79)
Lam et al, ²⁴ 1999 (California)	1988-1990	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.1-28.3; overweight: included in recommended and obese categories obese: >28.3 ^b	Gastroschisis, 104 (88) ^e
Shaw et al, ²⁵ 2000 (California)	Study A: 1989-1991; study B: 1987-1988	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤ 29 ; overweight: included in recommended category; obese: >29 ^d	Study 1: neural tube defects, 500; study 2: neural tube defects, 247; outflow tract anomalies, 202; cleft lip and cleft palate, 426; cleft palate, 207; all limb anomalies, 156 ⁱ
Hendricks et al, ²⁶ 2001 (Texas)	1995-2000	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥ 30 ^d	Neural tube defects, 149 (146)
Shaw et al, ²⁷ 2001 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤ 29 ; overweight: included in recommended category; obese: >29 ^d	Neural tube defects, 538 ^j
Watkins and Botto, ²⁸ 2001 (Georgia)	1968-1980	BMI	Retrospectively self-reported by mother	Stillbirths, livebirths	Recommended: 19.9-22.7; overweight: 26.1-29; obese: >29 (for all cardiovascular anomalies) or >26 (for named subtypes) ^h	All cardiovascular anomalies, 851 (408); double outlet arteriosus, 5; outflow tract anomalies, 132; septal anomalies, 221 (96); tetralogy of Fallot, 45 (24); transposition of the great arteries, 60 (29); truncus arteriosus, 16 ^f
Cedergren et al, ²⁹ 2002 (Sweden)	1982-1996	BMI	Measured at first antenatal visit	"Infants born"	Recommended: 19.8-26.0; overweight: 26.1-28.9; obese: ≥ 29 ^b	Medical records study: all cardiovascular anomalies, 231 (181)
Cedergren et al, ³⁰ 2002 (Sweden)	1973-1990	BMI	Measured at first antenatal visit	"Infants born"	Recommended: <29; overweight: included in recommended category; obese: ≥ 29 ^b	All cardiovascular anomalies, 246 ⁱ
Shaw et al, ³¹ 2002 (California)	1993-1996	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤ 29 ; overweight: included in recommended category; obese: >29 ^d	Multiple anomalies, 80 ⁱ

(continued)

Table 1. Overview of Case-Control Studies Included in the Systematic Review (continued)

Study (Location)	Study Period	Risk Factor	Measurement of Maternal Weight	Pregnancy Outcomes Included	Definition of RBMI, Overweight, and Obese ^a	Congenital Anomaly Groups and Subtypes, No. of Cases (No. Used in Meta-analysis)
Cedergren and Källén, ³² 2003 (Sweden)	1992-2001	BMI	Measured at first antenatal visit	Stillbirths, livebirths	Recommended: 19.8-26; overweight: 26.1-29; obese: >29 ^d	All cardiovascular anomalies, 7535 (6174); coarctation of the aorta, 117; hypoplastic left heart, 166; septal anomalies, 4220 (3840); tetralogy of Fallot, 223 (195); transposition of the great arteries, 164 (154) ^f
Honein et al., ³³ 2003 (Georgia)	1968-1980	BMI	Retrospectively self-reported by mother	Stillbirths, livebirths	Recommended: <25; overweight: 25-29.9; obese: ≥30 ^h	All urinary anomalies, 169; hydronephrosis, 91; renal agenesis, 41; renal multicystic dysplasia, 26; renal or ureter duplications, 11; urinary obstruction anomalies, 117 ⁱ
Krauss et al., ³⁴ 2003 (Missouri)	1993-1999	BMI	Birth certificates	Livebirths	Recommended: 19.9-26.0; overweight: 26.1-29.0; obese: ≥29.1 ^b	Microcephaly, 360 (276)
Shaw et al., ³⁵ 2003 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤29; overweight: included in recommended category; obese: >29 ^d	Neural tube defects, 454 ^j
Waller et al., ³⁶ 2003 (US, Canada)	1993-1997	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 21.1-25.0; overweight: 25.1-29; obese: >29 ^b	Diaphragmatic hernia, 85 (50)
Watkins et al., ³⁷ 2003 (Georgia)	1993-1997	BMI	Retrospectively self-reported by mother	Terminations (≥20 weeks gestation), stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30 ^h	Hydrocephaly, 14 (13); neural tube defects, 43 (40); anencephaly, 12 (11); encephalocele, 9; spina bifida, 22 (20); all cardiovascular anomalies, 195 (175); coarctation of the aorta, 12; hypoplastic left heart, 22; septal anomalies, 55 (49); tetralogy of Fallot, 19 (17); transposition of the great arteries, 25 (21); cleft lip, 26 (23); cleft lip and palate, 34 (33); cleft palate, 30 (29); diaphragmatic hernia, 17 (15); esophageal atresia, 20 (19); large intestinal atresia, 32; small intestinal atresia, 9; gastroschisis, 23 (22); omphalocele, 18; all urinary anomalies, 106; renal agenesis, 20; renal multicystic dysplasia, 30; urinary obstruction anomalies, 67; hypospadias, 21 (19); all limb anomalies, 45; craniosynostosis, 28 (24); multiple anomalies, 96 ^{f,k}
Anderson et al., ³⁸ 2005 (Texas)	1997-2001	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30 ^h	Holoprosencephaly, 41; hydrocephaly, 115 (94); neural tube defects, 302 (235); anencephaly, 119 (93); spina bifida, 183 (154) ^f
Martinez-Frias et al., ³⁹ 2005 (Spain)	1995-2001	BMI	Retrospectively self-reported by mother	"Infants delivered"	Recommended: 21-24.9; overweight: 25-29.9; obese: ≥30 ^h	Holoprosencephaly, NS; All cardiovascular anomalies, 764 (565); All urinary anomalies, NS; spine/rib defects, NS ^l
Velie et al., ⁴⁰ 2006 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30 ^d	Neural tube defects, 538 (265) ^k
Carmichael et al., ⁴¹ 2007 (US)	1997-2000	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 19.8-26; overweight: >26-29; obese: >29 ^b	Hypospadias, 502 ^j
Waller et al., ⁴² 2007 (US)	1997-2002	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: 18.5-24.9; overweight: 25-29.9; obese: ≥30 ^h	Hydrocephaly, 156 (146); neural tube defects, 618 (588); anencephaly, 193 (183); spina bifida, 425 (405); all cardiovascular anomalies, 4128 (3873); cleft lip and palate, 1064 (972); cleft palate, 592 (559); anorectal atresia, 380 (363); diaphragmatic hernia, 286 (271); esophageal atresia, 278 (261); small intestinal atresia, 163; gastroschisis, 400 (359); omphalocele, 177; hypospadias, 793 (750); limb reduction anomalies, 509 (477); craniosynostosis, 422 (400); microtia and anotia, 216 (205) ^f

Abbreviations: NA, not applicable; NS, not specified; RBMI, recommended body mass index; UK, United Kingdom; US, United States.

^aCalculated as weight in kilograms divided by height in meters squared.

^bDiabetes status not specified or reported.

^cExcluded from meta-analysis because BMI not reported.

^dIncluded pregestational and/or gestational diabetes.

^eIncluded some cases in obese meta-analysis only.

^fSome cases excluded from meta-analysis because the associated anomaly group had fewer than 150 relevant cases.

^gSome cases excluded from meta-analysis because there were 0 recorded cases in the risk group.

^hExcluded pregestational and/or gestational diabetes.

ⁱExcluded from meta-analysis because RBMI included underweight.

^jExcluded from meta-analysis because data set reported elsewhere.

^kIncluded some cases in overweight meta-analysis only.

^lIncluded cardiovascular anomaly cases without gestational diabetes.

Table 2. Overview of Cohort Studies Included in the Systematic Review

Study (Location)	Study Period	Risk Factor	Measurement of Maternal Weight	Pregnancy Outcomes Included	Definition of RBMI, Overweight, and Obese ^a	Congenital Anomaly Groups and Subtypes, No. of Cases (No. Used in Meta-analysis)
Naeye, ⁴³ 1990 (US)	1959-1966	BMI	Retrospectively self-reported by mother	Livebirths	Recommended: 20-24; overweight: 25-30; obese: >30 ^b	"Major congenital malformations," 2504 ^c
Berkowitz et al, ⁴⁴ 1995 (New York)	1987-1990	BMI	NS	Livebirths	Recommended: <27.3; overweight: included in recommended and obese categories; obese: ≥27.3 ^b	Cryptorchidism, 63 ^d
Källén, ⁴⁵ 1998 (Sweden)	1983-1989 and 1992-1993	BMI	Retrospectively self-reported by mother and estimated from weight at delivery	Stillbirths, livebirths	Recommended: 19.8-26; overweight: 26.1-29; obese: >29 ^e	Neural tube defects, 621 (287); anencephaly, 79; encephalocele, 50; spina bifida, 492 (232)
Feldman et al, ⁴⁶ 1999 (US)	NS	Weight	Measured "shortly before biochemical screening"	Unclear ("pregnancy outcomes")	NA ^e	Neural tube defects, 79 ^f
Moore et al, ⁴⁷ 2000 (US)	1984-1987	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: <28; overweight: included in recommended and obese categories; obese: ≥28 ^g	Hydrocephaly, 12; Neural tube defects, 48; Hypoplastic left heart, 11; Septal anomalies, 20; All orofacial clefts, 16; Lung hypoplasia, 3; Pyloric stenosis, 9; All abdominal wall anomalies, 11; Renal agenesis, 4; All genital anomalies, 30; Lower limb reduction anomalies, 4; Talipes, 14; Polydactyly, 3; Congenital cataracts, 2 ^{d,h}
Shaw et al, ⁴⁸ 2000 (California)	1989-1991	BMI	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	Recommended: ≤29; overweight: included in recommended category; obese: >29 ^b	Spina bifida, 277 ^d
Cedergren et al, ²⁹ 2002 (Sweden)	1982-1996	BMI	Measured at first antenatal visit	"Infants born"	Recommended: 19.8-26.0; overweight: 26.1-28.9; obese: ≥29 ^e	Register study: all cardiovascular anomalies, 2208; coarctation of the aorta, 95; hypoplastic left heart, 33; septal anomalies, 824; tetralogy of Fallot, 55; transposition of the great arteries, 65
Mikhail et al, ⁴⁹ 2002 (Illinois)	1982-1994	BMI	NS	"Delivered babies," terminations	Recommended: <27; overweight: included in recommended and obese categories; obese: ≥27 ⁱ	Neural tube defects, 17; all cardiovascular anomalies, 7; all abdominal wall anomalies, 8; renal agenesis, 13; multiple anomalies, 18 ^d
García-Patterson et al, ⁵⁰ 2004 (Spain)	1986-2002	BMI	NS	"Newborn infants"	1st tertile: 15.43-21.91; 2nd tertile: 21.92-24.77; 3rd tertile: 24.78-47.07 ^j	All cardiovascular anomalies, 29; all orofacial clefts, 4; all urinary anomalies, 16; hypospadias, 6; skeletal anomalies, 14 ^k
Cedergren and Källén, ⁵¹ 2005 (Sweden)	1992-2001	BMI	Measured at first antenatal visit	Stillbirths, livebirths	Recommended: 19.8-26; overweight: 26.1-29; obese: >29 ^e	Cleft lip, 425 (318); cleft lip and palate, 644 (475); cleft palate, 610 (476)
Ray et al, ⁵² 2005 (Canada)	1994-2000	Weight	Retrospectively self-reported by mother	Terminations, stillbirths, livebirths	NA ^b	Neural tube defects, 292 ^f
Callaway et al, ⁵³ 2006 (Australia)	1998-2002	BMI	Prepregnancy weight estimated from measurement at first antenatal visit	"Deliveries"	Recommended: 20.01-25; overweight: 25.01-30; obese: ≥30.01 ^b	Group/subtype unspecified: "birth defect(s)," 159 ^{c,l}
Cedergren and Källén, ⁵⁴ 2006 (Sweden)	1992-2001	BMI	Obtained from antenatal care center document	Stillbirths, livebirths	Recommended: 20-24.9; overweight: 25-29.9; obese: ≥30 ^l	All cardiovascular anomalies, 6346 ^m

Abbreviations: NA, not applicable; NS, not specified; RBMI, body mass index; UK, United Kingdom; US, United States.

^aCalculated as weight in kilograms divided by height in meters squared.

^bIncluded pregestational and/or gestational diabetes.

^cExcluded from meta-analysis because no specific anomaly reported.

^dExcluded from meta-analysis because RBMI included underweight.

^eDiabetes status not specified or reported.

^fExcluded from meta-analysis because BMI not reported.

^gStratified BMI by diabetes status.

^hNumbers excluded those with diabetes.

ⁱExcluded pregestational and/or gestational diabetes.

^jCohort included gestational cases only, no individuals with normal glucose tolerance.

^kExcluded from meta-analysis because BMI reported in nonstandard format (tertiles).

^lEstimated from reported percentages.

^mExcluded from meta-analysis because data set reported elsewhere.

were significantly different from the standard pooled OR or if it changed the significance of the comparison.

A sensitivity analysis was performed to examine the potential effects of varying methodological quality and inclusion criteria. We defined higher-quality articles as those that reported the inclusion of pregnancies ending in termination, excluded mothers with pregestational diabetes, and excluded cases that were chromosomal or syndromic. We also examined the effect of using an objective measure of weight. The pooled ORs for each alternative scenario were compared with the principal ORs using *t* tests performed on the logarithm of the ORs (the logarithm being necessary to equalize the distance of the point estimate from the confidence limits, from which standard errors were derived).

Statistical analyses were performed using Stata 9.2 (StataCorp, College Station, Texas). The *metan*,⁵⁹ *metabias*,⁶⁰ and *metatrim*⁶¹ macros were used for meta-analytic procedures. *P* values < .05 were considered statistically significant.

RESULTS

Thirty-nine articles met our inclusion criteria for the systematic review (Table 1 and Table 2). Of these, 25 were from the United States, 6 were from Sweden, 2 from the United Kingdom, 2 from Spain, 2 from across Canada and the United States, and 1 each from Canada and Australia. Twenty-nine articles reported the results of a case-control study and 12 of a cohort study (1 article reported a case-control and a cohort study²⁹ and 1 reported 2 case-control studies²⁵). Body mass index was the most frequent measure of overweight and obesity (33 articles) while 6 articles reported only maternal weight. Neural tube defects (22 articles) were the most frequently investigated congenital anomaly group followed by cardiovascular anomalies (14).

Articles included in the systematic review varied in the method used to measure weight and in the range of BMI categories (Table 1). Terminations of pregnancy for fetal anomaly were in-

cluded in 18 articles, stillbirths were included in 24 articles (definitions ranged from >19 weeks to >28 weeks), chromosomal anomalies were excluded in 16 articles, and diabetes status was reported in 27 articles.

Eighteen articles were included in the meta-analysis (TABLE 3). Among the 21 articles excluded, 6 did not report BMI,^{16-19,46,52} 1 grouped BMI into tertiles,⁵⁰ 8 included maternal underweight in the recommended BMI category,^{25,30,31,33,44,47-49} 4 reported data from the same population as a larger or earlier study included in the meta-analysis,^{27,35,41,54} and 2 did not report a specific congenital anomaly group or subtype.^{43,53} Pooled ORs for overweight and obesity were calculated for 16 and 15 anomaly groups or subtypes, respectively. Heterogeneity varied between 0% and 62.9%, with a median of 0.0%.

Neural Tube Defects

Obese mothers were at significantly increased odds of a pregnancy affected by a neural tube defect compared with mothers of recommended BMI (OR, 1.87; 95% CI, 1.62-2.15; *P* < .001) (FIGURE 2). Overweight mothers were also at significantly increased odds of a pregnancy affected by a neural tube defect (OR, 1.20; 95% CI, 1.04-1.38; *P* = .01); however, the trim and fill OR (including 3 simulated studies) was not significant (OR, 1.12; 95% CI, 0.98-1.28; *P* = .09).

Obese mothers were at significantly increased odds of a pregnancy affected by anencephaly compared with mothers of recommended BMI, although the effect size was much smaller than for all neural tube defects (OR, 1.39; 95% CI, 1.03-1.87; *P* = .03). The trim and fill OR (including 2 simulated studies) was not significant (OR, 1.17; 95% CI, 0.90-1.52; *P* = .24). No significant increased risk was found for maternal overweight.

There was a 2-fold increased odds of a pregnancy affected by spina bifida in obese mothers compared with mothers of recommended BMI, with an effect size that was much larger than for all

neural tube defects (OR, 2.24; 95% CI, 1.86-2.69; *P* < .001). No significant increased risk was found for maternal overweight.

Nine articles with unique data were excluded from the meta-analysis,^{17-19,25,46,47,49,52} of which 3 included more than 150 cases.^{25,52} Two of these identified significantly elevated odds among mothers of higher weight or BMI^{16,25,52} while the other reported a significant increase for anencephaly but not spina bifida.¹⁶ Of the 6 articles with fewer than 150 cases,^{17-19,46,47,49} 5 found no evidence of association^{18,19,46,47,49} while 1 reported a significantly lower weight among mothers with a pregnancy affected by anencephaly.¹⁷ In their reanalysis of a previously analyzed data set,²¹ Shaw et al⁴⁸ reported a higher OR among obese mothers specifically for spina bifida.

Two articles reported the relative odds of a pregnancy affected by encephalocele.^{20,37} Neither included more than 50 cases or identified evidence of an association with maternal BMI.

Cardiovascular Anomalies

Obese mothers were at significantly increased odds of a pregnancy affected by a cardiovascular anomaly compared with mothers of recommended BMI (OR, 1.30; 95% CI, 1.12-1.51; *P* = .001) (FIGURE 3). Significantly increased odds were also observed for overweight mothers (OR, 1.17; 95% CI, 1.03-1.34; *P* = .02). In both cases, there was significant evidence of heterogeneity. For the overweight category, there was also evidence of bias (*P* = .05) and the trim and fill OR (including 3 simulated studies) was not significant (OR, 1.08; 95% CI, 0.94-1.25; *P* = .27).

Obese mothers were at significantly increased odds of a pregnancy affected by a septal anomaly compared with mothers of recommended BMI (OR, 1.20; 95% CI, 1.09-1.31; *P* < .001) (Figure 3). No significant evidence of increased risk was found for maternal overweight.

No significant evidence of an association between maternal obesity and

Table 3. Summary Results of the Meta-analysis

Congenital Anomaly Group or Subtype (References)	Studies, No.	Cases, No.	Summary Estimates			Bias Test P Value	Trim and Fill Estimates ^a	
			OR (95% CI)	P Value	I ² Heterogeneity Index, % (P Value)		Missing Studies, No.	OR (95% CI)
Obese								
Neural tube defects								
All neural tube defects ^{20-23,26,37,38,42,45}	9	2093	1.87 (1.62-2.15) ^b	<.001	0.0 (.51)	.44	1	1.84 (1.60-2.12) <.001
Anencephaly ^{20,37,38,42}	4	373	1.39 (1.03-1.87) ^b	.03	27.0 (.25)	.19	2	1.17 (0.90-1.52) .24
Spina bifida ^{20,37,38,42,45}	5	863	2.24 (1.86-2.69) ^b	<.001	25.6 (.25)	.70	2	2.11 (1.68-2.59) <.001
Cardiovascular anomalies								
All cardiovascular anomalies ^{20,28,29,32,37,39,42}	7	9349	1.30 (1.12-1.51) ^c	.001	58.1 (.03)	.34	2	1.24 (1.06-1.44) .006
All septal anomalies ^{20,28,32,37}	4	3483	1.20 (1.09-1.31) ^b	<.001	9.8 (.34)	.09	2	1.18 (1.08-1.30) <.001
Tetralogy of Fallot ^{28,32,37}	3	211	1.10 (0.76-1.61) ^b	.62	0.0 (.63)	.97	1	1.06 (0.74-1.52) .76
Transposition of the great arteries ^{28,32,37}	3	182	1.41 (0.97-2.06) ^b	.07	0.0 (.56)	.48	0	
Orofacial clefts								
Cleft lip ^{37,51}	2	281	1.13 (0.82-1.57) ^b	.45	0.0 (.57)		0	
Cleft lip and palate ^{37,42,51}	3	1188	1.20 (1.03-1.40) ^b	.02	13.7 (.31)	.91	0	
Cleft palate ^{37,42,51}	3	865	1.23 (1.03-1.47) ^b	.02	0.0 (.54)	.11	0	
Other congenital anomalies								
Anorectal atresia ⁴²	1	273	1.48 (1.12-1.97) ^d	.006	NA			
Craniosynostosis ^{37,42}	2	312	1.18 (0.89-1.56) ^b	.25	0.0 (.59)		0	
Diaphragmatic hernia ^{20,36,37,42}	4	270	1.28 (0.95-1.71) ^b	.10	0.0 (.66)	.66	0	
Gastroschisis ^{24,42}	2	379	0.17 (0.10-0.30) ^b	<.001	0.0 (.84)		1	0.17 (0.10-0.28) <.001
Hydrocephaly ^{37,38,42}	3	188	1.68 (1.19-2.36) ^b	.003	38.6 (.20)	.88	0	
Hypospadias ^{37,42}	2	576	1.08 (0.86-1.34) ^b	.52	0.0 (.41)		0	
Limb reduction anomalies ⁴²	1	354	1.34 (1.03-1.73) ^d	.03	NA			
Microcephaly ³⁴	1	234	1.10 (0.82-1.48) ^d	.54	NA			
Microtia and anotia ⁴²	1	159	1.11 (0.75-1.63) ^d	.61	NA			
Esophageal atresia ^{37,42}	2	222	1.27 (0.60-2.67) ^c	.54	50.6 (.16)		1	0.99 (0.49-2.00) .97
Overweight								
Neural tube defects								
All neural tube defects ^{22,23,26,37,38,40,42,45}	8	1523	1.20 (1.04-1.38) ^b	.01	0.0 (.55)	.17	3	1.12 (0.98-1.28) .09
Anencephaly ^{37,38,42}	3	233	1.12 (0.83-1.50) ^b	.46	0.0 (.52)	.68	2	0.99 (0.77-1.28) .93
Spina bifida ^{37,38,42,45}	4	621	1.12 (0.92-1.37) ^b	.25	0.0 (.92)	.16	1	1.11 (0.91-1.35) .29
Cardiovascular anomalies								
All cardiovascular anomalies ^{28,29,32,37,39,42}	6	9630	1.17 (1.03-1.34) ^c	.02	62.9 (.02)	.05	3	1.08 (0.94-1.25) .27
All septal anomalies ^{32,37}	2	3355	1.15 (0.71-1.85) ^c	.58	51.9 (.15)		3	0.99 (0.64-1.52) .96
Tetralogy of Fallot ^{32,37}	2	183	0.82 (0.53-1.25) ^b	.35	20.0 (.26)		1	0.74 (0.41-1.35) .33
Orofacial clefts								
Cleft lip ^{37,51}	2	298	1.29 (0.97-1.71) ^b	.08	0.0 (.90)		0	
Cleft lip and palate ^{37,42,51}	3	1237	1.00 (0.87-1.15) ^b	>.99	0.0 (.48)	.27	2	0.95 (0.84-1.07) .41
Cleft palate ^{37,42,51}	3	890	1.02 (0.86-1.20) ^b	.86	0.0 (.88)	.71	0	
Other congenital anomalies								
Anorectal atresia ⁴²	1	288	1.19 (0.91-1.54) ^d	.20	NA			
Craniosynostosis ^{37,42}	2	353	1.24 (0.98-1.58) ^b	.07	0.0 (.43)		1	1.21 (0.96-1.53) .10
Diaphragmatic hernia ^{36,37,42}	3	272	0.95 (0.72-1.26) ^b	.72	0.0 (.69)	.50	2	0.89 (0.69-1.15) .38
Gastroschisis ^{37,42}	2	369	0.83 (0.39-1.77) ^c	.63	59.5 (.12)		1	0.64 (0.32-1.27) .20
Hydrocephaly ^{37,38,42}	3	198	1.28 (0.93-1.75) ^b	.13	0.0 (.50)	.71	2	1.10 (0.84-1.44) .48
Hypospadias ^{37,42}	2	646	1.13 (0.94-1.35) ^b	.21	0.0 (.61)		1	1.12 (0.93-1.34) .24
Limb reduction anomalies ⁴²	1	387	1.22 (0.97-1.53) ^d	.09	NA			
Microcephaly ³⁴	1	210	1.21 (0.85-1.73) ^d	.30	NA			
Microtia and anotia ⁴²	1	170	0.97 (0.69-1.37) ^d	.86	NA			
Esophageal atresia ^{37,42}	2	234	0.89 (0.66-1.21) ^b	.46	11.1 (.29)		0	

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

^aThe trim and fill method simulates studies that are likely to be missing from the literature due to publication (or other forms of) bias; the trim and fill OR estimates what the pooled OR would be if these "missing" studies were present in the literature.

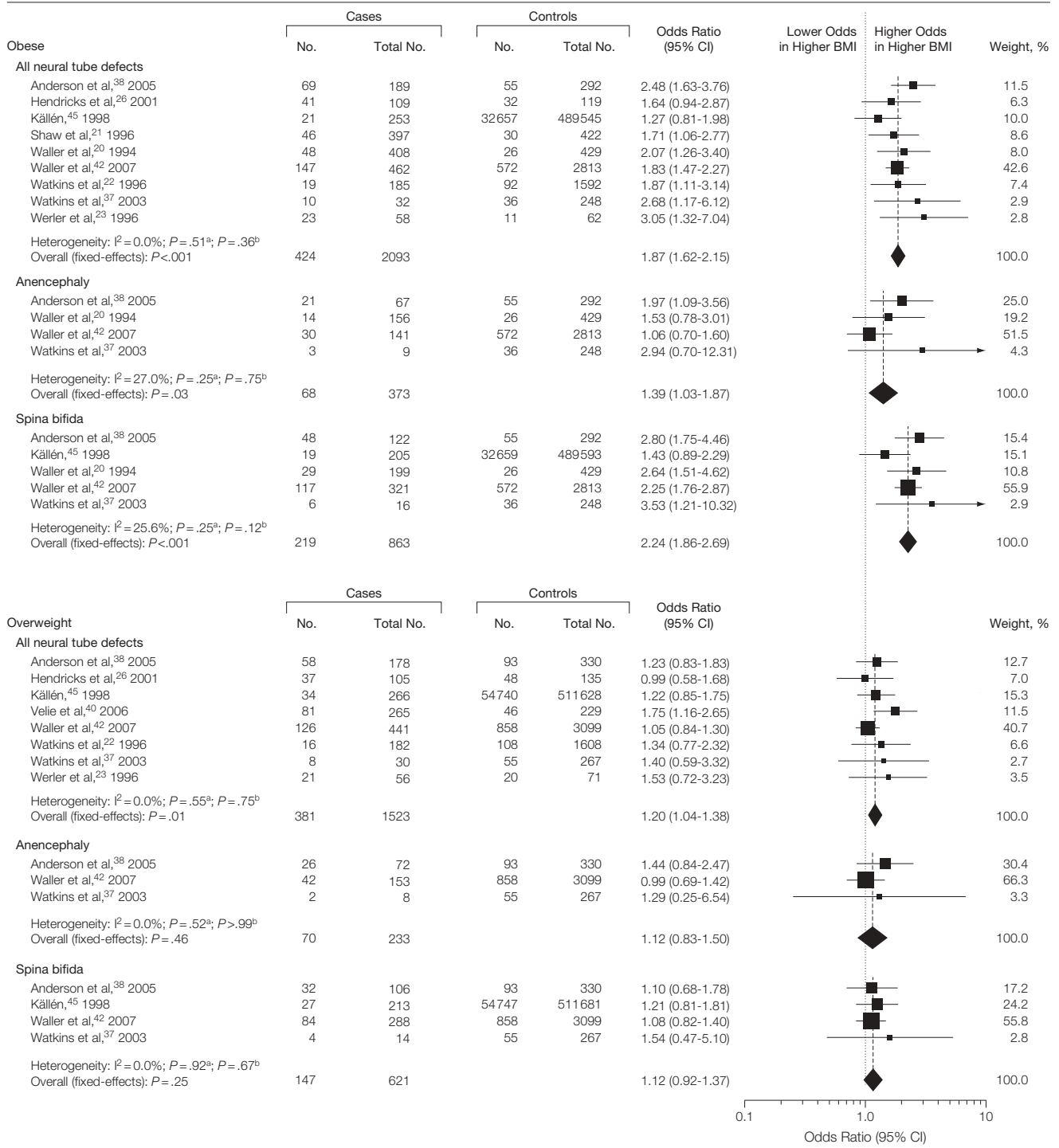
^bFixed-effects pooling method.

^cRandom-effects pooling method.

^dNo pooling method was used because the data were derived from a single study (with greater than 150 cases across the risk and comparison groups).

tetralogy of Fallot or transposition of the great arteries was found, although the OR for transposition of the great arteries was close to significance (OR, 1.41; 95% CI, 0.97-2.06; $P = .07$) (Figure 3). When overweight mothers were compared with mothers of recommended BMI, there was no significant difference in the occurrence of te-

Figure 2. Forest Plot for Neural Tube Defects



Data markers within each subplot are proportional to the assigned study weight.

^aTest for heterogeneity between studies.

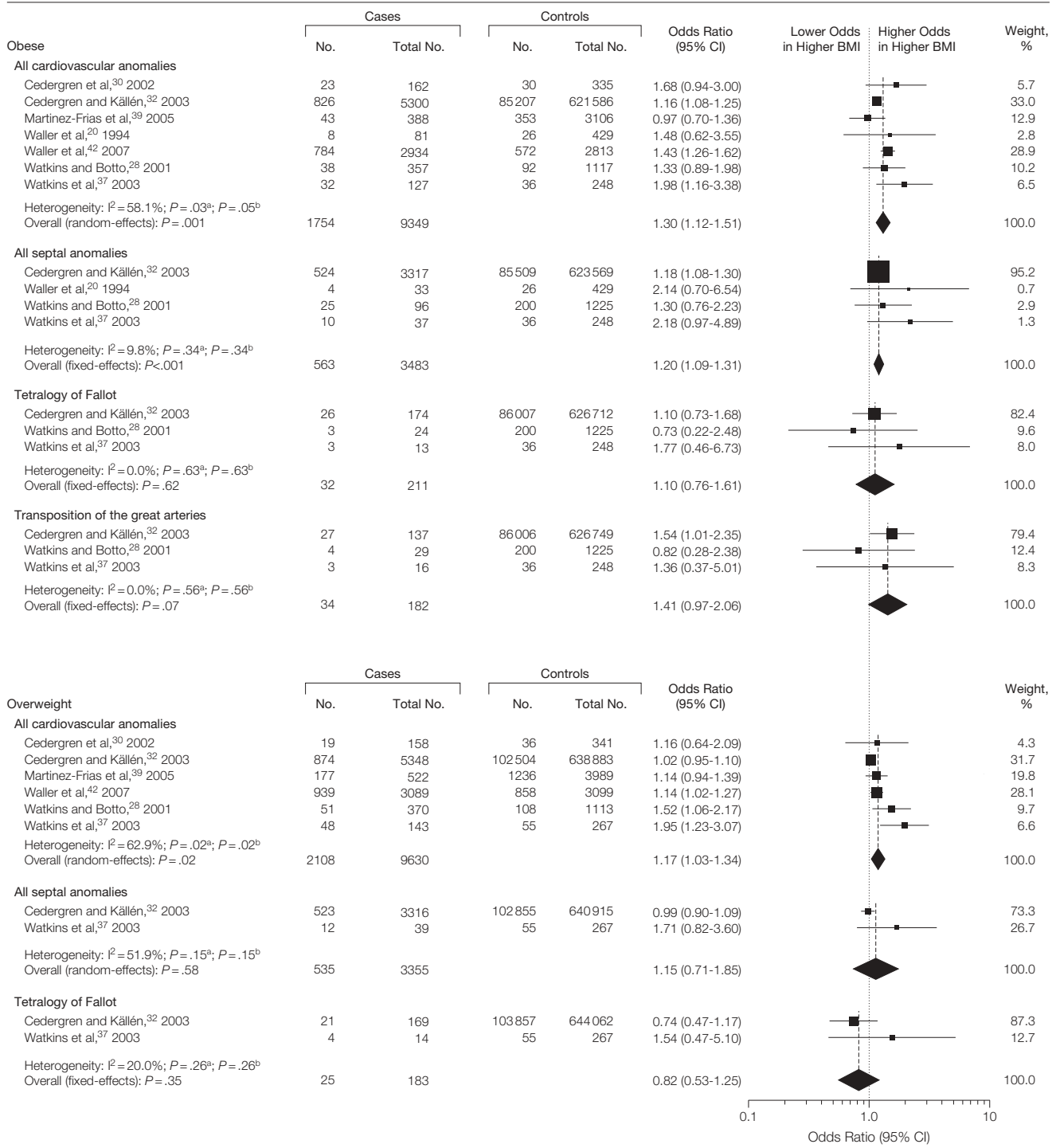
^bTest for heterogeneity between definitions of obese/overweight.

tralogy of Fallot, and there were insufficient cases of transposition of the great arteries for analysis.

Five articles with unique data were excluded from the meta-analysis,^{16,30,47,49,50} including 1 with more than

150 cases that found no evidence of an association between maternal obesity and the odds of a pregnancy being af-

Figure 3. Forest Plot for Cardiovascular Anomalies



Data markers within each subplot are proportional to the assigned study weight.

^aTest for heterogeneity between studies.

^bTest for heterogeneity between definitions of obese/overweight.

ected by a cardiovascular anomaly.³⁰ Of the 4 articles with fewer than 150 cases, 3 found no evidence of association^{16,47,50} while 1 reported significantly higher odds among obese mothers.⁴⁹ Additional data provided in Cedergren et al²⁹ also identified increased odds of cardiovascular anomalies associated with maternal obesity.

Two additional articles reported the relative odds of a pregnancy affected by an outflow tract anomaly,^{25,28} including 1 with more than 150 cases.²⁵ Neither

identified a significant association with maternal obesity. Body mass index or weight data were also reported in relation to hypoplastic left heart,^{32,37,47} coarctation of the aorta,^{32,37} patent ductus arteriosus,¹⁶ and aortic anomalies.¹⁶ No significant evidence of an association was identified in any of these articles.

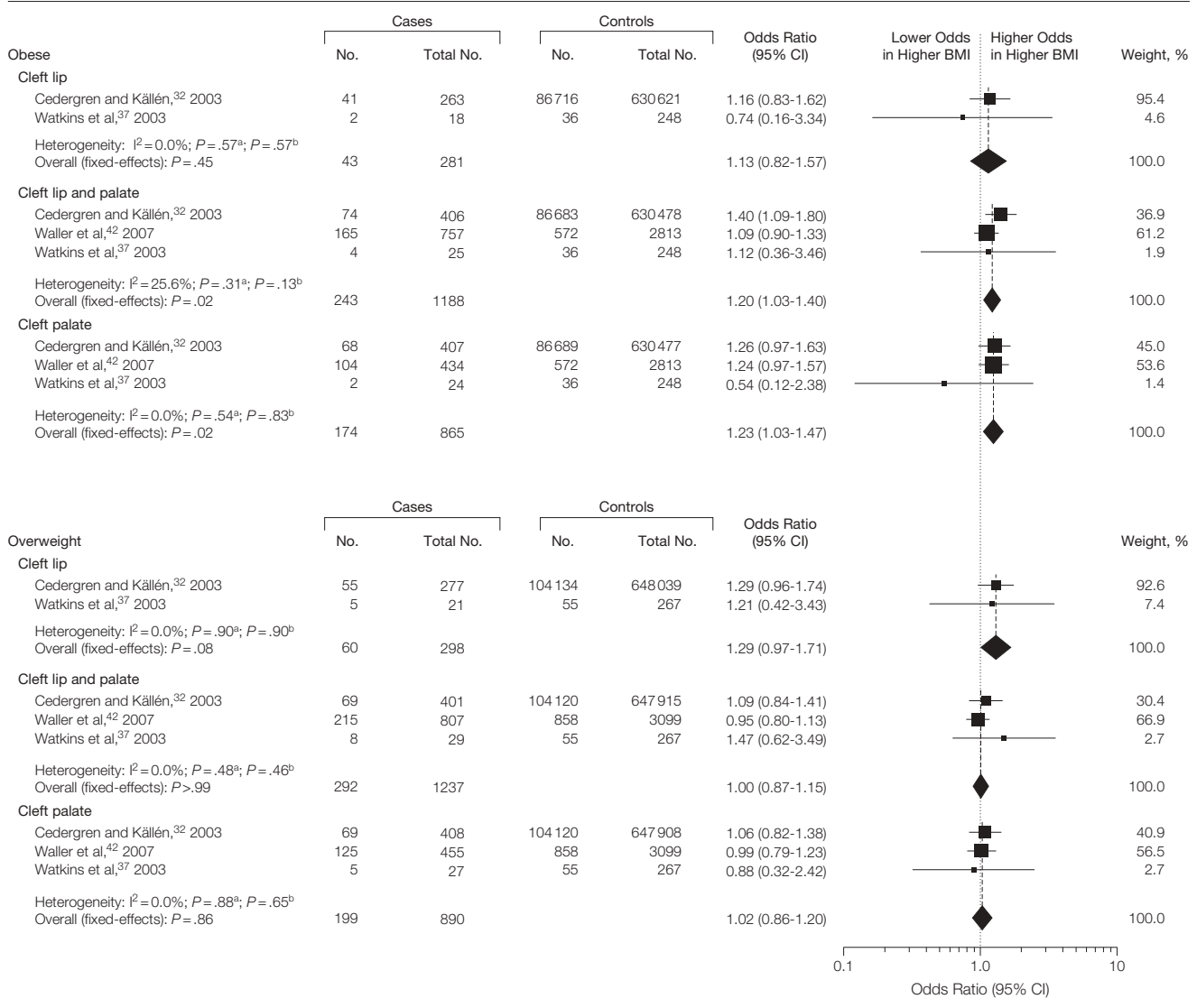
Orofacial Clefts

Obese mothers were at significantly increased odds of a pregnancy affected by either cleft palate (OR, 1.23; 95% CI,

1.03-1.47; *P* = .02) or cleft lip and palate (OR, 1.20; 95% CI, 1.03-1.40; *P* = .02) compared with mothers of recommended BMI (FIGURE 4) but not for cleft lip alone. Cleft lip, cleft palate, or cleft lip and palate did not occur more frequently in mothers who were overweight, although, for cleft lip, the OR was close to significance (OR, 1.29; 95% CI, 0.97-1.71; *P* = .08).

Three articles with unique data were excluded from the meta-analysis,^{16,25,47} including 1 with more than

Figure 4. Forest Plot for Orofacial Clefts



Data markers within each subplot are proportional to the assigned study weight.

^aTest for heterogeneity between studies.

^bTest for heterogeneity between definitions of obese/overweight.

150 cases that found no evidence of an association between maternal obesity and the risk of a pregnancy affected by an orofacial cleft.²⁵ Of the 2 others, one included evidence of an increased risk associated with maternal obesity⁴⁷ while the other found no evidence of an association.¹⁶

Other Congenital Anomalies

Obese mothers were at significantly increased odds of a pregnancy affected by anorectal atresia compared with mothers of recommended BMI (OR, 1.48; 95% CI, 1.12-1.97; $P=.006$). There was no evidence of an association with maternal overweight.

Obese mothers were at significantly increased odds of a pregnancy affected by hydrocephaly compared with mothers of recommended BMI (OR, 1.68; 95% CI, 1.19-2.36; $P=.003$). No significant increased risk was found for maternal overweight.

There was an increased risk of a pregnancy affected by a limb reduction anomaly (OR, 1.34; 95% CI, 1.03-1.73; $P=.03$) among obese mothers compared with mothers of recommended BMI. There was no association with maternal overweight, although the OR was close to significance (OR, 1.22; 95% CI, 0.97-1.53; $P=.09$).

The prevalence of gastroschisis was significantly lower among mothers who were obese compared with mothers of recommended BMI (OR, 0.17; 95% CI, 0.10-0.30; $P<.001$). There was no association with maternal overweight.

There was no association between either maternal overweight or obesity and the risk of a pregnancy affected by diaphragmatic hernia, esophageal atresia, hypospadias, microcephaly, or microtia/anotia. The OR for a pregnancy affected by craniosynostosis was close to significance (OR, 1.24; 95% CI, 0.98-1.58; $P=.07$) among overweight mothers, but no evidence of an association was observed for maternal obesity.

Two additional articles that were not included in the meta-analysis reported maternal BMI data in relation to hydrocephaly⁴⁷ and limb reduction anomalies.¹⁶ Neither included more

than 150 cases nor found evidence of an association with maternal obesity.

Several additional congenital anomaly subtypes were reported that could not be included in the meta-analysis. Of 6 articles involving urinary anomalies^{20,33,37,50} and/or renal agenesis specifically,^{20,37,47,49} only 1 had more than 150 cases.³³ Neither this article nor 4 of the others^{20,37,47,49} found an association with maternal obesity.

Three articles considered abdominal wall anomalies;^{20,47,49} 2 specifically considered omphalocele,^{37,42} 1 of which had more than 150 cases.⁴² These articles identified a significantly increased risk of an omphalocele among obese mothers. One article reported a significantly elevated risk of an abdominal wall defect among obese mothers²⁰ while the others did not.^{47,49}

Four articles investigated the relative odds of multiple anomalies.^{20,31,37,49} Two articles reported significantly increased odds among obese mothers^{31,37} while 2 found no association.^{20,49}

Body mass index or weight data were reported for holoprosencephaly,³⁸ lung hypoplasia,⁴⁷ upper alimentary anomalies,²⁰ pyloric stenosis,^{16,20,47} small intestinal atresia,^{37,42} large intestinal atresia,³⁷ renal multicystic dysplasia,³⁷ urinary obstruction,³⁷ all genital anomalies,^{20,47} cryptorchidism,⁴⁴ limb anomalies,³⁷ talipes,^{16,47} hip dislocation or dysplasia,¹⁶ skeletal anomalies,⁵⁰ skin anomalies,¹⁶ eye or ear anomalies,¹⁶ and urinary or genital anomalies.¹⁶ Only 2 articles reported an association with maternal weight or BMI; 1 reported increased odds of cryptorchidism, although the association with preterm birth was not analyzed,⁴⁴ and the other reported increased odds of talipes among obese mothers.¹⁶

Sensitivity Analysis

Changing the pooling model or any of the methodological inclusion or exclusion criteria did not significantly modify the pooled ORs for either neural tube defects or cardiovascular anomalies (FIGURE 5). Omitting articles with fewer than 150 cases did not significantly alter any of the pooled ORs, although

larger effect sizes were reported, consistent with a publication bias effect.

COMMENT

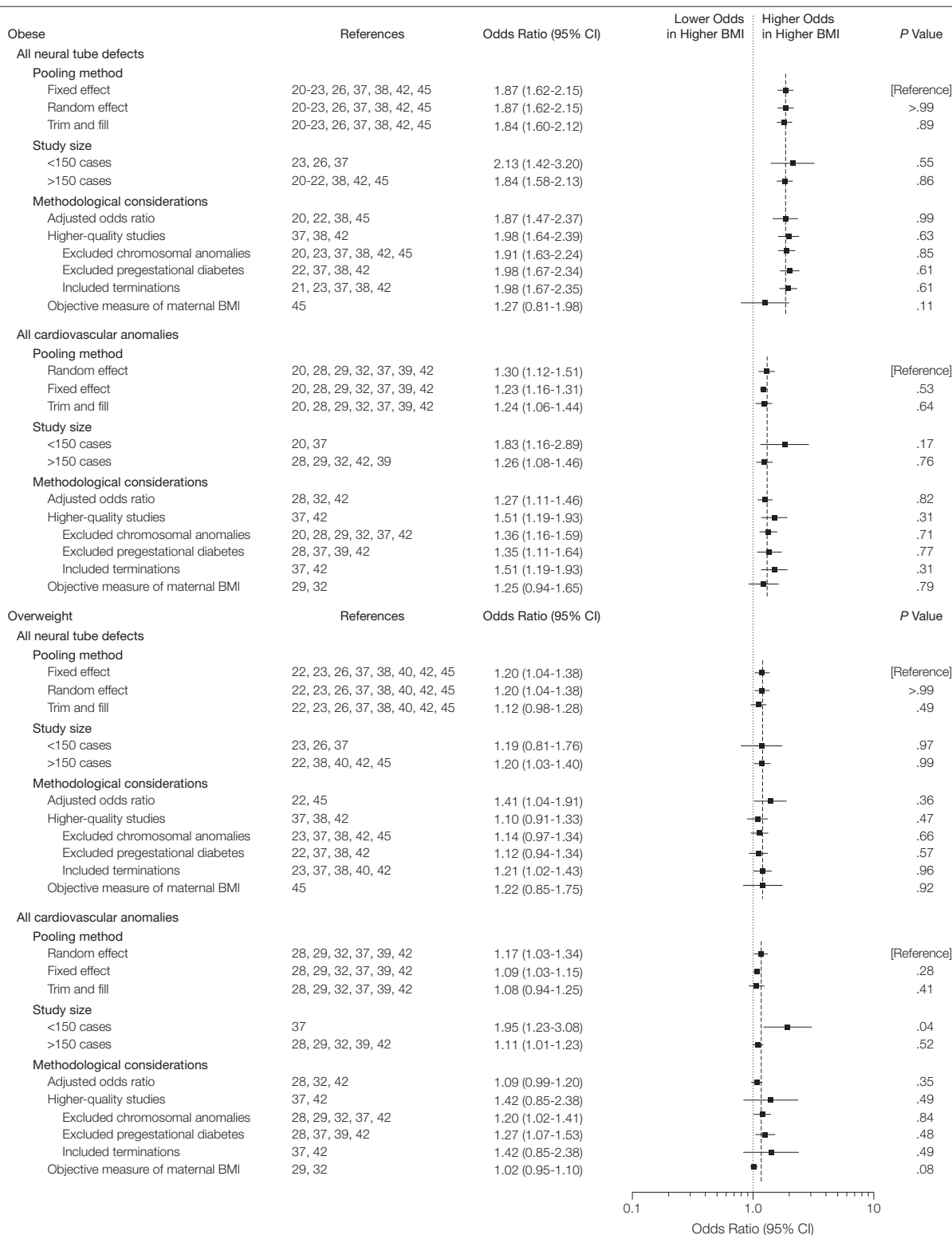
This systematic review investigated the effect of greater-than-recommended maternal weight, either prepregnancy or early pregnancy, on congenital anomaly risk. In women who were obese at the start of pregnancy, the meta-analysis demonstrated a significantly increased risk of a pregnancy affected by a neural tube defect, including spina bifida; cardiovascular anomaly, including a septal anomaly; cleft palate and cleft lip and palate; anorectal atresia; hydrocephaly; and a limb reduction anomaly. The risks of anencephaly among obese mothers, and for neural tube defects and cardiovascular anomalies among overweight mothers, were also significantly elevated, but these results were not robust to potential bias. The risk of gastroschisis among obese mothers was significantly reduced.

Articles included in the systematic review but not included in the meta-analysis generally had low power to find an effect, and thus, the majority found no evidence of association between increased maternal BMI or weight and the risk of congenital anomaly. Of the congenital anomaly subgroups not analyzed in the meta-analysis, it is noteworthy that the risks of omphalocele and multiple congenital anomalies were both found to be significantly higher among obese mothers.

We report results for neural tube defects similar to those reached in a recent meta-analysis,⁶² which reported pooled ORs of 1.70 (95% CI, 1.34-2.15) and 1.22 (95% CI, 0.99-1.49) for obese and overweight mothers, respectively. The range of articles included in that analysis differed from those presented here. Notably, we were able to include a large, recently published article.⁴² Rasmussen et al⁶² also included weight alongside BMI in their meta-analysis and employed Bayesian pooling methods.

Our study, thus, extends the findings of this previous analysis. First, our

Figure 5. Sensitivity Analysis



Dashed lines indicate the value of the odds ratio for the default model in each subcategory (reference). P values are for difference from reference odds ratio. Adjusted odds ratios were adjusted for maternal age, cigarette smoking status, and vitamin supplementation. BMI indicates body mass index; CI, confidence interval.

extensive examination of publication bias helps confirm that the effect of obesity on neural tube defects is unlikely to be the result of differential publication. Second, by analyzing spina bifida and anencephaly separately, we are able to confirm previous observations^{20,21,63} that the effect of obesity is distinct between anencephaly and spina bifida. Finally, our study investigates numerous other congenital anomaly groups and subtypes.

Study Strengths and Limitations

The use of exhaustive search techniques and validated systematic review methods, following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,¹⁴ strengthens our conclusions. Our approach enabled the subdivision of several congenital anomaly groups, reducing the problem of combining anomalies with potentially heterogeneous etiologies. We also examined the possible impact of maternal overweight on congenital anomaly risk. In the meta-analysis, robust statistical procedures were used to estimate the presence of bias, and we further employed the trim and fill method to estimate the impact of bias as has been recommended.⁵⁸

There are several methodological limitations. The exclusion of non-English publications means that potentially relevant articles may have been missed. For example, our literature search identified 1 non-English language article in which statistically significant associations were found between maternal obesity and encephalocele, common truncus arteriosus, orofacial clefts, eye anomalies, Potter syndrome, and anomalies of the urogenital system.⁶⁴

Inherent in a systematic review is the risk of publication bias, and indeed smaller studies consistently reported larger effect sizes. We did not attempt to access "gray literature," which may contain smaller null-result studies that were not accepted for publication.

In the meta-analysis, articles were pooled regardless of their internal defi-

nitions of overweight and obesity. Weight categories were therefore not identical across the studies; recommended BMI ranged from 18.1 to 28.3, overweight from 22.8 to 30, and obese from less than 26 to greater than 30. However, many articles used predefined BMI categories (such as the World Health Organization¹⁵ and Institute of Medicine⁶⁵ classifications); thus, broadly similar definitions were used. Furthermore, for the majority of congenital anomaly subtypes, no significant heterogeneity was found between articles adopting different definitions of obesity (Figures 2, 3, and 4). However, it is possible that the pooling of data based on these different definitions will have introduced some random error.

As with all meta-analyses, the validity of the results is limited by the conduct and reporting of the studies from which the data were extracted and pooled. One issue was the ascertainment of maternal weight. In most studies, prepregnancy or early pregnancy maternal weight was based on self-report. Since weight is usually differentially underreported by heavier individuals,^{66,67} the pooled ORs in this meta-analysis are likely to be overestimates. This appears to be supported by the reduced (albeit nonsignificantly) ORs for cardiovascular anomalies taken from the 2 articles that had an objective measure of maternal BMI.

False negatives are possible where only a limited number of cases were available for a particular congenital anomaly group or subtype. For this reason, any congenital anomaly with fewer than 150 total cases was not included in the meta-analysis. However, for subtypes with a small number of cases, a null result should not be taken as evidence of no effect. For some congenital anomalies, the published data were insufficient to draw firm conclusions. For others, no evidence is available.

We performed a sensitivity analysis to examine how alternative inclusion criteria may have altered the results of our meta-analysis. The observation that

none of the ORs from the more selective, alternative models were significantly different from the reference ORs, and that none would have altered the conclusions of significance (except for the small models that only included articles with objective measures of BMI), supports the primary conclusions and suggests that our results are robust to confounding influences.

Only articles that reported maternal BMI and included a recommended BMI reference category were included in the meta-analysis. Although some potentially relevant studies may therefore have been excluded, the reported risk estimates are independent of height, and are less likely to be biased by the inclusion of underweight or (in most instances) overweight mothers in the reference category.

Potential Mechanisms

A number of potential explanations for an association between maternal overweight and obesity and congenital anomaly have been posited. Obesity and diabetes share similar metabolic abnormalities, including insulin resistance and hyperglycemia,⁶⁸⁻⁷⁰ and obesity is a strong risk factor for type 2 diabetes. Maternal diabetes is an established risk factor for congenital anomaly, especially central nervous system and cardiovascular anomalies.^{71,72} Thus, undiagnosed diabetes and hyperglycemia in obese pregnant women is one potential explanation for the increased risk of congenital anomalies.

Maternal obesity has also been associated with nutritional deficiencies, specifically reduced folate levels,^{73,74} and the protective effect of folic acid in reducing the risk of a neural tube defect may not be observed in obese women.²³ It is notable that many of the congenital anomalies implicated in this review have similar developmental timing and responsiveness to folic acid, suggesting a common underlying etiology. Deficiencies in other nutrients may underlie the association with other congenital anomalies.

Ultrasound scanning is more difficult in obese women,⁷⁵ potentially

resulting in fewer terminations of pregnancy for fetal anomaly and therefore increased prevalence at birth. This would explain the discordant effect sizes of anencephaly and spina bifida, as prenatal detection of spina bifida is less sensitive than anencephaly,⁷⁶ providing a greater opportunity for differentially missed cases. However, the sensitivity analysis found no evidence of a smaller OR when considering only articles that included terminations of pregnancy.

The observation that the risk of gastroschisis was reduced among obese mothers is most likely due to correlation with maternal age, since low maternal age is an established risk factor for gastroschisis⁷⁷ and BMI is itself associated with age.⁷⁸

Implications

Our review confirms that maternal obesity raises the risk of a range of congenital anomalies, including neural tube defects, cardiovascular anomalies, cleft palate, hydrocephaly, and limb reduction anomalies. Further research should be powered to investigate the complete range of BMI to investigate the possible pattern of dose response, which may contribute to understanding the etiology of these congenital anomalies.

Furthermore, large, high-quality, population-based studies are needed to confirm or refute associations for several other congenital anomaly groups or subtypes that have currently only been investigated in very small numbers, such as renal anomalies and genital anomalies, or have not been investigated at all, such as respiratory anomalies.

The sensitivity analyses suggested that inclusion of affected pregnancies ending in termination, inclusion of women with diabetes, exclusion of chromosomal anomalies, and adjustment for other factors (such as smoking and parity) had limited impact on the effect estimates because the summary ORs were not significantly different between the default model and any of the models with more complete inclusion criteria. That we did not

identify a detectable confounding influence by maternal diabetes corresponds with several of the constituent articles, which individually found no evidence of confounding after mothers with diabetes were excluded.* However, it was difficult to evaluate the impact of retrospective self-reporting of prepregnancy or early pregnancy weight because of its widespread use. Nevertheless, future studies are encouraged to consider these, and other, factors as possible confounders because the sensitivity analysis may not have had sufficient power to rule out subtle potential confounding influences.

An estimated 3% of all livebirths in the United States are affected by a structural anomaly⁷⁹ with 0.68 per 1000 births being affected by a neural tube defect and 2.25 per 1000 births being affected by a serious heart anomaly. Given the findings of this review, and the BMI profile of the female population during the period when these estimates were generated,⁸⁰ we calculate that the absolute risk of a pregnancy affected by a neural tube defect or a serious heart anomaly is respectively 0.47 per 1000 births and 0.61 per 1000 births greater in an obese woman than a woman of recommended BMI in prepregnancy or early pregnancy. This has health implications, particularly given the continued rise in the prevalence of obesity in many countries.

Author Contributions: Mr Tennant had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rankin, Bell.

Acquisition of data: Stothard.

Analysis and interpretation of data: Stothard, Tennant, Bell, Rankin.

Drafting of the manuscript: Stothard, Tennant.

Critical revision of the manuscript for important intellectual content: Stothard, Tennant, Bell, Rankin.

Statistical analysis: Tennant.

Obtained funding: Rankin, Bell.

Study supervision: Rankin, Bell.

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*References 20, 21, 23, 25, 26, 31, 38, 48, 52.

role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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