Maternal Obesity and Infant Mortality: A Meta-Analysis

BACKGROUND AND OBJECTIVES: Despite numerous studies reporting an elevated risk of infant mortality among women who are obese, the magnitude of the association is unclear. A systematic review and meta-analysis was undertaken to assess the association between maternal overweight or obesity and infant mortality.

METHODS: Four health care databases and gray literature sources were searched and screened against the protocol eligibility criteria. Observational studies reporting on the relationship between maternal overweight and obesity and infant mortality were included. Data extraction and risk of bias assessments were performed.

RESULTS: Twenty-four records were included from 783 screened. Obese mothers (BMI $\geq 30$) had greater odds of having an infant death (odds ratio 1.42; 95% confidence interval, 1.24–1.63; $P < .001$; 11 studies); these odds were greatest for the most obese (BMI $> 35$) (odds ratio 2.03; 95% confidence interval, 1.61–2.56; $P < .001$; 3 studies).

CONCLUSIONS: Our results suggest that the odds of having an infant death are greater for obese mothers and that this risk may increase with greater maternal BMI or weight; however, residual confounding may explain these findings. Given the rising prevalence of maternal obesity, additional high-quality epidemiologic studies to elucidate the actual influence of elevated maternal mass or weight on infant mortality are needed. If a causal link is determined and the biological basis explained, public health strategies to address the issue of maternal obesity will be needed.

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KEY WORDS maternal, pregnancy, overweight, obesity, BMI, infant, death, mortality

ABBREVIATIONS CI—confidence interval
CMACE—Centre for Maternal and Child Enquiries
OR—odds ratio
WHO—World Health Organization

Mr Meehan developed the protocol, executed the search strategy, screened all records, assessed risk of bias, extracted data, carried out the data analysis, interpreted results, and prepared the manuscript draft; Dr Beck advised on study methods and analysis, extracted data, assessed methodological quality, and reviewed and revised the manuscript; Mr Mair-Jenkins extracted data, assessed methodological quality, and reviewed and revised the manuscript; Dr Leonardi-Bee advised on study methods and analysis, provided arbitration, critically appraised the analysis, and reviewed and revised the manuscript; Dr Puleston supervised the study, screened all records for eligibility, extracted data and prepared, and reviewed and revised the manuscript; and all authors approved the manuscript for submission.

The protocol is registered at the National Institute for Health Research international prospective register of systematic reviews (identifier CRD42012002171).

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The World Health Organization (WHO) estimates that the global prevalence of obesity doubled from 1980 to 2008, with more than 1.4 billion adults overweight in 2008.1 Overweight and obesity are associated with premature mortality, diabetes, ischemic heart disease, and cancer.1

Overweight and obesity are increasing in women of childbearing age and during pregnancy.2 The prevalence of maternal obesity ranges from 1.8% to 25.3% across different countries.3 A recent study from the United States showed an increase in the prevalence of obesity during pregnancy from 13.0% in 1993 to 22.0% in 2003.4 Obese pregnant women are likely to be older, have higher parity, and live in areas of higher deprivation than nonobese women.5

Although global infant mortality rates have declined from 61 to 40 deaths per 1000 live births between 1990 and 2010 (ranging from 2 [Iceland and Singapore] to 121 [Sierra Leone] in 2010), reducing infant mortality remains a priority, as reflected in the United Nations Millennium Development Goals.5–7 The causes of infant death vary, ranging from prematurity to nonaccidental injury. However, infant mortality rates are highest in developing countries, where infectious diseases exact a substantial toll.8,9 Other risk factors associated with infant mortality have been identified, including socioeconomic status, maternal health and age, low birth weight, and ethnicity.10 Maternal obesity is an identified risk factor for stillbirth and congenital abnormalities.11,12 However, some studies have also reported an elevated risk of infant mortality for this group. Tennant et al14 reported odds of infant death of 2.47 (95% CI, 1.33–4.58) and Baeaton et al13 reported odds of infant death between 1.5 (95% CI, 1.0–2.3) and 2.0 (95% CI, 1.2–3.1) depending on the degree of maternal obesity. Conversely, Salihu et al15 reported a nonsignificant hazard of neonatal death of 1.1 (95% CI, 1.0–1.2) with moderately obese mothers and a just significant risk in infants of more severely obese mothers. These studies illustrate that the magnitude of the association is unclear.11,14 Given the rising prevalence of maternal obesity, the relationship to infant mortality is important to define because even a modest effect on obesity could have a substantial population impact. We therefore conducted a systematic review and meta-analysis to assess the magnitude of the association.

METHODS

Protocol and Registration
The protocol is registered at the National Institute for Health Research international prospective register of systematic reviews (identifier CRD42012002171).16 Amendments were made to the original protocol, clarifying the search strategy and eligibility criteria. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.17

Eligibility Criteria
Observational studies (cohort, case–control, and case series) or systematic reviews, with or without meta-analysis, reporting on the relationship between maternal overweight or obesity and infant mortality were eligible. The study population included live singleton births and their mothers. The exposure was maternal weight or BMI, measured before or during pregnancy, and the outcome was infant mortality before 1 year of age.18

Information Sources
Medline, Embase, Allied and Complementary Medicine Database, and Cumulative Index to Nursing and Allied Health Literature databases were searched to identify relevant studies. Gray literature was identified from National Health Service Evidence and a thesis database. Reference tracking was also used.

Search Strategy
Searches were performed in April 2012. Results were limited to studies published in English since 1993 (the year of Consolidated Standards of Reporting Trials statement inception).19

Selection Process
After deduplication, identified studies were sequentially screened (study title, abstract, and full text) independently in duplicate by 2 reviewers, with any differences resolved by discussion with a third reviewer. Screening was managed in EndNoteX3.0.1 (Thomson Reuters [Scientific] Inc, New York, NY).

Data Collection Process
Data were extracted independently in duplicate by 4 reviewers using a piloted template. Any disparity was resolved by discussion, with arbitration by a fifth reviewer if necessary. Corresponding authors were contacted for additional information where necessary.

Data Items
The study characteristic variables extracted were design, timing, duration, country, and number of centers. Population variables were eligibility criteria, participants, loss to follow-up, and total number studied. Comparator variables were exposure definition, classification, and ascertainment. Outcome measure variables were outcome definition, classification, measurement, follow-up duration, results, analysis performed, and adjustment for confounding variables.

Risk of Bias in Individual Studies
The Newcastle–Ottawa Quality Assessment Scale was used to assess the risk of bias.20 Assessments were performed independently, in parallel by 4 reviewers. Consensus was reached by discussion, with arbitration by a fifth reviewer.
if needed. Studies were considered higher quality when ≥7 stars were awarded and lower quality for ≤6 stars. Abstract-only papers were not assessed for risk of bias.

Summary Measures
Summary measures were calculated to compare obese mothers (BMI ≥30), mothers with a greater level of obesity (BMI ≥35), and all overweight or obese mothers with those with a healthy BMI (18.5–24.9). Where possible, the most adjusted data were used for the meta-analysis; otherwise, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the raw reported data.

Synthesis of Results
A random effects meta-analysis of pooled ORs was undertaken for estimating the effect size of obese mothers (BMI ≥30), mothers with a greater level of obesity (BMI ≥35), and all overweight or obese mothers compared with those with a healthy BMI (18.5–24.9) (Review Manager version 5.2; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark, 2012). Heterogeneity was quantified ($I^2$) and meta-analysis rejected where there was high study heterogeneity (85%). A P value <.05 was regarded as statistically significant. Narrative synthesis was performed by using an evaluated method.

Risk of Bias Across Studies
Publication bias was assessed graphically with funnel plots of OR versus SE of the natural log OR for the primary meta-analysis and each sensitivity analysis.

Sensitivity Analyses
Sensitivity analyses were undertaken to explore the effect on outcome of studies by obesity (where the definition did not conform to the WHO boundaries), where adjustment was made for confounding, for studies that had a low risk of bias, and by study design. Additionally, sensitivity analysis of each category of timing of death against obese mothers was undertaken. These comparisons were all between obese mothers (BMI ≥30) and normal-BMI mothers (BMI 18.5–24.9).

RESULTS
Study Selection
The selection process is summarized in Fig 1. The search identified 783 records (211 were duplicates); 464 records were excluded at title and then abstract screening; 108 full-text records were assessed for final eligibility, with another 86 excluded at this point. Reference tracking identified 2 additional eligible records. For 3 of the screened articles, there was insufficient information in texts to determine suitability for inclusion; their authors were therefore contacted to obtain clarification. Two responded, resulting in 1 manuscript being included in the review (the other was excluded because it did not examine the outcome of interest). For the third, no clarification could be obtained, and therefore this article was excluded.

Of the 24 included studies, 11 were included in the systematic review, 11 were included in the primary meta-analysis examining the measure of effect of maternal obesity on infant mortality (obese mothers [BMI ≥30] relative to normal-BMI mothers [BMI 18.5–24.9]).

Risk of Bias Within Studies
The median Newcastle–Ottawa Quality Assessment Scale score was 7 (range 5–9). Five abstract studies were not assessed because limited information was available. Of the 19 studies appraised (Supplemental Table 3), 14 (74%) achieved the higher methodological quality threshold of 7 or more, and 5 (26%) achieved the lower methodological quality threshold of 6 or less. Twelve studies adjusted for potential confounders and 8 adjusted for deprivation or a suitable proxy, but only 5 provided adjusted data suitable for extraction and use in the main meta-analysis (all of which adjusted for

1995 international classification of overweight used overweight grade boundaries 1 to 3 (corresponding to BMI 25–29.9, 30–39.9, and 40+, respectively). The classification was subsequently revised to preobese and obese classes 1 to 3 (corresponding to BMI 25–29.9 and 30–34.9, 35–39.9, and 40+, respectively) in the publication of the WHO Consultation on Obesity in 2000. Given the changes in grading and to avoid the potential for confusion, for the meta-analysis data were extracted according to BMI boundaries rather than obesity classes and compared with the WHO normal-BMI group (18.5–24.9). Studies not using the WHO classification varied in the BMI boundary limits used for classifying their obese and control groups or used weight for the determination of obesity. One study predated the WHO 1995 international classification of adult overweight and obesity and did not use BMI.

Various infant death classifications were used, such as infant death or mortality (birth to under the age of 1 year), early neonatal death or death of a live birth due to immaturity (birth to 7 days old), neonatal death (birth to 28 days old), or postneonatal death (29 days old to <1 year old). The classification of infant death was not stated in 8 studies.

The characteristics of the eligible studies are summarized in Supplemental Table 2. Of the 24 included studies, 8 were from the United States, 6 the United Kingdom, 3 Sweden, 2 Denmark, and 1 each from Jamaica, Germany, China, and India, and another study did not state location. Twenty-three were cohort studies, and 1 was a case–control study. BMI was the principal measure of exposure in all but 2 studies, but the boundaries used varied. The WHO

195 international classification of over-
deprivation), although another 3 adjusted using hazard ratios (also adjusted for deprivation) and were subject to a separate, adjusted data meta-analysis.11,14,15,25,26,28–30,33,39,41,42

Measure of Effect

Meta-analysis was performed for obese mothers (BMI ≥30), mothers with a greater level of obesity (BMI ≥35), and all overweight or obese mothers (BMI ≥25). Although 19 studies had extractable data suitable for inclusion in the meta-analysis, only 11 used a consistent BMI definition for the referent group or for obesity; therefore, only these were included in the primary analysis comparing obese and nonobese mothers and the odds of them experiencing an infant death. For all obese mothers with a BMI ≥30 the odds of having an infant death were 1.42 (95% CI, 1.24–1.63; P < .001; I² = 56%; 11 studies). The coprimary exposure of overweight or obese mothers (BMI ≥25) compared with healthy BMI was significantly associated with greater odds of infant death (OR 1.27; 95% CI, 1.14–1.42; P < .001; I² = 63%; 11 studies). There was also an increasing trend in the pooled measure of effect OR of infant death with increased maternal BMI, with BMI ≥35 having the highest ORs (OR 2.03; 95% CI, 1.61–2.56; P < .001; I² = 0%; 3 studies).

Sensitivity Analysis

A sensitivity analysis that included all studies with a normal BMI reference group and obesity BMI group was undertaken. This included studies where the definition for normal BMI or obese BMI did not accord with the WHO classification boundaries. The measure of effect found was comparable to the primary analysis (OR 1.35; 95% CI, 1.22–1.49; P < .001; I² = 51%; 19 studies). Sensitivity analyses according to the timing of death (early neonatal, neonatal, and postneonatal) are summarized in Table 1. Sensitivity analysis was also undertaken for the 3 studies
Results of Individual Studies and Synthesis of Results: Narrative Analyses

A narrative analysis was undertaken for 5 studies where it was not possible to include their data in the meta-analysis. Two studies were from the United Kingdom, 2 from the United States, and 1 from Jamaica. A study by Shah et al of 53,250 deliveries from the United Kingdom that used data from 30,167 singleton pregnancies (including 78 neonatal deaths) assessed the effect of maternal obesity on neonatal deaths (where accurate data on maternal weight and height were recorded at booking). The measure of effect for obese mothers (BMI ≥30) was OR 1.66; 95% CI, 1.00–2.75; P not stated, compared with that for women with a BMI ≤29.9. Because the comparator group included overweight, normal, and underweight BMI and only ORs were presented, these data could not be included in the meta-analysis. The definition of neonatal deaths was not given. It is possible that there may have been some data overlap with another study by Tennant et al, but only data from the latter were included in the meta-analysis.14,38

In the Centre for Maternal and Child Enquiries (CMACE) study of 1049 severely obese women (BMI ≥35) from the United Kingdom, BMI was measured or professionally assessed at any point in the pregnancy. A combination of recorded BMI ≥35 during pregnancy, recorded maternal weight >100 kg during pregnancy, or professional judgment that the BMI was ≥35 was used to determine inclusion. The highest BMI at any point in pregnancy was used for classification. There were 6 early neonatal deaths (rate 1.2 per 1000 live births, no CIs given). There was no comparator group to assess the odds of death compared with a normal maternal weight.

A US-based study of 21,681 singleton births presented an increased rate of neonatal mortality with increasing obesity in women who delivered vaginally after having had a caesarean section in a previous pregnancy. Of these, 2.5% had a vaginal birth after a previous caesarean, and there were 99 neonatal deaths. The neonatal death rate per 1000 live births was 4.1, 3.2, 4.5, and 14.3 for obesity classes 1, 2, 3, and superobese mothers, respectively. BMI was assessed at the first prenatal visit, but the mode of assessment and definition of neonatal death were not defined. The details of the BMI boundaries for obesity classes 1 to 3 were also not defined.

Another US-based study found that maternal BMI was significantly related to infant mortality (multivariate logistic regression). This survey-based study was looking primarily at the effect of maternal alcohol consumption on outcome but also collected data on BMI as a confounder (self-reported height and prepregnancy weight). Data were available on 9953 live births and 5332 infant deaths (deaths before first birthday). At analysis (logistic regression) for each unit increase in BMI, the odds of death were 1.02, P < .001. However, confidence limits were not given.44

The Jamaican study (9596 infants, including 1234 perinatal deaths) examined the social and environmental factors associated with perinatal mortality on the island.32 At analysis (logistic regression), the odds of a perinatal death was 1.44 (95% CI, 1.07–1.95) for obese mothers compared with mothers of normal weight, but perinatal death was not further subdivided. The definition of obesity was not defined, nor did the study state how or when obesity status was determined.

Risk of Bias Across Studies

Funnel plots constructed for the meta-analyses described suggested that publication bias was not present in the primary analysis (Fig 3) or the sensitivity analyses (not shown).

<table>
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<th>TABLE 1 Summary of Meta-Analysis Results</th>
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<td>Obese, BMI ≥35</td>
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DISCUSSION

This systematic review and meta-analysis is the first to assess the association between maternal obesity or overweight and infant mortality. The results suggest that for obese mothers with a BMI $\geq 30$ the odds of having an infant death were 1.42 (95% CI, 1.24–1.63), with an increasing trend for greater body mass (with those with BMI $>35$ having the highest ORs [OR, 2.03; 95% CI, 1.61–2.56]).

For all overweight and obese mothers, there was a 1.27 (95% CI, 1.14–1.42) times increase in the odds of experiencing an infant death compared with those with a healthy maternal BMI. Unknown residual confounding factors may explain these findings (eg, undiagnosed diabetes, gestational age at birth, dietary quality), and therefore we cannot state conclusively that maternal obesity is a risk factor per se for infant mortality. Nonetheless, maternal obesity has also been implicated in increasing the risk of stillbirth. A meta-analysis published in 2007 showed similar odds of stillbirth to those of infant death in our study, 1.45 (95% CI, 1.08–1.94) for overweight and 2.07 (95% CI, 1.59–2.74) for obese mothers compared to normal weight mothers.45

We noted that the odds of infant mortality may increase with increasing maternal obesity. This correlation could be influenced by absolute maternal BMI alone or BMI and gestational weight gain. However, our study did not consider the effect of gestational weight gain on outcomes. The UK National Collaborating Centre for Women's and Children's Health (National Institute for Health and Clinical Excellence) commented in its guidance on antenatal care (routine care for the healthy pregnant woman) that repeated maternal weight measurement during pregnancy was unnecessary and that although maternal weight gain is correlated with birth weight, it is not a sufficiently good indicator to identify infants who are small for gestational age.66 This contrasts with the US Institute of Medicine, which in 2009 recommended that obese women should gain between 5 and 9 kg during pregnancy. However, it also commented that there was insufficient evidence to make more specific recommendations.47 More recent evidence found that obese women with little or no weight gain in pregnancy were less likely to experience complications. However, only short-term outcomes were assessed, and the effects on infant mortality were not considered.48

The results from our review suggest that compared with the primary analysis, there is an elevated risk of infant death in the early neonatal and post-neonatal periods where the mother was obese. There was too much statistical heterogeneity for neonatal period studies to allow meta-analysis for this period. Our study design could not examine causality, but maternal obesity can result in premature birth, macrosomia, and congenital anomalies, which may explain the elevated odds of death across the spectrum from early neonatal to postneonatal deaths.49

Limitations

In the protocol, studies included in the systematic review were limited to those published in 1993 or later (the year of inception of the Consolidated Standards of Reporting Trials statement). Ideally, we should have searched back to the inception of the respective databases; however, this restriction was necessary to limit the size of the task. In retrospect, a more suitable cutoff point would have been the 1995 publication of the WHO overweight and obese BMI thresholds, but using this cutoff would have resulted in only 1 more study being excluded from the overall systematic review. This study did not provide sufficient information to allow inclusion in the meta-analysis, and so adjusting the cutoff post hoc would not have altered the measure of effect findings.34

The studies included in the review were generally consistent in their definitions of infant death, although many did not specify the data source for this outcome.
Additionally, studies with populations from multiple centers may have missed deaths outside their population definition. There was significant potential for ascertainment bias to have affected the findings of some of the studies in respect of maternal weight or body mass measurement because of substantial variation in the method and timing of when BMI was measured or recorded, which could have resulted in measurement bias. Prepregnancy weight and early maternal weight were based on self-reporting in 37.5% of studies (n = 9). Self-reporting has been shown to become less reliable and more subject to bias with increasing weight, especially in overweight women; this bias could have led to an underestimation of the measure of effect.\textsuperscript{50} For some studies, it was not possible to assess the robustness of data collection systems or the validity and reliability of data collection for both exposure and outcome because insufficient detail was provided. The potential for selection bias was notable in some studies, with restrictions having been applied to the population studied or for those with missing data.

It was possible to assess the effect of adjustment for potential confounders in only 5 of the studies for the meta-analysis; however, our comparison of adjusted studies and the primary analysis made little difference to the pooled measure of effect. We had planned to assess for the effect of gestational age on the outcome through sensitivity analysis; however, this was not possible because insufficient studies stratified by this variable. It would have also been appropriate to undertake a separate sensitivity analysis for the potential confounding effect of congenital anomalies alone; however, this was not possible. Only 5 studies commented on the presence or absence of congenital anomalies. Of these, only 1 presented data in a form that could be analyzed; the other 4 either had no normal-BMI comparator group or did not present congenital anomalies, as separate data to allow independent assessment of the effect of this variable with BMI alone on the measure of effect. However, two studies using hazard ratios did adjust for congenital anomaly presence (but not severity) in their multivariate analysis with other potential confounders and their adjusted data was included in the separate sensitivity analysis of studies reporting hazard ratios. The measure of effect was similar to the primary analysis. (The remaining studies either explicitly excluded any subjects with a congenital anomaly or made no mention of these.)

Last, the scope of this review did not include exploring the effect of diabetes, multiple pregnancy, or stillbirth as potential effect modifiers of infant mortality in the presence of maternal obesity or overweight. Separate reviews or, where appropriate, additional primary research may be needed to address these gaps.

**Implications for Public Health Practice**

International evidence suggests that improvements in care during pregnancy, childbirth, and the postnatal period have significantly affected infant mortality.\textsuperscript{51} Interventions including the early detection and management of problems and defects in pregnancy, improved maternal nutrition, reducing asphyxia and birth trauma, management of preterm infants, and access to vaccines have all contributed.\textsuperscript{51} However, 40% of all deaths in children <5 years old occur in the first 28 days of life, with the majority being caused by diseases associated with poverty.\textsuperscript{51} We have shown an association of an increased odds of infant death with an increased maternal body mass or weight. However, other unknown factors linked to maternal obesity could explain this association. Nonetheless the improvements in infant mortality rates are slowing down.\textsuperscript{6} Depending on the local context, policymakers may need to explore what additional public health interventions can further affect infant mortality levels. Our research demonstrates a public health need to elucidate the effect of maternal obesity...
on outcomes of pregnancy (after other explanatory factors are excluded), because if the association is found to be correct, then steps to address maternal obesity could affect infant mortality rates. Currently, however, there is a paucity of international guidance on maternal obesity prevention. Additional research, such as well-designed, large epidemiologic studies, to assess the effects of confounding influences on infant mortality outcomes in obese mothers (e.g., gestational age, congenital anomalies, multiple pregnancies) and the effects of obesity intervention strategies in pregnant women, is warranted. If a causal link between increased maternal weight or body mass and increased infant mortality is established, then research into the biological mechanisms that cause the outcome will also be needed.

CONCLUSIONS

Our results suggest that obese maternal BMI is associated with a 1.42 times increase in the odds of infant death compared with healthy maternal BMI and that these odds are highest in those with a BMI $\geq$35 (OR 2.03); however, residual confounding may explain these findings. Given the rising prevalence of maternal obesity, additional work to elucidate the actual influence of elevated maternal mass or weight on infant mortality is needed, and if a causal link determined, public health strategies to address the issue of maternal obesity will be needed.

REFERENCES


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### Maternal Obesity and Infant Mortality: A Meta-Analysis

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