Maternal Body Mass Index and the Risk of Fetal Death, Stillbirth, and Infant Death
A Systematic Review and Meta-analysis

Dagfinn Aune, MS; Ola Didrik Saugstad, MD, PhD; Tore Henriksen, MD, PhD; Serena Tonstad, MD, PhD

IMIMPORTANCE Evidence suggests that maternal obesity increases the risk of fetal death, stillbirth, and infant death; however, the optimal body mass index (BMI) for prevention is not known.

OObJECTIVE To conduct a systematic review and meta-analysis of cohort studies of maternal BMI and risk of fetal death, stillbirth, and infant death.

DDATA SOURCES The PubMed and Embase databases were searched from inception to January 23, 2014.

STUDY SELECTION Cohort studies reporting adjusted relative risk (RR) estimates for fetal death, stillbirth, or infant death by at least 3 categories of maternal BMI were included.

DATA EXTRACTION Data were extracted by 1 reviewer and checked by the remaining reviewers for accuracy. Summary RRs were estimated using a random-effects model.

MAIN OUTCOMES AND MEASURES Fetal death, stillbirth, and neonatal, perinatal, and infant death.

RESULTS Thirty eight studies (44 publications) with more than 10 147 fetal deaths, more than 16 274 stillbirths, more than 4311 perinatal deaths, 11 294 neonatal deaths, and 4983 infant deaths were included. The summary RR per 5-unit increase in maternal BMI for fetal death was 1.21 (95% CI, 1.09-1.35; \( I^2 = 77.6\% \); n = 7 studies); for stillbirth, 1.24 (95% CI, 1.18-1.30; \( I^2 = 80\% \); n = 18 studies); for perinatal death, 1.16 (95% CI, 1.00-1.35; \( I^2 = 93.7\% \); n = 11 studies); for neonatal death, 1.18 (95% CI, 1.07-1.23; \( I^2 = 78.5\% \); n = 12 studies); and for infant death, 1.18 (95% CI, 1.09-1.28; \( I^2 = 79\% \); n = 4 studies). The test for nonlinearity was significant in all analyses but was most pronounced for fetal death. For women with a BMI of 20 (reference standard for all outcomes), 25, and 30, absolute risks per 10 000 pregnancies for fetal death were 76, 82 (95% CI, 76-88), and 102 (95% CI, 93-112); for stillbirth, 40, 48 (95% CI, 46-51), and 59 (95% CI, 55-63); for perinatal death, 66, 73 (95% CI, 67-81), and 86 (95% CI, 76-98); for neonatal death, 20, 21 (95% CI, 19-23), and 24 (95% CI, 22-27); and for infant death, 33, 37 (95% CI, 34-39), and 43 (95% CI, 40-47), respectively.

CONCLUSIONS AND RELEVANCE Even modest increases in maternal BMI were associated with increased risk of fetal death, stillbirth, and neonatal, perinatal, and infant death. Weight management guidelines for women who plan pregnancies should take these findings into consideration to reduce the burden of fetal death, stillbirth, and infant death.


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Methods

Search Strategy and Inclusion Criteria
PubMed and Embase databases were searched from inception (1966 and 1947, respectively) to January 23, 2014. Details of the search strategy are reported online (eTable 1, eTable 2 in Supplement).

Study Selection
Cohort studies that reported on maternal BMI before or in early pregnancy and risk of fetal death, miscarriage, stillbirth, and neonatal, perinatal and infant death were included. Publications that provided adjusted relative risk (RR) estimates such as risk ratios, incidence rate ratios, hazard ratios or odds ratios and 95% CIs (CIs) for 3 or more categories of BMI were eligible. Thirty eight studies (44 publications) were included. 4-47

Data Extraction
The following data were extracted from each study: first author's surname, publication year, country or region of the study origin, number of participants or pregnancies, number of deaths, the exposure variable (BMI) by subgroup (when reported), cutoff values for BMI categories, RRs (95% CIs), and adjustment for potentially confounding factors.

Statistical Methods
Summary RRs for the association between maternal BMI and fetal and infant death were calculated using the random-effects model by DerSimonian and Laird. 48 The weighted mean of the natural logarithm of the RRs was estimated and the RRs were weighted by the method of DerSimonian and Laird. 48 A 2-sided P value of less than .05 was considered statistically significant. For studies that reported results separately by race, 7-9 parity, 39 or diabetes status, 9 the risk estimates were pooled using a fixed-effects model before including the study in the overall analysis. Results were similarly pooled for pregnancy weeks 13 and earlier and weeks 14 through 19, 4 and for miscarriage and for stillbirth 29 to generate a result for miscarriage and fetal death, respectively. For one study, which provided 99% CIs for the risk estimates, the CIs were recalculated to correspond with 95% CIs. 20 To investigate whether specific levels of BMI were associated with fetal or infant death, the method described by Greenland and Longnecker 49 was used to conduct dose-response analyses by computing study-specific slopes (linear trends) and 95% CIs from the natural log of the RRs and CIs across categories of BMI. The method of Hamling et al 50 was used to convert risk estimates when the reference category used in the analyses was not the lowest category. To assess the influence of these conversions on the results, sensitivity analyses were conducted by simply excluding the reference category instead of converting the risk estimates. For each BMI category, the average of the upper and lower bound was used as a midpoint and the respective RRs were assigned to each midpoint. When extreme categories were open ended,
a lower BMI value of 15 was used for the lowest category (BMI <18.5 or BMI <20), but 18.5 was used as the lower cutoff when it indicated a normal weight category (BMI <25). For the highest category, the size of the adjacent interval was used to calculate an upper cutoff value, which in most cases was in increments of 5 BMI units (30-<35, 35-<40, 40-<45). A potential nonlinear dose-response relationship between BMI and fetal and infant death was assessed on a multiplicative scale using fractional polynomial models and the best fitting second-order fractional polynomial regression model was determined—a defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity. Absolute risks were calculated by applying the adjusted RR estimates from the nonlinear dose-response analysis to the pooled unadjusted absolute risk in the reference category across studies. Publication bias was assessed using the Egger test. Sensitivity analyses were conducted by omitting 1 study at a time from the analyses and assessing its effect on the overall findings. Subgroup and meta-regression analyses were conducted by study characteristics, such as geographic location, number of deaths, adjustment for confounding factors, study quality (which was assessed using a modified Newcastle-Ottawa scale; see eBox 1 in Supplement), and by the outcome definition (Box) to investigate sources of heterogeneity. The statistical analyses were conducted using Stata statistical software version 10.1 (StataCorp LP).

Results

After ineligible studies were excluded (eTable 3 in Supplement), 38 studies (44 publications) were included in the dose-response analysis of BMI and fetal death, stillbirth, neonatal death, perinatal death, or infant death or subtypes of these outcomes (eTables 4-8 in Supplement, Figure 1). Six of the studies were from North America, 19 from Europe, 2 from Latin America, 6 from Australia, 4 from Asia, and 1 from Africa.

Fetal Death

Seven cohort studies investigated the association between maternal BMI and fetal death and included more than 10 147 deaths among 690 622 participants (eTable 4 in Supplement). In the dose-response analysis, the summary RR per 5 BMI units was 1.21 (95% CI, 1.09-1.35; \( P = .001 \) for heterogeneity; Figure 2a). There was no evidence of publication bias using the Egger test (\( P = .43 \)). There was evidence for a nonlinear association (\( P <.001 \) for nonlinearity) with a steeper curve at the higher levels of BMI (Figure 2b, Table). For BMI levels of 20, 25, and 30, absolute risks per 10 000 pregnancies were 76 (reference standard), 102 (95% CI, 102-112), and 105 (95% CI, 105-115), respectively (Table). Five studies were included in the analysis of maternal BMI and miscarriages and the summary RR per 5 BMI units was 1.16 (95% CI, 1.07-1.26; \( P = .30 \) for heterogeneity; eFigure 1 in Supplement).

Stillbirth

Eighteen cohort studies* were included in the analysis of maternal BMI and stillbirth risk and included more than 16 274 stillbirths among 3 288 688 participants (eTable 5 in Supplement). The summary RR per 5 BMI units was 1.24 (95% CI, 1.18-1.30; \( P = .001 \) for heterogeneity; Figure 3a). There was evidence of publication bias using the Egger test (\( P = .02 \); eFigure 2 in Supplement). When excluding the largest study, the Egger test was no longer significant (\( P = .34 \)). Although the test for nonlinearity was significant (\( P <.001 \) for nonlinearity), the curve appeared to be almost linear (Figure 3b, Table). For BMI levels of 20, 25, and 30, absolute risks per 10 000 pregnancies were 40 (reference standard), 62 (95% CI, 59-64), and 70 (95% CI, 68-73), respectively (Table). Analyzing studies that reported results for antepartum and intrapartum stillbirths gave summary RRs of 1.28 (95% CI, 1.15-1.43; \( P <.001 \) for nonlinearity) for antepartum and 1.38 (95% CI, 1.21-1.57; \( P <.001 \) for nonlinearity) for intrapartum stillbirths.

BMI indicates body mass index; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; SIDS, sudden infant death syndrome.

*Exact reasons for exclusions were not documented.

References 4, 6-8, 11-13, 20, 21, 23, 25, 27-32, 47
Maternal BMI, Stillbirth, Fetal and Infant Death

Perinatal Death

Eleven cohort studies\(^5,6,8,9,14,33-38\) were included in the analysis of maternal BMI and perinatal death and included more than 4311 deaths among 982 236 participants (eTable 6 in Supplement). The summary RR per 5 BMI units was 1.16 (95% CI, 1.00-1.36; \(P = 0.01\) for heterogeneity; eFigure 4 in Supplement) per 5 BMI units, respectively.

Neonatal and Postneonatal Death

Twelve cohort studies\(^6,8,10-12,30,39-42,47\) were included in the analysis of maternal BMI and neonatal death and included 11 294 deaths among 3 321 555 participants (eTable 7 in Supplement). The summary RR per 5 BMI units was 1.15 (95% CI, 1.07-1.23; \(P = 0.003\) for heterogeneity; eFigure 5 in Supplement) per 5 BMI units.

Infant Death

Four cohort studies\(^6,10,43,44\) were included in the analysis of maternal BMI and infant death and included 4983 deaths among 1 491 879 participants (eTable 8 in Supplement). The summary RR per 5 BMI units was 1.18 (95% CI, 1.09-1.28; \(P = 0.003\) for heterogeneity; eFigure 6 in Supplement) per 5 BMI units.
Maternal BMI, Stillbirth, Fetal and Infant Death

Table. Relative Risks From Nonlinear Dose-Response Analysis for Maternal BMI and Fetal Death, Stillbirth, and Neonatal, Perinatal, and Infant Death

<table>
<thead>
<tr>
<th>BMI*</th>
<th>17</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>37.5</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Death (n = 6)*</td>
<td>1.02</td>
<td>1.07</td>
<td>1.17</td>
<td>1.34</td>
<td>1.59</td>
<td>1.97</td>
<td>2.58</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.95-1.10)</td>
<td>(1.00-1.15)</td>
<td>(1.08-1.28)</td>
<td>(1.22-1.47)</td>
<td>(1.43-1.77)</td>
<td>(1.71-2.28)</td>
<td>(2.08-3.20)</td>
</tr>
<tr>
<td>AR</td>
<td>0.92</td>
<td>1.00</td>
<td>1.09</td>
<td>1.20</td>
<td>1.30</td>
<td>1.42</td>
<td>1.55</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.86-0.99)</td>
<td>(1.01-1.12)</td>
<td>(1.07-1.24)</td>
<td>(1.14-1.36)</td>
<td>(1.09-1.16)</td>
<td>(1.15-1.48)</td>
<td>(1.25-1.65)</td>
</tr>
<tr>
<td>AR</td>
<td>1.04</td>
<td>1.05</td>
<td>1.12</td>
<td>1.20</td>
<td>1.30</td>
<td>1.42</td>
<td>1.55</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.94-1.16)</td>
<td>(0.97-1.14)</td>
<td>(1.01-1.23)</td>
<td>(1.08-1.33)</td>
<td>(1.16-1.45)</td>
<td>(1.27-1.59)</td>
<td>(1.38-1.74)</td>
</tr>
<tr>
<td>AR</td>
<td>1.01</td>
<td>1.03</td>
<td>1.10</td>
<td>1.19</td>
<td>1.30</td>
<td>1.43</td>
<td>1.58</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.93-1.09)</td>
<td>(1.00-1.08)</td>
<td>(1.03-1.18)</td>
<td>(1.09-1.19)</td>
<td>(1.10-1.29)</td>
<td>(1.19-1.42)</td>
<td>(1.30-1.57)</td>
</tr>
<tr>
<td>AR</td>
<td>1.00</td>
<td>1.01</td>
<td>1.10</td>
<td>1.19</td>
<td>1.30</td>
<td>1.43</td>
<td>1.58</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.93-1.09)</td>
<td>(1.00-1.08)</td>
<td>(1.03-1.18)</td>
<td>(1.09-1.19)</td>
<td>(1.10-1.29)</td>
<td>(1.19-1.42)</td>
<td>(1.30-1.57)</td>
</tr>
</tbody>
</table>

Abbreviations: AR, absolute risk; BMI, body mass index; RR, relative risk.
* BMI is calculated as weight in kilograms divided by height in meters squared.
a Data are reported per 10 000 pregnancies.
b Two studies were excluded (14,33,36,37) because the model did not converge when included; and 1 study was excluded (39) because it provided only a continuous estimate.

CI: 34-39), and 43 (95% CI: 40-47) infant deaths per 10 000 pregnancies, respectively (Table).

Subgroup Analyses and Sensitivity Analyses
In subgroup analyses stratified by geographic location, assessment of weight and height, number of deaths, and adjustment for confounding factors, little evidence was found of heterogeneity between subgroups (eTable 9, eTable 10 in Supplement). A stronger association was found among European studies than in one study from Latin America for fetal death (P = .03 for heterogeneity) and in European compared to North American studies for perinatal death (P = .003 for heterogeneity) (eTable 9 in Supplement), while in studies of stillbirth, the association was stronger in studies that adjusted for height (P = .006 for heterogeneity), alcohol (P = .04 for heterogeneity), or coffee/caffeine (P = .04 for heterogeneity) than in studies without these adjustments (eTable 9 in Supplement).

In general, the quality of the studies was high and there was little evidence that the results varied by study quality (eTable 9, eTable 10 in Supplement). Because the definitions of stillbirth and perinatal death varied between studies (and possibly regions), additional subgroup analyses were conducted in the studies that provided the definition of stillbirth and perinatal death. The outcome definitions used in the studies are reported online (eTables 11-15 in Supplement). The summary RR per 5 BMI units was compared between studies that defined stillbirth by different gestational timeframes: stillbirth defined as fetal death after at least 20, 22, or 24 completed weeks (RR per 5 BMI units, 1.18 [95% CI, 1.11-1.25]; P = .004 for heterogeneity; in 7 studies6,23,25,27,29,33) vs stillbirth defined as a fetal death after at least 28 completed weeks (RR per 5 BMI units, 1.45 [95% CI, 1.25-1.68]; F = 60.2%; P = .08 for heterogeneity; in 3 studies5,7,27) with a P value of .04 for heterogeneity. Subgroup analyses also compared the summary RR per 5 BMI units between studies that defined perinatal death differently: perinatal death defined as early neonatal death in addition to stillbirth (RR per 5 BMI units, 1.43 [95% CI, 1.37-1.48]; F = 0%; P = .40 for heterogeneity; in 3 studies5,6,9) vs perinatal death defined as all neonatal death in addition to stillbirth (RR per 5 BMI units, 0.96 [95% CI, 0.69-1.32]; F = 92.8%; P < .001 for heterogeneity; in 4 studies4,33,36,37) with a P value of .11 for heterogeneity. To clarify if potentially intermediate conditions such as pregestational diabetes, hypertension, preeclampsia or congenital anomalies explained part of the association between BMI and stillbirth, we analyzed 2 studies6,8 in which participants with such conditions had been excluded, but the summary RR was 1.57 (95% CI, 1.28-1.92; F = 61.4%; P = .11 for heterogeneity) per 5 BMI units.

In sensitivity analyses that excluded 1 study at a time from each analysis, most of the results appeared to be robust to the influence of individual studies (eFigures 7-11 in Supplement). The results were also not materially altered when the lowest category was excluded when not used as a reference category instead of converting the risk estimates (eTable 16 in Supplement).
Maternal BMI, Stillbirth, Fetal and Infant Death

Discussion

In this meta-analysis of cohort studies, moderate to strong increases in the RR of fetal death, stillbirth, neonatal death, perinatal death and infant death were found with increasing maternal BMI. In linear dose-response analyses, the RR per 5-unit increase in maternal BMI ranged from 1.15 to 1.24. Although the test for nonlinearity was significant in all analyses, the nonlinearity was most pronounced for fetal death and the curve showed a steeper increase at higher levels of BMI; whereas for stillbirth, the association appeared to be almost linear. In the remaining analyses, the associations appeared to be broadly linear above a certain threshold, which differed slightly between the different outcomes (approximately 24-25 for perinatal and infant death and approximately 26-27 for neonatal death). However, the greatest risk was observed in the category of severely obese women; women with a BMI of 40 had an approximate 2- to 3-fold increase in the RR of these outcomes vs those with a BMI of 20, with absolute risks in the range of 0.69% to 2.7% for BMI of 40 vs 0.20% to 0.76% for BMI of 20. The differences in the shape of the curves and strength of the associations might partly be because different studies were included in the different analyses, but they could also reflect differences in the etiology between the types of outcomes. Our findings are consistent with 2 previous meta-analyses of maternal overweight and obesity and risk of stillbirth, but included a larger number of studies, more detailed dose-response, sensitivity and subgroup analyses, assessment of study quality, and analyses of absolute risks. To our knowledge, this is the first meta-analysis to comprehensively summarize results for the relationship between maternal BMI and fetal, perinatal, neonatal, and infant death as well. In addition, subtypes of outcomes including miscarriage, antepartum and intrapartum stillbirth, early neonatal death, and post-neonatal death were analyzed in this study. The null association

Figure 3. Association Between Maternal BMI and Risk of Stillbirth

### A Risk of stillbirth per 5 maternal BMI units

<table>
<thead>
<tr>
<th>Source</th>
<th>Stillbirth Participants</th>
<th>Maternal BMI Comparison</th>
<th>Relative Risk per 5 BMI Units (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deverson et al.42 2014</td>
<td>546 124 280</td>
<td>≥20 vs &lt;18.5</td>
<td>1.14 (1.07-1.22)</td>
</tr>
<tr>
<td>Gardosi et al.22 2013</td>
<td>389 90 350</td>
<td>≥35 vs &lt;18.5</td>
<td>1.15 (1.04-1.27)</td>
</tr>
<tr>
<td>Scott-Pillai et al.21 2013</td>
<td>126 30 298</td>
<td>≥40 vs &lt;18.5</td>
<td>1.19 (1.02-1.39)</td>
</tr>
<tr>
<td>McIntyre et al.6 2012</td>
<td>337 75 432</td>
<td>≥40 vs &lt;18.5</td>
<td>1.21 (1.10-1.34)</td>
</tr>
<tr>
<td>Wallace et al.30 2012</td>
<td>293 55 105</td>
<td>≥35 vs &lt;18.5</td>
<td>1.37 (1.22-1.54)</td>
</tr>
<tr>
<td>Liu et al. 13 2011</td>
<td>27 50 47</td>
<td>≥28 vs &lt;18.5</td>
<td>1.88 (1.18-2.99)</td>
</tr>
<tr>
<td>Ovesen et al.27 2011</td>
<td>1113 369 347</td>
<td>≥35 vs &lt;18.5</td>
<td>1.26 (1.19-1.33)</td>
</tr>
<tr>
<td>Stringer et al.28 2011</td>
<td>1273 60 954</td>
<td>≥26 vs &lt;19.8</td>
<td>1.29 (1.18-1.41)</td>
</tr>
<tr>
<td>Syngelaki et al.29 2011</td>
<td>NA 41 577</td>
<td>≥35 vs &lt;25</td>
<td>1.28 (1.16-1.47)</td>
</tr>
<tr>
<td>Tennant et al.4 2011</td>
<td>146 29 856</td>
<td>≥30 vs &lt;18.5</td>
<td>1.43 (1.21-1.67)</td>
</tr>
<tr>
<td>Khashan et al.11 2009</td>
<td>433 99 403</td>
<td>≥40 vs &lt;18.5</td>
<td>1.04 (0.96-1.13)</td>
</tr>
<tr>
<td>Haugr et al.25 2008</td>
<td>351 46 964</td>
<td>≥30 vs &lt;18.5</td>
<td>1.07 (0.93-1.23)</td>
</tr>
<tr>
<td>Leung et al.14 2008</td>
<td>78 29 303</td>
<td>≥30 vs &lt;18.5</td>
<td>1.31 (0.92-1.86)</td>
</tr>
<tr>
<td>Salihu et al.17 2007</td>
<td>8240 1</td>
<td>≥40 vs &lt;18.5</td>
<td>1.14 (1.11-1.16)</td>
</tr>
<tr>
<td>Kristensen et al.20 2005</td>
<td>112 24 505</td>
<td>≥30 vs &lt;18.5</td>
<td>1.33 (1.04-1.70)</td>
</tr>
<tr>
<td>Nohr et al.5 2005</td>
<td>149 51 300</td>
<td>≥30 vs &lt;18.5</td>
<td>1.71 (1.42-2.07)</td>
</tr>
<tr>
<td>Cnattinigius and Lambe,22 2002</td>
<td>1318 453 801</td>
<td>≥30 vs ≥2.49</td>
<td>1.37 (1.27-1.46)</td>
</tr>
<tr>
<td>Sebire et al.30 2001</td>
<td>1343 287 213</td>
<td>≥30 vs 20-25</td>
<td>1.16 (1.08-1.25)</td>
</tr>
<tr>
<td>Overall (I² = 80.0%; P &lt; .001 for heterogeneity)</td>
<td></td>
<td></td>
<td>1.24 (1.18-1.30)</td>
</tr>
</tbody>
</table>

### B Nonlinear dose-response analysis

Linear (panel A) and nonlinear (panel B) dose-response analyses for stillbirth using a random effects model. BMI indicates body mass index.

A, The relative risks (RRs) are represented by squares and the 95% CIs are represented by lines through the squares. Larger studies have greater weight, indicated by larger-sized squares. The summary RR is represented by the diamond and risk estimate at the bottom of the plot.
between studies rather than a lack of association. It is possible
be related to differences in the size of the effect estimates be-
henogeneity was rather high in all analyses, but this appeared to
cluded, there was no evidence of publication bias. Hetero-
total number of stillbirths and which found a weaker associa-
in the analysis of stillbirth. This appeared to be explained by
lished confounding factors such as maternal age, parity, and
associations observed. Most of the studies adjusted for estab-
confounding by other risk factors could partially explain the
related complications that could result in stillbirth, while the
ings are further supported by 2 studies of interpregnancy
ring than the overall summary estimate. When this study was
dition than or equal to 22, 24, or 28 weeks as the cutoff points. It has
point than among studies using earlier cutoff points, and
among studies of perinatal death that only included early neo-
tal death vs early.4 When studies were grouped according to the definition of stillbirth and perinatal
t, there was some suggestion of a stronger association
between the first and the second pregnancy.56-57
This meta-analysis has some limitations. It is possible that
confounding by other risk factors could partially explain the
associations observed. Most of the studies adjusted for estab-
confounding factors such as maternal age, parity, and
smoking, and the results persisted in subgroup analyses with
such adjustments. There was some evidence of publication bias
in the analysis of stillbirth. This appeared to be explained by a
very large US study23 that contributed more than 51% of the
total number of stillbirths and which found a weaker associa-
tion than the overall summary estimate. When this study was
cluded, there was no evidence of publication bias. Hetero-
genosity was rather high in all analyses, but this appeared to
be related to differences in the size of the effect estimates be-
tween studies rather than a lack of association. It is possible
that different definitions of stillbirth could have contributed
to the lower summary estimates in studies from North and
Latin America compared with European ones. Some of the
studies from North and Latin America defined stillbirth as a
fetal death of at least 20 or 22 completed weeks of gestation,
while the European studies tended to use completion of more
than or equal to 22, 24, or 28 weeks as the cutoff points. It has
been shown that maternal BMI is more strongly associated with
fetal death in later pregnancy vs early.4 When studies were
grouped according to the definition of stillbirth and perinatal
death, there was some suggestion of a stronger association
among the studies of stillbirth that used week 28 as the cutoff
point than among studies using earlier cutoff points, and
among studies of perinatal death that only included early neo-
natal death compared with all neonatal deaths in addition to
stillbirth. This is consistent with the weaker association that
was observed for neonatal death compared with early neonatal
death and stillbirth.
Most of the studies included in this meta-analysis were
from Europe and North America where fetal and infant death
rates are much lower than in low- and medium-income coun-
tries. Thus, it is unclear whether the results can be general-
ized to other settings. One African study28 and 2 studies from

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Figure 4. Association Between Maternal BMI and Risk of Perinatal Death

A Risk of perinatal death per 5 maternal BMI units

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events</th>
<th>Perinatal Death</th>
<th>Maternal BMI Comparison</th>
<th>Relative Risk per 5 BMI Units (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magann et al, 2013</td>
<td>80</td>
<td>4490</td>
<td>≥45 vs &lt;18.5</td>
<td>1.08 (0.93-1.25)</td>
</tr>
<tr>
<td>Manzanares Galan, 2012</td>
<td>85</td>
<td>3016</td>
<td>&gt;35 vs &lt;18.5</td>
<td>1.26 (1.04-1.53)</td>
</tr>
<tr>
<td>McIntyre et al, 2012</td>
<td>599</td>
<td>75432</td>
<td>≥40 vs &lt;18.5</td>
<td>1.25 (1.16-1.33)</td>
</tr>
<tr>
<td>Persson et al, 2012</td>
<td>3130</td>
<td>767955</td>
<td>≥30 vs 18.5-24.9</td>
<td>1.43 (1.38-1.49)</td>
</tr>
<tr>
<td>Dodd et al, 2011</td>
<td>NA</td>
<td>11233</td>
<td>≥40 vs &lt;18.5</td>
<td>1.06 (0.90-1.24)</td>
</tr>
<tr>
<td>Tennant et al, 2011</td>
<td>179</td>
<td>29856</td>
<td>≥30 vs &lt;18.5</td>
<td>1.44 (1.23-1.67)</td>
</tr>
<tr>
<td>Abenhaim et al, 2007</td>
<td>NA</td>
<td>18633</td>
<td>≥40 vs ≤19.9</td>
<td>1.06 (0.89-1.26)</td>
</tr>
<tr>
<td>Raxtikainen et al, 2006</td>
<td>147</td>
<td>25601</td>
<td>≥30 vs ≤25</td>
<td>1.36 (1.13-1.63)</td>
</tr>
<tr>
<td>Jensen et al, 2005</td>
<td>14</td>
<td>24593</td>
<td>≥30 vs 18.5-24.9</td>
<td>1.00 (0.85-1.54)</td>
</tr>
<tr>
<td>Lumme et al, 1995</td>
<td>77</td>
<td>9015</td>
<td>≥30 vs &lt;19</td>
<td>1.60 (1.10-2.33)</td>
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<tr>
<td>Cattanach et al, 1993</td>
<td>NA</td>
<td>34546</td>
<td>24.5-30.3 vs &lt;20</td>
<td>0.61 (0.54-0.71)</td>
</tr>
<tr>
<td>Overall (I²=93.7%; P&lt;.001 for heterogeneity)</td>
<td>1.16 (1.00-1.35)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Maternal BMI, Stillbirth, Fetal and Infant Death

The positive dose-response relationship between increasing maternal BMI and risk of fetal and infant death suggests an underlying biological relationship between maternal adiposity and fetal and infant death. Several biological mechanisms could explain these associations. Overweight and obesity has been associated with increased risk of preeclampsia, gestational diabetes, type 2 diabetes, gestational hypertension, and congenital anomalies. All of these conditions, but in particular congenital anomalies, have been strongly associated with risk of fetal and infant death. However, we found the risk estimates were similar in studies that adjusted for some of these possibly intermediate end points compared with studies in which no such adjustment had been made, and the positive associations persisted also when the analyses were restricted to 2 studies in which cases of pre-eclampsia and pregestational diabetes had been excluded from the analyses. It has been estimated that congenital anomalies only represent 5% of stillbirths; thus other mechanisms may also be involved. It has been suggested that thinner women may be better at recognizing decreased fetal movements, which may precede fetal deaths. In addition, obese women, even without clinical disease, have increased inflammatory responses, vascular and endothelial dysfunction, and altered lipid metabolism, alterations similar to those observed in pre-eclamptic women. Hyperlipidemia may cause a reduction in prostacyclin secretion and increased thromboxane production, which can increase the risk of placental thrombosis, decrease placental perfusion, and further lead to both infarction and abruption of the placenta in later pregnancy.

A recent study reported obstetric conditions (29.3%) and placental abnormalities (23.6%) as the most common causes of stillbirth, and one study reported a 5-fold increase in risk of stillbirth caused by maternal obesity. However, data are too limited to draw firm conclusions, and further prospective cohort studies are needed from these locations, the present evidence does not suggest there are major differences in the direction of these associations based on geography for most of the outcomes investigated.

Asia regarding stillbirth were consistent with the findings from European and North and South American studies. In addition, 1 small study from Ghana that could not be included in the dose-response analysis of stillbirth and a large cross-sectional study of neonatal death in 27 countries in sub-Saharan Africa reported an increased risk with overweight and obesity. Thus, although data are too limited to draw firm conclusions, and further prospective cohort studies are needed from these locations, the present evidence does not suggest there are major differences in the direction of these associations based on geography for most of the outcomes investigated.

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Maternal BMI, Stillbirth, Fetal and Infant Death

Figure 6. Association Between Maternal BMI and Risk of Infant Death

A Risk of infant death per 5 maternal BMI units

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events</th>
<th>Infant Death</th>
<th>Maternal BMI</th>
<th>Relative Risk per 5 BMI Units (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nohr et al. 2012</td>
<td>3481</td>
<td>1199183</td>
<td>≥35 vs &lt;18.5</td>
<td>1.21 (1.16-1.26)</td>
</tr>
<tr>
<td>Tennant et al. 2011</td>
<td>81</td>
<td>29856</td>
<td>≥30 vs &lt;18.5</td>
<td>1.27 (1.06-1.53)</td>
</tr>
<tr>
<td>Thompson et al. 2008</td>
<td>1015</td>
<td>166301</td>
<td>≥40 vs &lt;18.5</td>
<td>1.09 (1.04-1.14)</td>
</tr>
<tr>
<td>Baeten et al. 2001</td>
<td>406</td>
<td>96539</td>
<td>≥30 vs &lt;20</td>
<td>1.26 (1.11-1.44)</td>
</tr>
<tr>
<td>Overall (I² = 79.0%; P = .003 for heterogeneity)</td>
<td>73,744</td>
<td>19931436</td>
<td>1.18 (1.09-1.28)</td>
<td></td>
</tr>
</tbody>
</table>

B Nonlinear dose-response analysis

Conclusions

Even modest increases in maternal BMI were associated with increased risk of fetal death, stillbirth, neonatal death, perinatal death, and infant death. Weight management guidelines for women who plan pregnancies should take these findings into consideration to reduce the burden of fetal deaths, stillbirths, and infant deaths.
intellectual content: Aune, Saugstad, Henrikse, Tønsdahl.

Statistical analysis: Aune.

Obtained funding: Aune, Saugstad, Tønsdahl.

Study supervision: Henrikse, Tønsdahl.

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REFERENCES


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Research Original Investigation


