Original Investigation

Maternal Body Mass Index and the Risk of Fetal Death, Stillbirth, and Infant Death

A Systematic Review and Meta-analysis

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IMPORTANCE 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.

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

DATA 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, 1.15 (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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Worldwide, approximately 2.65 million stillbirths occurred in 2008, most of which were in low- and middle-income countries.[1] Stillbirths account for a large part of all perinatal deaths.[1] In addition, an estimated 3.6 million neonatal deaths occur each year.[2] Several studies have suggested that greater maternal body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) before or during early pregnancy is associated with an increased risk of fetal death,[3-6] stillbirth,[4,6,7] perinatal death,[5,6,8,9] neonatal death,[6-8,10] and infant death (**Box**).[6,10] However, not all studies found a significant association,[11-14] some possibly due to a low sample size or a low number of deaths.[11-14] The optimal prepregnancy BMI to prevent fetal and infant death has not been established. Some studies have reported J-shaped associations with a small increase in risk among women with low or moderate BMI (although not statistically significant),[6,7,12,14] while other studies reported a linear association.[3-5,8,9] Determining whether there are any threshold effects between maternal BMI and fetal and infant death could be important with regard to public health recommendations for women who plan pregnancies. To clarify the association between maternal BMI and risk of fetal death, stillbirth, and infant death, we conducted a systematic review and meta-analysis of the available evidence from published cohort studies. This study specifically determined the strength of the association, the shape of the dose-response relationship, potential confounding, and potential sources of heterogeneity in the results (including the definition of stillbirth and perinatal death).[4]

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,[24] 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,

Box. Outcomes Definitions

Fetal death
Spontaneous death of a fetus during pregnancy or labor

Miscarriage
Death of a fetus or embryo before week 20 (definition varies as some studies include death up to 24 weeks of gestation)

Stillbirth
Death of a fetus at week 20 to 28 or more completed weeks of gestation (definition varies between studies and different cut-off points have been used)

Antepartum stillbirth
Stillbirth in which there was no evidence of life during labor

Intrapartum stillbirth
Stillbirth in which the fetus died during labor

Neonatal death
Death following live birth of an infant but before age 28 days

Early neonatal death
Neonatal death before age 7 days

Perinatal death
Stillbirth and early neonatal death (neonatal death is included in some studies)

Postneonatal death
Death of an infant older than 28 days old but younger than 1 year

Infant death
Death of a live-born infant before age 1 year

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[51] and the best fitting second-order fractional polynomial regression model was determined—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.[51] 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.[52] 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[53]; 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).

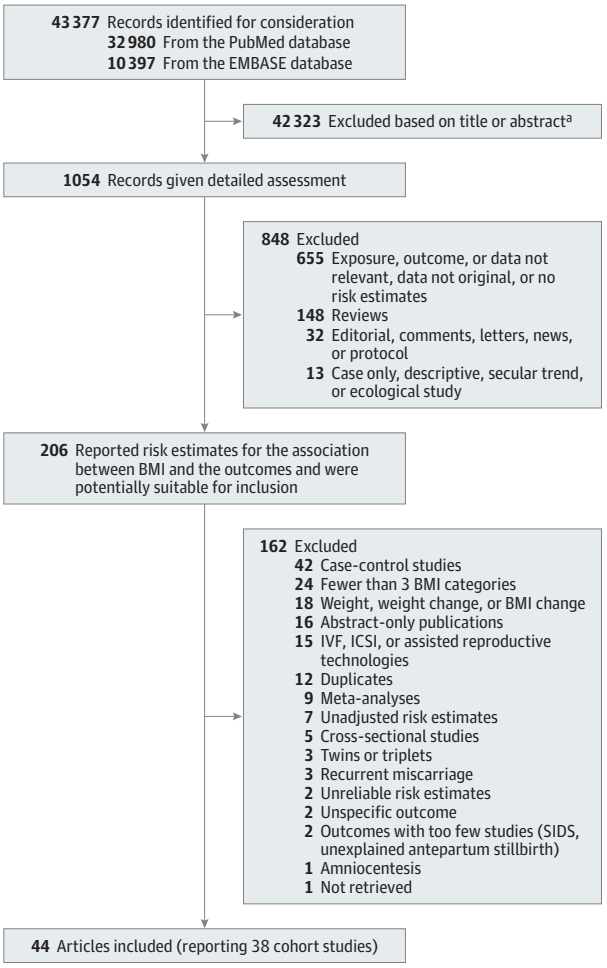
Results

After ineligible studies were excluded (eTable 3 in Supplement), 38 studies (44 publications)[4-47] 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[4-6,15-17,29] 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; I^2 = 77.6%; P <.001 for heterogeneity; **Figure 2**a). 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), 82 (95% CI, 76-88), and 102 (95% CI, 93-112), respectively (Table). Five studies[4,6,18,19,29] 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; I^2 = 33.0%; P = .20 for heterogeneity; eFigure 1 in Supplement).

Figure 1. Study Selection for Maternal BMI and the Risk of Fetal Death, Stillbirth, and Infant Death



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

[a] Exact reasons for exclusions were not documented.

Stillbirth

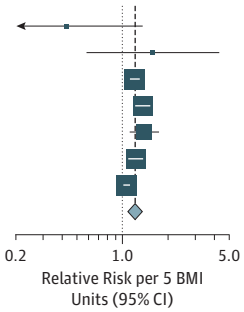
Eighteen cohort studies* were included in the analysis of maternal BMI and stillbirth risk and included more than 16 274 stillbirths among 3 288 688 participants (eTable 5 in Supplement). The summary RR per 5 BMI units was 1.24 (95% CI, 1.18-1.30; I^2 = 80%; P <.001 for heterogeneity; **Figure 3**a). There was evidence of publication bias using the Egger test (P = .02; eFigure 2 in Supplement). When excluding the largest study,[23] 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), 48 (95% CI, 46-51), and 59 (95% CI, 55-63), respectively (Table). Analyzing studies that reported results for antepartum[6,22,24,26,45,46] and intrapartum[6,24] stillbirths gave summary RRs of 1.28 (95% CI, 1.15-1.43;

*References 4, 6-8, 11-13, 20, 21, 23, 25, 27-32, 47

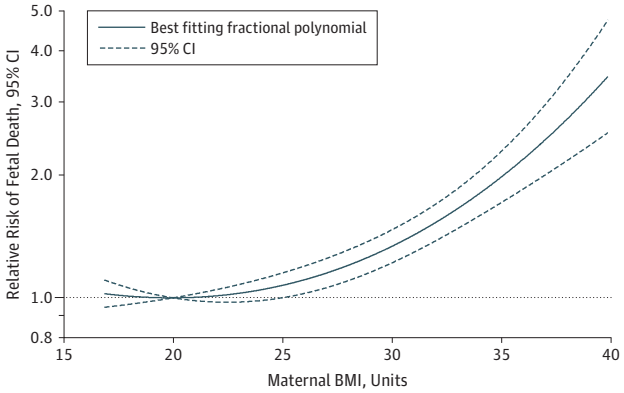
Figure 2. Association Between Maternal BMI and Risk of Fetal Death

A Risk of fetal death per 5 maternal BMI units

Source	No. Fetal Death	No. Participants	Maternal BMI Comparison	Relative Risk per 5 BMI Units (95% CI)
Choi et al,[16] 2011	11	2413	≥25 vs <18.5	0.43 (0.14-1.36)
Joshi et al,[17] 2011	8	1200	≥30 vs 20-24.9	1.58 (0.58-4.30)
Syngelaki et al,[29] 2011	NA	41577	≥35 vs <25	1.20 (1.12-1.30)
Tennant et al,[6] 2011	196	29856	≥30 vs <18.5	1.36 (1.21-1.52)
Raatikainen et al,[5] 2006	91	25601	≥30 vs ≤25	1.39 (1.11-1.73)
Nohr et al,[4] 2005	674	54133	≥30 vs <18.5	1.22 (1.09-1.36)
Conde-Agudelo et al,[15] 2000	9167	535842	>29 vs <19.8	1.06 (1.01-1.11)
Overall (I^2 = 77.6%; P for heterogeneity <.001)				1.21 (1.09-1.35)



B Nonlinear dose-response analysis



Linear (panel A) and nonlinear (panel B) dose-response analyses for fetal death 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.

I^2 = 83.7%; P <.001 for heterogeneity; eFigure 3 in Supplement) and 0.90 (95% CI, 0.76-1.06; I^2 = 0%; P = .99 for heterogeneity; eFigure 4 in Supplement) per 5 BMI units, respectively.

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, 1.00-1.35; I^2 = 93.7%; P <.001 for heterogeneity; **Figure 4**a). Excluding 1 study[33] that appeared to be an outlier gave a summary RR of 1.25 (95% CI, 1.14-1.36) and reduced the heterogeneity (I^2 = 79.1%). There was no evidence of publication bias using the Egger test (P = .15). There was evidence of a nonlinear association between maternal BMI and perinatal death (P <.001 for nonlinearity) with a flattening of the curve at lower BMI levels (Figure 4b, Table). For BMI levels of 20, 25, and 30, absolute risk was 66 (reference standard), 73 (95% CI, 67-81), and 86 (95% CI, 76-98) perinatal deaths per 10 000 pregnancies, respectively (Table).

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; I^2 = 78.5%; P<.001 for heterogeneity; **Figure 5**a). There was no evidence of publication bias with the Egger test (P = .18). There was evidence for a nonlinear association (P = .01 for nonlinearity), with a flattening of the curve at the lower BMI levels (Figure 5b, Table). For BMI values of 20, 25, and 30, absolute risk was 20 (reference standard), 21 (95% CI, 19-23), and 24 (95% CI, 22-27) neonatal deaths per 10 000 pregnancies, respectively (Table). Analyzing 2 studies[6,22] of early neonatal death gave a summary RR of 1.31 (95% CI, 1.22-1.41; I^2 = 0%; P = .84 for heterogeneity; eFigure 5 in Supplement) per 5 BMI units and analyzing 2 studies[6,10] on postneonatal death gave a summary RR of 1.14 (95% CI, 1.06-1.22; I^2 = 0%; P = .94 for heterogeneity; eFigure 6 in Supplement) per 5 BMI units.

Infant Death

Four cohort studies[6,1043,44] 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; I^2 = 79.0%; P = .003 for heterogeneity; **Figure 6**a). There was no evidence of publication bias using the Egger test (P = .56). There was evidence of a nonlinear association (P <.001 for nonlinearity) with a flattening of the curve at lower BMI levels (Figure 6b, Table). For BMI values of 20, 25, and 30, absolute risk was 33 (reference standard), 37 (95%

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

	BMI[a]									
	17	20	22.5	25	27.5	30	32.5	35.0	37.5	40
Fetal Death (n = 6)[b]										
RR (95% CI)	1.02 (0.95-1.10)	1 [Reference]	1.02 (0.98-1.06)	1.07 (1.00-1.15)	1.17 (1.08-1.28)	1.34 (1.22-1.47)	1.59 (1.43-1.77)	1.97 (1.71-2.28)	2.58 (2.08-3.20)	3.54 (2.56-4.89)
AR (95% CI)[c]	78 (72-84)	76	78 (75-81)	82 (76-88)	89 (82-98)	102 (93-112)	121 (109-135)	150 (130-174)	197 (159-244)	270 (195-373)
Stillbirth (n = 18)										
RR (95% CI)	0.92 (0.86-0.99)	1 [Reference]	1.09 (1.05-1.13)	1.20 (1.14-1.26)	1.32 (1.24-1.40)	1.46 (1.37-1.55)	1.61 (1.51-1.72)	1.78 (1.67-1.91)	1.97 (1.84-2.12)	2.19 (2.03-2.36)
AR (95% CI)[c]	37 (34-40)	40	44 (42-46)	48 (46-51)	53 (50-57)	59 (55-63)	65 (61-69)	72 (67-77)	80 (74-86)	88 (82-95)
Perinatal Death (n = 11)										
RR (95% CI)	0.99 (0.89-1.11)	1 [Reference]	1.04 (0.98-1.10)	1.11 (1.01-1.22)	1.20 (1.07-1.34)	1.31 (1.15-1.48)	1.43 (1.25-1.65)	1.59 (1.37-1.84)	1.76 (1.50-2.08)	1.97 (1.63-2.36)
AR (95% CI)[c]	65 (58-73)	66	69 (65-73)	73 (67-81)	79 (71-88)	86 (76-98)	94 (83-109)	105 (90-121)	116 (99-137)	130 (108-156)
Neonatal Death (n = 9)[d]										
RR (95% CI)	1.04 (0.94-1.16)	1 [Reference]	1.01 (0.96-1.06)	1.05 (0.97-1.14)	1.12 (1.01-1.23)	1.20 (1.08-1.33)	1.30 (1.16-1.45)	1.42 (1.27-1.59)	1.55 (1.38-1.74)	1.71 (1.51-1.94)
AR (95% CI)[c]	21 (18-23)	20	20 (19-21)	21 (19-23)	22 (20-25)	24 (22-27)	26 (23-29)	29 (25-32)	31 (28-35)	34 (30-39)
Infant Death (n = 4)										
RR (95% CI)	1.01 (0.93-1.09)	1 [Reference]	1.03 (1.00-1.08)	1.10 (1.03-1.18)	1.19 (1.10-1.29)	1.30 (1.19-1.42)	1.43 (1.30-1.57)	1.58 (1.43-1.74)	1.75 (1.58-1.95)	1.95 (1.73-2.19)
AR (95% CI)[c]	34 (31-36)	33	34 (33-36)	37 (34-39)	40 (37-43)	43 (40-47)	48 (43-52)	53 (48-58)	58 (53-65)	65 (58-73)

Abbreviations: AR, absolute risk; BMI, body mass index; RR, relative risk.

[a] BMI is calculated as weight in kilograms divided by height in meters squared.

[b] One study ([30])was excluded because the model did not converge when included.

[c] Data are reported per 10 000 pregnancies.

[d] Two studies were excluded ([39,40]) because the model did not converge when included; and 1 study was excluded ([42]) 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

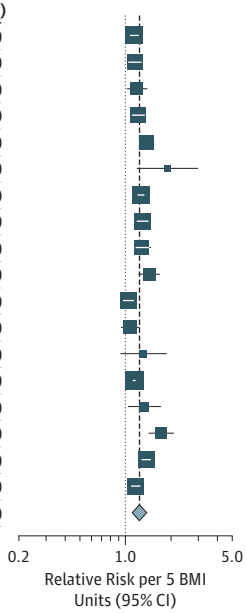
In subgroup analyses stratified by geographic location, assessment of weight and height, number of deaths, and adjustment for confounding factors, little evidence was found of heterogeneity between subgroups (eTable 9, eTable 10 in Supplement). A stronger association was found among European studies 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]; I^2 = 79.4%; P <.001 for heterogeneity; in 7 studies[6,12,23,25,27,29,32]) 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]; I^2 = 60.2%; P = .08 for heterogeneity; in 3 studies[4,7,21]), 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]; I^2 = 0%; P = .40 for heterogeneity; in 3 studies[5,6,9]) vs perinatal death defined as all neonatal death in addition to stillbirth (RR per 5 BMI units, 0.96 [95% CI, 0.69-1.33]; I^2 = 93.8%; P <.001 for heterogeneity; in 4 studies[14,33,36,37]), 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 studies[4,6] in which participants with such conditions had been excluded, but the summary RR was 1.57 (95% CI, 1.28-1.92; I^2 = 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).

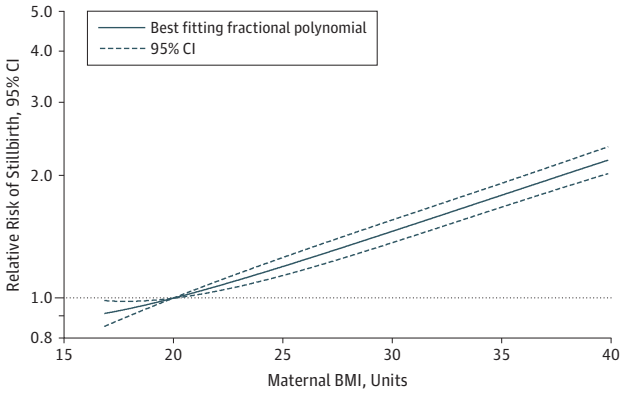
Figure 3. Association Between Maternal BMI and Risk of Stillbirth

A Risk of stillbirth per 5 maternal BMI units

Source	No. Stillbirth Death	No. Participants	Maternal BMI Comparison	Relative Risk per 5 BMI Units (95% CI)
Denison et al,[47] 2014	546	124 280	≥40 vs <18.5	1.14 (1.07-1.22)
Gardosi et al,[32] 2013	389	90 350	≥35 vs <18.5	1.15 (1.04-1.27)
Scott-Pillai et al,[31] 2013	126	30 298	≥40 vs <18.5	1.19 (1.02-1.39)
McIntyre et al,[8] 2012	337	75 432	≥40 vs <18.5	1.21 (1.10-1.34)
Wallace et al,[30] 2012	293	55 105	≥35 vs ≤18.5	1.37 (1.22-1.54)
Liu et al,[13] 2011	27	5047	≥28 vs <18.5	1.88 (1.18-2.99)
Ovesen et al,[27] 2011	1113	369 347	≥35 vs <18.5	1.26 (1.19-1.33)
Stringer et al,[28] 2011	1273	60 954	>26 vs <19.8	1.29 (1.18-1.41)
Syngelaki et al,[29] 2011	NA	41 577	≥35 vs <25	1.28 (1.16-1.47)
Tennant et al,[6] 2011	146	29 856	≥30 vs <18.5	1.43 (1.21-1.67)
Khashan et al,[12] 2009	433	99 403	≥40 vs <18.5	1.04 (0.96-1.13)
Hauger et al,[25] 2008	351	46 964	≥30 vs ≤18.5	1.07 (0.93-1.23)
Leung et al,[11] 2008	78	29 303	≥30 vs <18.5	1.31 (0.92-1.86)
Salihu et al,[23] 2007	8240	1 413 953	≥40 vs <18.5-24.9	1.14 (1.11-1.16)
Kristensen et al,[7] 2005	112	24 505	≥30 vs <18.5	1.33 (1.04-1.70)
Nohr et al,[4] 2005	149	51 300	≥30 vs <18.5	1.71 (1.42-2.07)
Cnattingius and Lambe,[21] 2002	1318	453 801	≥30 vs ≤24.9	1.37 (1.27-1.46)
Sebire et al,[20] 2001	1343	287 213	>30 vs 20-25	1.16 (1.08-1.25)
Overall (I^2 = 80.0%; P < .001 for heterogeneity)				1.24 (1.18-1.30)



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.

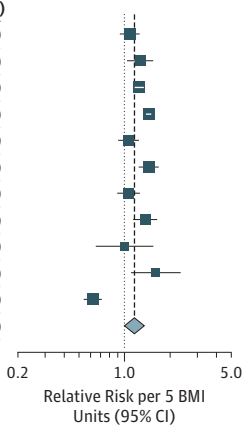
Discussion

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,[54,55] 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 postneonatal death were analyzed in this study. The null association

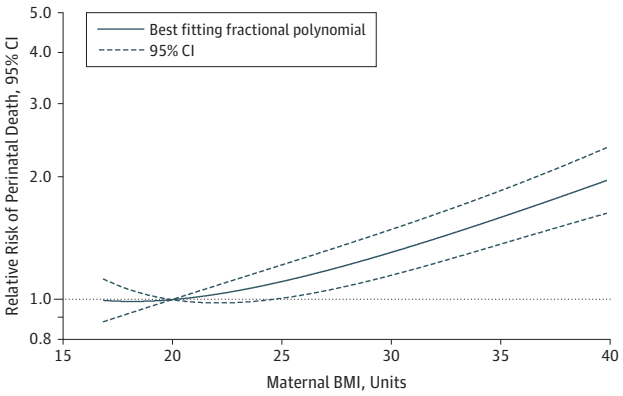
Figure 4. Association Between Maternal BMI and Risk of Perinatal Death

A Risk of perinatal death per 5 maternal BMI units

Source	No. of Events: Perinatal Death	No. of Events: Participants	Maternal BMI Comparison	Relative Risk per 5 BMI Units (95% CI)
Magann et al,[38] 2013	80	4490	≥45 vs <18.5	1.08 (0.93-1.25)
Manzanares Galan,[37] 2012	85	3016	>35 vs <18.5	1.26 (1.04-1.53)
McIntyre et al,[8] 2012	599	75432	≥40 vs <18.5	1.25 (1.16-1.33)
Persson et al,[9] 2012	3130	767955	≥30 vs 18.5-24.9	1.43 (1.38-1.49)
Dodd et al,[36] 2011	NA	11233	≥40 vs <18.5	1.06 (0.90-1.24)
Tennant et al,[6] 2011	179	29856	≥30 vs <18.5	1.44 (1.23-1.67)
Abenhaim et al,[14] 2007	NA	18633	≥40 vs ≤19.9	1.06 (0.89-1.26)
Raatikainen et al,[5] 2006	147	25601	≥30 vs ≤25	1.36 (1.13-1.63)
Jensen et al,[35] 2003	14	2459	≥30 vs 18.5-24.9	1.00 (0.65-1.54)
Lumme et al,[34] 1995	77	9015	≥30 vs <19	1.60 (1.10-2.33)
Cattanach et al,[33] 1993	NA	34546	24.5-30.3 vs <20	0.61 (0.54-0.71)
Overall (I^2 = 93.7%; P < .001 for heterogeneity)				1.16 (1.00-1.35)



B Nonlinear dose-response analysis



Linear (panel A) and nonlinear (panel B) dose-response analyses for perinatal death 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.

for intrapartum stillbirth might be because the medical care received during childbirth is sufficient to alleviate any obesity-related complications that could result in stillbirth, while the remaining associations were consistent with the overall findings of increased risk with greater maternal adiposity. Our findings are further supported by 2 studies of interpregnancy weight change that reported increased risk of stillbirth in the second pregnancy among women who gained weight between the first and the second pregnancy.[56,57]

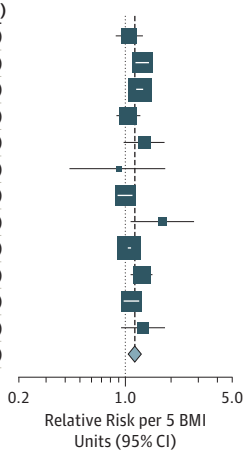
This meta-analysis has some limitations. It is possible that confounding by other risk factors could partially explain the associations observed. Most of the studies adjusted for established confounding factors such as maternal age, parity, and smoking, and the results persisted in subgroup analyses 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 study[23] that contributed more than 51% of the total number of stillbirths and which found a weaker association than the overall summary estimate. When this study was excluded, there was no evidence of publication bias. Heterogeneity was rather high in all analyses, but this appeared to be related to differences in the size of the effect estimates between 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 neonatal 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 countries. Thus, it is unclear whether the results can be generalized to other settings. One African study[28] and 2 studies from

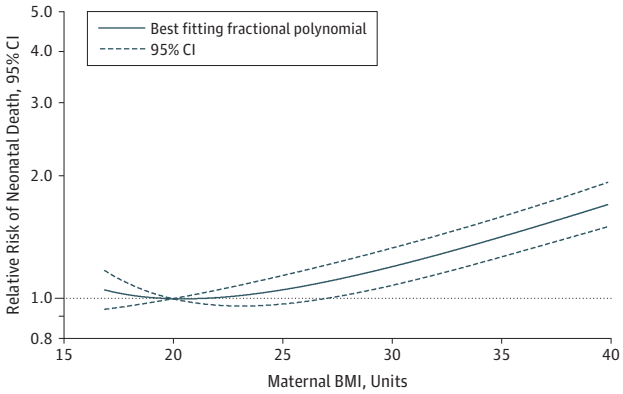
Figure 5. Association Between Maternal BMI and Risk of Neonatal Death

A Risk of neonatal death per 5 maternal BMI units

Source	No. Neonatal Death	No. Participants	Maternal BMI Comparison	Relative Risk per 5 BMI Units (95% CI)
Denison et al,[47] 2013	61	124 280	≥40 vs ≤18.49	1.06 (0.86-1.30)
McIntyre et al,[8] 2012	262	75 432	≥40 vs <18.5	1.28 (1.16-1.42)
Nohr et al,[10] 2012	2215	1 199 183	≥35 vs <18.5	1.23 (1.17-1.30)
Wallace et al,[30] 2012	175	55 105	≥35 vs ≤18.5	1.04 (0.87-1.25)
Tennant et al,[6] 2011	52	29 856	≥30 vs <18.5	1.32 (0.97-1.79)
Narchi and Skinner,[42] 2010	10	6125	Per category	0.91 (0.43-1.82)
Khashan and Kenny,[12] 2009	207	99 403	≥40 vs <18.5	0.99 (0.88-1.11)
Leung et al,[11] 2008	47	29 303	≥30 vs <18.5	1.74 (1.08-2.81)
Salihu et al,[41] 2008	7622	1 405 698	≥40 vs 18.5-24.9	1.06 (1.03-1.08)
Nohr et al,[40] 2007	230	85 375	≥30 vs <18.5	1.27 (1.08-1.49)
Smith et al,[39] 2007	338	187 290	≥35 vs <20	1.09 (0.97-1.22)
Kristensen et al,[7] 2005	75	24 505	≥30 vs <18.5	1.30 (0.93-1.81)
Overall (I^2 = 78.5%; P < .001 for heterogeneity)				1.15 (1.07-1.23)



B Nonlinear dose-response analysis



Linear (panel A) and nonlinear (panel B) dose-response analyses for neonatal death 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.

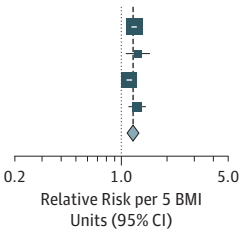
Asia[11,13] regarding stillbirth were consistent with the findings from European and North and South American studies. In addition, 1 small study from Ghana that could not be included in the dose-response analysis of stillbirth[58] and a large cross-sectional study of neonatal death in 27 countries in sub-Saharan Africa reported an increased risk with overweight and obesity.[59] 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 that there are major differences in the direction of these associations based on geography for most of the outcomes investigated.

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,[60] gestational diabetes,[61] type 2 diabetes,[62] gestational hypertension,[63] and congenital anomalies.[64] All of these conditions, but in particular congenital anomalies, have been strongly associated with risk of fetal and infant death.[6] 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[4,6] in which cases of preeclampsia and pregestational diabetes had been excluded from the analyses. It has been estimated that congenital anomalies only represent 5% of stillbirths;[1] 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.[65] In addition, obese women, even without clinical disease, have increased inflammatory responses, vascular and endothelial dysfunction, and altered lipid metabolism,[66] alterations similar to those observed in preeclamptic women.[67] Hyperlipidemia may cause a reduction in prostacyclin secretion and increased tromboxane production,[68] which can increase the risk of placental thrombosis, decrease placental perfusion,[67] and further lead to both infarction and abruption of the placenta in later pregnancy.[69,70] A recent study reported obstetric conditions (29.3%) and placental abnormalities (23.6%) as the most common causes of stillbirth,[71] and one study reported a 5-fold increase in risk of stillbirth caused

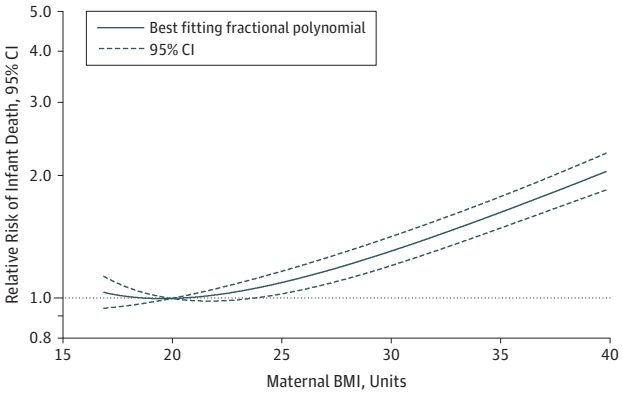
Figure 6. Association Between Maternal BMI and Risk of Infant Death

A Risk of infant death per 5 maternal BMI units

Source	No. of Events: Infant Death	No. of Events: Participants	Maternal BMI Comparison	Relative Risk per 5 BMI Units (95% CI)
Nohr et al,[10] 2012	3481	1 199 183	≥35 vs <18.5	1.21 (1.16-1.26)
Tennant et al,[6] 2011	81	29 856	≥30 vs <18.5	1.27 (1.06-1.53)
Thompson et al,[44] 2008	1015	166 301	≥40 vs <18.5	1.09 (1.04-1.14)
Baeten et al,[43] 2001	406	96 539	≥30 vs <20	1.26 (1.11-1.44)
Overall (I^2 = 79.0%; P = .003 for heterogeneity)				1.18 (1.09-1.28)



B Nonlinear dose-response analysis



Linear (panel A) and nonlinear (panel B) dose-response analyses for infant death 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.

by placental dysfunction among obese women,[4] but few studies have had statistical power, sufficient information, or a combination of both to analyze these associations by causes of death. Thus further studies are needed to investigate the mechanisms involved. Maternal obesity has been associated with increased risk of preterm birth,[8,9] which accounts for approximately 29% of all neonatal deaths worldwide,[2] and of respiratory distress syndrome,[8] which is an important cause of death in preterm infants. In addition, maternal adiposity is associated with increased risk of macrosomia,[27,43,72] which in turn is associated with increased risk of neonatal and infant death[73,74] and deaths due to asphyxia and infections.[74]

Strengths of our meta-analysis include the detailed dose-response analyses, subgroup and sensitivity analyses, assessment of study quality, and the large sample size. The associations appeared to be independent of important confounding factors and most of the associations were robust to the influence of single studies. Because this analysis only included cohort studies, recall bias is not likely to have affected the results and there is also less potential for selection bias. The large sample size in this meta-analysis provided sufficient statistical power to detect significant associations. More studies are needed in low- and medium-income countries, and future studies should use more consistent definitions of outcomes and report definitions in the publications to increase comparability between studies. When possible, reporting on several different outcomes could also clarify differences in the risk associated with overweight and obesity for the different outcomes. In addition, further studies are needed to clarify the association between gestational weight gain and fetal and infant death.[75,76]

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.

ARTICLE INFORMATION

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