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Mortality in infants of obese mothers: is risk modified by mode of delivery?

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Abstract

Objective. To examine the association between maternal obesity and infant mortality, while including information about mode of delivery and interpregnancy weight change. *Design.* Register-based cohort study. *Setting and population.* A total of 1 199 183 singletons, including 3481 infant deaths, from the Swedish Birth Register 1992–2006. *Methods.* Maternal body mass index (BMI) was obtained from self-reports in early pregnancy and categorized as underweight (<18.5 kg/m^2), normal-weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30–34.9 kg/m^2) and extremely obese (≥35 kg/m^2). Cox regression was used to estimate hazard ratios (95% confidence intervals). Infants of normal-weight women were the referent. *Main outcome measures.* Neonatal and infant mortality. *Results.* Infant mortality increased with increasing maternal fatness [adjusted hazard ratios 1.2 (1.1–1.3), 1.4 (1.2–1.6) and 2.1 (1.8–2.5) for overweight, obesity and extreme obesity, respectively]. When accounting for mode of delivery, neonatal mortality was increased in infants of obese and extremely obese mothers after spontaneous births [adjusted hazard ratios 1.8 (1.4–2.4) and 2.6 (1.8–4.0), respectively, after term births, and 1.4 (1.1–1.9) and 2.2 (1.5–3.3), respectively, after preterm births]. No excess risk was present for infants of obese mothers after induced term and preterm births (p-values for interaction <0.05). For post-neonatal mortality, no interaction between mode of delivery and maternal obesity was observed. In women with two subsequent pregnancies, high interpregnancy weight change >1 BMI unit (1 kg/m^2) seemed to involve a modest increase in neonatal mortality in the second infant, but only after spontaneous births [adjusted odds ratio 1.3 (0.9–1.7)]. *Conclusions.* Maternal obesity, especially at levels that may involve cardiometabolic morbidity, was associated with increased mortality in the offspring.

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

Introduction

It is well established that maternal obesity correlates with increased risks of spontaneous abortion (1), stillbirth (2,3) and congenital malformations, especially those of the heart and the neural tube (4). Infants of obese mothers are more often born either very preterm or after prolonged gestation (5,6), and obese women have an increased risk of labor complications (7,8). Infants born to obese women are more often macrosomic, have lower Apgar scores and are more often admitted to a neonatal unit (5,6).

Nevertheless, it is not clear whether excess mortality in infants of obese mothers is caused by pregnancy complications, because previous studies have either been too small or lacked pregnancy data (5,9–13). Increases in weight between pregnancies have been shown to be a reproductive hazard in a second pregnancy, supporting a causal link between excess fat tissue and adverse pregnancy outcomes (14). Also, emerging

evidence indicates that prenatal exposure to maternal obesity may leave the child more susceptible to diseases and impaired health during the life course (15–18). Such susceptibility may also increase risk of death during the first year of life.

An increased risk of infant death in very preterm infants born to obese mothers was observed in British data from the 1980s (19). American data from the 1960s showed an obesity-related increased risk of perinatal mortality, mainly attributed to an increased risk of early preterm birth (20). In a previous study based on data from the Danish National Birth Cohort (12), we found that risk of neonatal death in infants of obese mothers was significantly higher in preterm infants born after premature preterm rupture of the membranes, but the number of deaths was small. We therefore carried out a large cohort study on maternal obesity and infant mortality using data from the Swedish Birth Register, which provided 1.2 million births, including more than 3400 infant deaths. The aim was to examine the association between maternal obesity and mortality in the first year of life, while accounting for the timing and subtype of birth, interpregnancy weight changes, and a number of important maternal and neonatal factors.

Material and methods

The Swedish Medical Birth Register was established in 1973 and includes more than 99% of all births in Sweden (21). Starting with the first antenatal visit, information is collected in standardized records on demographic characteristics, reproductive history, anthropometry (weight and height from 1992 onwards), complications during pregnancy and delivery, and neonatal outcomes. Using each person's unique registration number, the Birth Register can be linked to other Swedish data sources. For this study, we initially considered 1 423 183 singletons born during the period 1992–2006. We excluded 1889 singletons without information about gestational age at delivery. Furthermore, we restricted the final study population to the 1 199 328 singletons (84.3%) whose mothers had provided self-reported data needed to calculate pre-pregnancy body mass index (BMI; weight in kilograms divided by height in meters squared). Pre-pregnancy BMI was categorized according to the World Health Organization as follows: underweight (BMI <18.5 kg/m^2), normal weight ($18.5 \leq$BMI<25 kg/m^2), overweight ($25 \leq$BMI<30 kg/m^2), obese ($30 \leq$BMI<35 kg/m^2) and extremely obese (BMI ≥ 35 kg/m^2; 22).

Infant mortality was defined as death of a liveborn infant within the first 365 days of life. It was further divided into neonatal mortality (deaths within the first 28 days of life) and post-neonatal mortality (deaths after 28 days of life but before the first birthday).

Subtype and timing of birth was defined as follows. Spontaneous births were births where labor started with contractions or ruptured membranes, leading to a total of 990 516 spontaneous deliveries. Induced deliveries were births where induction or cesarean section had been carried out before the onset of labor ($n = 183\,790$). In 25 022 infants, we had no data to define a subtype of birth. Preterm birth was defined as birth of a liveborn child before 37 completed weeks of gestation. Gestational age was mainly estimated by ultrasound, because early second-trimester ultrasound is and was routinely offered to all pregnant women in Sweden, and 95% accept this offer (23). Related to findings from our previous study (12), we divided spontaneous preterm births into premature preterm rupture of the membranes and spontaneous labor without premature preterm rupture of the membranes by using ICD-9 and ICD-10 codes, but found similar excess risks of neonatal mortality in infants of obese mothers for these two types of deliveries. They were therefore combined into one category (spontaneous preterm birth), similar to the one applied to term births.

From the Birth Register, we also obtained information about the age of the mother at delivery, parity, smoking habits at the first antenatal visit, whether the woman was living with the father, and involuntary childlessness of longer than one year. The years of formal education and mother's country of birth were obtained by linking the Birth Register to the Education Register and the Register of the Total Population, respectively.

Information about medical complications and neonatal outcomes was also derived from the Birth Register. Based on ICD-9 and ICD-10 codes, we generated variables for all types of diabetes mellitus (gestational diabetes, type 1 and type 2 diabetes) and all types of hypertensive disorders (essential and gestational hypertension, pre-eclampsia and eclampsia). We obtained information about sex of the infant, birthweight, Apgar score and congenital malformations. Standardized birthweight for gestational age (z-score) was defined according to the reference curve given by Marsal et al. (24). Covariates were categorized according to Table 1.

We estimated hazard ratios (HRs) for the association between categorical maternal BMI and mortality in the first year of life by use of Cox regression. All infants were followed from birth to death or censored after 28 days (neonatal mortality) or 365 days of life (infant mortality). For post-neonatal mortality, infants entered the study after 28 days of life and were censored at death or after 365 days. Newborns born to normal-weight mothers served as reference. Beforehand, we planned the following adjustment strategy. In the first adjusted model, we controlled for the following maternal factors: age, parity, height, involuntary childlessness, smoking, cohabiting with the father of the infant, educational level and country of birth. In order to investigate whether neonatal factors may be in the causal pathway between BMI and neonatal mortality, we then extended the adjustment in a second model to include mode of delivery, gestational age in

Table 1. Maternal and neonatal characteristics by body mass index and early mortality.

Characteristic	All births[a] *n*	Pre-pregnancy body mass index (kg/m²) <18.5	18.5–24.9	25–29.9	30–34.9	≥35	Neonatal mortality Events/1000	Post-neonatal mortality Events/1000
Population (*n*)	1 199 328	33 016	776 956	279 969	80 228	29 159	2215	1266
Row percentages		2.8	64.8	23.3	6.7	2.4	1.8	1.1
Age at conception (years)				Column percentages				
<20	22 864	5.0	2.0	1.5	1.4	1.2	2.7	1.8
20–24	186 801	27.0	15.5	14.5	15.7	15.5	1.9	1.5
25–29	418 204	36.3	35.5	33.5	33.6	34.1	1.7	1.0
30–34	383 221	23.4	32.3	32.3	31.1	31.3	1.8	0.9
≥35	188 238	8.3	14.8	18.2	18.2	17.9	2.2	1.0
Parity								
Primipara	513 711	51.0	45.3	38.2	35.1	34.2	1.9	0.8
Second para	438 963	35.8	36.6	37.0	36.2	35.7	1.6	1.1
Multipara	246 654	13.3	18.2	24.8	28.7	30.1	2.2	1.5
Height (cm)								
<160	152 721	14.6	11.8	14.2	15.5	15.5	2.3	1.4
160–167	521 147	40.3	42.8	44.8	45.9	45.6	1.8	1.1
168–175	445 779	38.3	38.4	35.0	33.3	33.6	1.8	0.9
>175	79 681	6.8	7.1	6.0	5.4	5.4	1.5	0.9
Smoking								
Non-smoker	1 011 900	81.4	87.3	85.7	82.9	81.4	1.8	0.9
0–10 cigarettes/day	107 090	12.5	8.6	9.4	10.9	11.2	2.1	1.9
>10 cigarettes/day	52 819	6.1	4.0	4.9	6.1	7.4	2.8	3.1
Missing	27 519							
Mother's country of birth								
Sweden	1 000 467	75.4	84.6	82.3	82.4	84.8	1.8	1.0
Other Nordic countries	30 456	2.5	2.5	2.6	2.8	3.0	2.1	1.4
Other	165 219	22.1	13.0	15.1	14.9	12.2	2.1	1.2
Missing	3186							
Cohabiting with child's father								
Yes	1 105 589	92.0	95.2	95.1	94.3	93.6	1.8	1.0
No	58 699	8.0	4.8	4.9	5.7	6.4	2.4	1.8
Missing	35 040							
Educational level								
9 years compulsory school	138 302	20.0	11.4	14.0	17.5	20.3	2.2	1.9
Secondary school, 2 years	326 784	29.6	28.5	33.3	36.7	37.9	2.1	1.2
Secondary school, 3 years	246 519	22.5	22.6	23.5	24.2	25.1	1.6	0.8
Higher education, <3 years	173 183	13.5	17.3	14.9	11.9	9.3	1.7	0.7
Higher education, ≥3 years	190 448	14.4	20.2	14.5	9.8	7.4	1.5	0.7
Missing	124 092							
Childlessness >1 year	78 748	5.1	6.1	7.0	8.5	10.8	2.2	0.8
Obesity-related diseases in pregnancy								
Hypertensive disorders	48 212	2.2	3.0	5.1	8.1	11.2	4.5	1.9
Any diabetes	15 531	0.5	0.8	1.7	3.2	5.8	2.8	1.5
Mode of delivery								
Cesarean section	161 162	10.1	11.7	15.7	19.6	24.3	6.3	2.3
Operative vaginal	85 783	7.2	7.4	7.0	6.2	5.8	1.5	0.8
Spontaneous vaginal	952 383	82.7	80.9	77.4	74.2	69.9	1.1	0.9
Sex of infant								
Male	615 858	50.7	51.3	51.4	51.5	51.6	2.1	1.2
Female	583 470	49.3	48.7	48.6	48.5	48.4	1.6	0.9
Apgar score at five minutes								
7–10	1 178 598	98.4	98.4	98.1	97.8	97.3	0.7	0.9
4–6	9333	0.6	0.7	0.9	1.2	1.5	50.4	11.5
0–3	2856	0.2	0.2	0.3	0.3	0.4	204.1	12.8
Not reported	8541	0.8	0.7	0.7	0.7	0.8	33.7	5.3
Congenital malformations	26 914	1.9	2.1	2.4	2.6	3.1	14.0	7.8

Table 1. Continued.

Characteristic	All births[a] *n*	Pre-pregnancy body mass index (kg/m^2) <18.5	18.5–24.9	25–29.9	30–34.9	≥35	Neonatal mortality Events/1000	Post-neonatal mortality Events/1000
Gestational days, mean	281.3	279.5	281.1	281.6	281.9	282.2	242.4	266.9
Gestational days, standard deviation	14.1	14.6	13.7	14.3	15.3	16.5	43.3	31.0
Birthweight z-score[b], mean	0.05	−0.44	−0.04	0.21	0.33	0.46	−0.75	−0.64
Birthweight z-score[b], standard deviation	1.10	0.97	1.05	1.13	1.22	1.33	2.03	1.50

Data are expressed as percentages, events/1000 (two last columns), numbers (first column and first row), or means (SD) (four last rows).

[a] Live singleton births with information about maternal body mass index prior to pregnancy.

[b] Standardized birthweight for gestational age.

days, Apgar score at five minutes, standardized birthweight z-score and the presence of malformations. In a third model, we restricted the fully adjusted analysis to infants without congenital malformations and with mothers without hypertensive disorders and diabetes.

Next, we investigated whether the association between maternal BMI and neonatal mortality was modified by the timing (term or preterm) or type of delivery (spontaneous or induced). Thus, we included these two variables in the model, while adding an interaction term with maternal BMI for both of them. In this model, we also investigated the association between maternal BMI, added as a continuous variable, and neonatal mortality.

To examine associations between excess maternal fatness and early survival better, we identified women who provided information on both their first and second livebirth (n = 272 185). We calculated the interpregnancy weight change in BMI units (kg/m^2) and divided it into the following categories: <–1, –1 to 1, 1 to <2, 2 to <3 and ≥3. One BMI unit is equivalent to approximately 3 kg in a woman of average height in Sweden. We estimated odds ratios for neonatal mortality in the infant born after the second pregnancy according to interpregnancy weight change. The category '–1 to 1' served as referent. In a subsequent analysis, we adjusted for maternal age (≤24, 25–29, 30–34 and ≥35 years) and smoking (yes/no) in a second pregnancy, education level by December 2005 (≤9, 10–11, 12, 13–14 and ≥15 years) and BMI before the first pregnancy (≤18.5, 18.5–24.9, 25–29.9 and ≥30 kg/m^2). This methodological approach has been reported in more detail elsewhere (14).

A two-sided significance level of 0.05 was used in all statistical tests, and hazard ratios are presented with 95% confidence intervals (CIs). Effect modification was assessed by computing ratios of hazard ratios. The assumption of no effect modification was accepted if this ratio did not differ significantly from one. All analyses were done in STATA version 9.0 (StataCorp, College Station, TX, USA). The study was approved by the Research Ethics Committee at Karolinska Institute, Stockholm (number 2011/195-31/2). The data set did not include personal identifiers or any other variables that made it possible to identify the individual woman. Informed consent was therefore not required by the research ethics committee.

Results

Twenty-three per cent of infants were born to overweight women (BMI 25–29.9 kg/m^2) and 9% to women who were obese (BMI ≥30 kg/m^2) prior to pregnancy. Compared with normal-weight mothers, mothers who had a pre-pregnancy BMI of 25 kg/m^2 or more were older, of higher parity, smoked more during pregnancy, had a lower educational level and were less often cohabiting with the father of the infant (Table 1). The frequency of involuntary childlessness of at least one year increased across BMI categories, as did frequencies of diabetes, hypertensive disorders and the risk of having a cesarean section. Birthweight and length of gestation also increased across maternal BMI categories. Likewise, the chance of giving birth to a male infant, the risk of a low Apgar score at five minutes and the prevalence of malformations were positively related to maternal BMI.

We observed 3481 deaths during the first year of life (infant mortality rate 2.9 per 1000 live births). Of these, 2215 occurred during the first 28 days of life (neonatal deaths) and 1266 thereafter (post-neonatal deaths). Associations between maternal and neonatal characteristics and rates of neonatal and post-neonatal mortality are presented in Table 1.

The infant mortality rate increased with increasing maternal obesity from 2.6 in normal-weight mothers to 3.3 in overweight, 3.7 in obese and 5.7 in extremely obese mothers (Table 2). After adjustment for maternal factors, the excess mortality risk was 20% in overweight women, 40% in obese women and 110% in extremely obese women. Further adjustments for neonatal factors only attenuated these associations slightly. Also, restricting the fully adjusted analyses to infants without congenital malformations and to mothers without

Table 2. Risk of early mortality according to maternal body mass index.

		Crude	Adjusted[a]		Adjusted[b]	
Pre-pregnancy BMI (kg/m^2)	Events/1000	HR	HR	95% CI	HR	95% CI
Infant mortality (n = 1 199 328, with 3481 deaths)						
−18.5	2.9	1.1	1.0	0.8–1.3	0.9	0.7–1.1
18.5–24.9	2.6	1.0	1.0	Reference	1.0	Reference
25–29.9	3.3	1.3	1.2	1.1–1.3	1.3	1.1–1.4
30–34.9	3.7	1.4	1.4	1.2–1.6	1.3	1.2–1.5
≥35	5.7	2.2	2.1	1.8–2.5	1.9	1.5–2.2
Neonatal mortality (n = 1 199 328, with 2215 deaths)						
−18.5	1.7	1.0	0.9	0.7–1.3	0.8	0.6–1.1
18.5–24.9	1.6	1.0	1.0	Reference	1.0	Reference
25–29.9	2.1	1.3	1.2	1.1–1.4	1.2	1.1–1.4
30–34.9	2.4	1.5	1.5	1.3–1.8	1.4	1.1–1.6
≥35	3.7	2.3	2.2	1.8–2.8	1.8	1.4–2.2
Post-neonatal mortality (n = 1 197 113, with 1266 deaths)						
−18.5	1.3	1.3	1.2	0.8–1.7	1.0	0.7–1.4
18.5–24.9	0.9	1.0	1.0	Reference	1.0	Reference
25–29.9	1.2	1.3	1.2	1.0–1.4	1.3	1.1–1.5
30–34.9	1.2	1.3	1.1	0.9–1.4	1.2	1.0–1.6
≥35	2.0	2.1	1.9	1.4–2.6	2.0	1.5–2.7

Abbreviations: BMI, body mass index; CI, confidence interval; and HR, hazard ratio.

[a] Adjusted for age at birth, parity, height, involuntary childlessness ≥1 year, smoking in pregnancy, cohabiting with father, educational level and mother's country of birth.

[b] Adjusted as above and also for mode of delivery, gestational age (in days), standardized birthweight (z-score), Apgar score after five minutes and congenital malformations.

obesity-related diseases during pregnancy produced essentially similar results (data not shown).

We repeated these analyses for neonatal and post-neonatal mortality. The patterns observed were the same for both outcomes, although the associations between maternal obesity and extreme obesity seemed to be slightly stronger for neonatal mortality [adjusted HRs 1.5 (95% CI 1.3–1.8) and 2.2 (95% CI 1.8–2.8), respectively] than for post-neonatal mortality [adjusted HRs 1.1 (95% CI 0.9–1.4) and 1.9 (95% CI 1.4–2.6), respectively].

Table 3 displays risks of neonatal mortality by time (term or preterm) and type of birth (spontaneous or induced). The crude rates of neonatal mortality increased with increasing maternal BMI in infants born after spontaneous term and preterm deliveries (Table 3). For spontaneous term births, the adjusted risk of neonatal mortality increased with 5% per one BMI unit increase (p-value for trend <0.001), while for spontaneous preterm births the corresponding increase was 4% (p-value for trend <0.001).

Compared with infants of normal-weight mothers, the excess risk of neonatal mortality in infants born after a spontaneous term delivery was 80% among obese mothers and 160% among extremely obese mothers (Table 3). For spontaneous preterm delivery, the same pattern was seen, with excess mortality risks of 40 and 120% in obese and extremely obese mothers, respectively. Further adjustment for neonatal factors that may explain some of the excess mortality in infants of obese women only attenuated the excess risk related to extreme maternal obesity slightly. Excluding infants born to women with obesity-related diseases and infants with congenital malformations produced results similar to those reported above (data not shown).

For induced deliveries, no excess risk was found in any period (p-values for effect modification by mode of delivery <0.05 for all six ratios of hazard ratios related to continuous BMI, obesity and extreme obesity; Table 3). In analysis of post-neonatal mortality, we found that mode of delivery did not modify the association between maternal obesity and mortality (data not shown).

Table 4 shows associations between interpregnancy weight change and neonatal mortality in 272 185 infants born after a second pregnancy. For spontaneous births, odds for neonatal death were increased by 40–50% in women who gained weight between pregnancies compared with women having no weight gain. Adjustment for a range of factors, including maternal BMI, attenuated these associations, but overall,

Table 3. Maternal body mass index and risk of neonatal mortality according to timing and subtype of birth[a].

	Events/ 1000	Crude HR	Adjusted[b] HR	Adjusted[b] 95% CI	Adjusted[c] HR	Adjusted[c] 95% CI
TERM BIRTHS						
Spontaneous (n = 950 076, with 683 deaths)						
Pre-pregnancy BMI (kg/m^2)						
<18.5	0.7	1.1	1.0	0.6–1.8	1.0	0.6–1.7
18.5–24.9	0.6	1.0	1.0	Reference	1.0	Reference
25.0–29.9	0.8	1.2	1.2	1.0–1.5	1.2	1.0–1.5
30–34.9	1.1	1.8	1.8	1.4–2.4	1.8	1.3–2.5
≥35	1.7	2.7	2.6	1.8–4.0	2.3	1.4–3.6
Per one BMI unit increase		1.05	1.05	1.04–1.07	1.05	1.03–1.07
Induced (n = 168 913, with 291 deaths)						
Pre-pregnancy BMI (kg/m^2)						
<18.5	1.5	0.9	0.9	0.3–2.3	1.0	0.4–2.7
18.5–24.9	1.6	1.0	1.0	Reference	1.0	Reference
25.0–29.9	1.9	1.2	1.2	0.9–1.5	1.2	0.9–1.6
30–34.9	1.5	0.9	1.0	0.6–1.5	1.1	0.7–1.7
≥35	2.2	1.3	1.3	0.7–2.2	1.4	0.8–2.5
Per one BMI unit increase		1.01	1.01	0.99–1.04	1.02	0.99–1.04
PRETERM BIRTHS						
Spontaneous (n = 40 440, with 711 deaths)						
Pre-pregnancy BMI (kg/m^2)						
<18.5	12.2	0.7	0.7	0.4–1.1	0.8	0.4–1.3
18.5–24.9	16.5	1.0	1.0	Reference	1.0	Reference
25.0–29.9	18.8	1.1	1.1	0.9–1.3	1.2	1.0–1.5
30–34.9	21.2	1.3	1.4	1.1–1.9	1.4	1.0–1.9
≥35+	34.4	2.1	2.2	1.5–3.3	2.1	1.4–3.1
Per one BMI unit increase		1.04	1.04	1.03–1.06	1.04	1.02–1.06
Induced (n = 14 877, with 392 deaths)						
Pre-pregnancy BMI (kg/m^2)						
<18.5	18.9	0.7	0.6	0.3–1.5	0.5	0.2–1.3
18.5–24.9	26.6	1.0	1.0	Reference	1.0	Reference
25.0–29.9	27.1	1.0	1.0	0.8–1.3	1.0	0.8–1.3
30–34.9	25.5	1.0	0.9	0.6–1.3	1.0	0.7–1.5
≥35	25.0	0.9	0.9	0.5–1.6	0.9	0.5–1.7
Per one BMI unit increase		1.00	1.00	0.98–1.02	1.01	0.98–1.03

Abbreviations: BMI, body mass index; CI, confidence interval; and HR, hazard ratio. One BMI unit (1 kg/m^2) is equivalent to approximately 3 kilos in a Swedish woman of average height.

[a] n = 1 174 306 liveborn singletons.

[b] Adjusted for age at birth, parity, height, involuntary childlessness ≥1 year, smoking in pregnancy, cohabiting with father, educational level and mother's country of birth.

[c] Adjusted as above and also for mode of delivery, gestational age (in days), standardized birthweight (z-score), Apgar score after five minutes and congenital malformations.

weight gain >1 kg/m^2 seemed to be associated with a modest increased risk of neonatal mortality [adjusted odds ratio 1.3 (95% CI 0.9–1.7)]. This pattern was less consistent for all births.

Discussion

Maternal obesity was associated with an increased risk of infant mortality. This is in accordance with most previous studies that report obesity-related excess mortality in the first year of life (9,10,13,19,25), in the neonatal (5,10–13,13,20,26) and in the post-neonatal period (10,13). In agreement with our observations, associations were stronger for neonatal than for post-neonatal mortality (10,13) and were especially high in infants of extremely obese women (25).

In the neonatal period, maternal obesity was mainly related to excess mortality in newborns born after a spontaneous

Table 4. Interpregnancy weight change and neonatal mortality for second infant in women with two successive pregnancies.

Interpregnancy weight change (BMI units)	Crude		Adjusted[a]	
	OR	95% CI	OR	95% CI
All births (272 572 infants, with 387 neonatal deaths)				
<−1	1.1	0.8–1.6	1.1	0.7–1.5
−1 to 1	1.0	Reference	1.0	Reference
1 to <2	1.3	1.0–1.7	1.2	0.9–1.6
2 to <3	1.3	0.9–1.8	1.3	0.9–1.9
≥3	1.2	0.9–1.7	1.1	0.7–1.5
Spontanous births only (230 094 infants, with 215 neonatal deaths)				
<−1	1.2	0.8–1.9	1.1	0.7–1.8
−1 to 1	1.0	Reference	1.0	Reference
1 to <2	1.4	1.0–2.0	1.2	0.8–1.8
2 to <3	1.4	0.9–2.2	1.4	0.9–2.2
≥3	1.5	1.0–2.4	1.3	0.8–2.2

Abbreviations: BMI, body mass index; CI, confidence interval; and OR, odds ratio. One BMI unit (1 kg/m^2) is equivalent to approximately 3 kg in a Swedish woman of average height.

[a] Adjusted for age and smoking at second pregnancy, education level by December 2005 and pre-pregnancy BMI at first pregnancy.

preterm or term delivery. This pattern was also present after adjustment for maternal and neonatal complications, which is in agreement with our previous report (12), but has to our knowledge not been reported by others. We speculate that the obesity-related excess neonatal mortality in preterm and term spontaneous deliveries may be associated with perturbed cardiometabolic profiles, because dyslipidemia, elevated leptin concentrations, insulin resistance, hyperglycemia, low-grade infection, endothelial dysfunction and elevated blood pressure all increase with severity of obesity (27–29). However, these markers of subclinical disease do not necessarily give symptoms during pregnancy, and available diagnostic tools may not define them as complications that should be acted upon. It is noteworthy that the highest mortality rate was seen in extremely obese women with spontaneous preterm birth, where disease or fetal crisis may be difficult to diagnose because of the excess fat tissue. This may leave the disease to progress unattended and eventually lead to spontaneous termination of pregnancy.

In contrast to the findings with spontaneous preterm and term deliveries, obesity was not associated with excess neonatal mortality risk in induced deliveries. Compared with normal-weight women, obese women have more pregnancy complications leading to induced delivery, but morbidity within the group of induced pregnancies probably does not differ across BMI groups. Thus, irrespective of mother's BMI, induced preterm and term newborns may have similarly high risks of having experienced a harmful fetal environment that may impair their chances of survival.

Maternal obesity was associated with increased risk of postneonatal mortality. This finding indicates that harmful effects of maternal obesity may extend beyond the first acute phase of survival. It has been suggested that fetal exposure to an obesigenic environment may leave the child more susceptible to diseases and impaired health that may present in different ways along the life course (15–18). Early excess mortality could be a manifestation of this susceptibility in the early period of life, when humans are especially vulnerable.

While these associations are strong and probably not due to chance, they do not necessarily represent causal links. Unmeasured factors, such as genes or insulin resistance caused by epigenetic changes, may cause both maternal obesity and early childhood mortality. To examine better whether mortality may be causally related to excess maternal fat tissue, we included an analysis of weight gain in the interpregnancy interval and neonatal mortality in the second infant. Although the increase in mortality risk with increasing maternal weight gain was small and did not reach statistical significance, it does not speak against a causal relation between morbid obesity and neonatal mortality. In women with this phenotype, obesity may often be present already before they start their reproductive period, and they are less likely to gain weight from the first pregnancy to the next (8,14). Also, it seems plausible that the observed association is mainly caused by harmful exposure to morbid obesity over a certain threshold and not excess fat as a continuous measure, but traditional observational data lack details to answer this question. For more frequent outcomes, additional empirical support can be provided by studies of obese women after bariatric surgery (30), studies including information on gene variants coding for the obese phenotype (31), and long-term follow up of randomized controlled trials of obese women with intentional weight loss. However, infant deaths are so rare that it restricts the potential for sound empirical evidence.

The strengths of the present study include its size and the population-based design. As we relied solely on register data, the women did not have to actively agree to participate, and it was also possible to have almost full follow up, keeping selection problems to a minimum. We believe, therefore, that our findings were not subject to selection bias. It should, however, be stressed that the observed associations only apply to affluent countries with similar low rates of infant mortality and high-quality antenatal care.

The availability of data from the high-quality Birth Register provided information about a large number of maternal as well as birth characteristics that could confound the association between maternal obesity and early mortality. Information was reported in the registry prior to birth, so any misclassification would most probably be nondifferential and lead to an underestimation of the true effect. We included more than one million births, which enabled us to

provide robust estimates and still carry out detailed analyses of the associations under study.

There are also limitations. Although we examined a wide range of maternal and neonatal factors, we were not able to identify mediators of the excess mortality risk related to maternal obesity. The same has been reported by others (9,11–13,19). In contrast, Chen et al. found that maternal obesity was most strongly associated with neonatal deaths related to maternal complications, low birthweight and short gestation and only weakly with deaths due to respiratory conditions, malformations and sudden infant death syndrome (10). Information about cause of death in deceased infants was unfortunately not available in our study. Clinical data on the entire disease process may further our understanding of the underlying mechanisms and could be an option in large register-based studies in the future owing to the widespread use of electronic patient records.

In conclusion, this study emphasizes that maternal obesity is a serious health problem that may have effects exceeding the perinatal period. In particular, extreme obesity may involve cardiometabolic changes harmful to the fetus, which should be taken into consideration in antenatal care.

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