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Maternal Obesity and Risk of Early-onset Neonatal Bacterial Sepsis: Nationwide Cohort and Sibling-controlled Studies

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Background. Maternal overweight and obesity are related to risks of pregnancy and delivery complications that, in turn, are associated with newborn infections. We examined the associations between early pregnancy body mass index (BMI; kg/m^2) and risk of early-onset neonatal bacterial sepsis (EOS).

Methods. We conducted a nationwide population-based retrospective cohort study of 1 971 346 live singleton infants born in Sweden between 1997 and 2016. Outcome was a culture-confirmed EOS diagnosis. We estimated hazard ratios (HR) of EOS according to BMI using proportional hazard models, and identified potential mediators. Among term infants, we conducted sibling-controlled analyses.

Results. EOS risk per 1000 live births was 1.48; 0.76 in term and 15.52 in preterm infants. Compared with infants of normal-weight mothers (BMI, 18.5–24.9), the adjusted HR (95% confidence interval [CI]) of EOS for BMI categories <18.5, 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40.0 were, respectively, 1.07 (.83–1.40), 1.19 (1.08–1.32), 1.70 (1.49–1.94), 2.11 (1.73–2.58), and 2.50 (1.86–3.38). Maternal overweight and obesity increased the risk of EOS by group B *Streptococcus*, *Staphylococcus aureus*, and *Escherichia coli*. Half of the association was mediated through preeclampsia, cesarean section delivery, and preterm delivery. A dose-response association was consistently apparent in term infants only. In sibling-controlled analyses, every kilogram per meter squared interpregnancy BMI change was associated with a mean 8.3% increase in EOS risk (95% CI, 1.7%–15.3%; $P = .01$).

Conclusions. Risk of EOS increases with maternal overweight and obesity severity, particularly in term infants.

Keywords. neonatal sepsis; maternal obesity; body mass index; pregnancy.

Sepsis is a major cause of infant morbidity and mortality, affecting 3 million newborns each year [1] and accounting for 15% of all neonatal deaths worldwide [2]. Early-onset neonatal sepsis (EOS) usually results from mother-to-infant transmission of bacteria and is typically diagnosed during the first 72 hours of life [3, 4]. EOS is most frequently caused by maternal genitourinary and intestinal bacteria, including group B *Streptococcus* (GBS) and *Escherichia coli* [5], often transmitted during delivery.

Risk factors for EOS involve perinatal conditions such as maternal chorioamnionitis, prolonged rupture of membranes, and obstetric procedures during labor or delivery. Infant characteristics include preterm birth, low birth weight, congenital malformations, low Apgar score, and male sex [6]. However, few prepregnancy factors are known. Obesity may be relevant because it is a risk factor for pregnancy and delivery complications that might lead to neonatal infection; it has been related to increased risks of severe infections in infants [7] and neonatal mortality [8]. Obesity could also impair B lymphocyte production of antibodies against bacteria [9], and diminished transplacental transfer of antibodies is related to increased susceptibility to neonatal GBS infection [10, 11]. An association between maternal obesity and neonatal sepsis has been suggested [12, 13] but it has not been interrogated in population-based studies with a sufficiently large sample size to allow analyses by specific bacteria and assessment of potential mechanisms.

Our aim in this nationwide study was to examine the association between early pregnancy body mass index (BMI) and risk of EOS. Secondary aims were to ascertain the associations of BMI with EOS by specific bacteria and to identify potential mediators of the association. To enhance causal inference, we also performed sibling-controlled analyses.

METHODS

Study Design

We conducted a population-based, retrospective cohort study among live singleton infants born at ≥22 completed gestational weeks who were recorded in the Swedish Medical Birth Register from 1997 through 2016. Information in the Birth

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Register [14] was cross-linked with the National Patient- [15], Cause of Death- [16], Total Population- [17], Education- [18], and Multigeneration [19] Registers, using the person-unique national registration number that is assigned to all Sweden residents [20]. The Birth Register includes prenatal, obstetric, and neonatal care data on more than 98% of all births. The National Patient Register includes diagnoses at discharge from hospital admissions, coded according to the *International Classification of Diseases*, *Tenth Revision* (ICD-10), since 1997.

The Regional Ethical Review Board in Stockholm, Sweden, approved the study. Informed consent was not required because all data were anonymous.

Exposure

Early pregnancy BMI (kg/m^2) was calculated from height and weight as recorded in the Birth Register. Height was self-reported and weight was measured in light clothing at the first prenatal visit, which occurred at a median 10.3 gestation weeks (interquartile range [IQR], 8.9–12.0). BMI (kg/m^2) was classified as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), obesity grade 1 (30.0–34.9), obesity grade 2 (35.0–39.9), and obesity grade 3 (≥40.0) [21]. BMI was also considered a continuous variable.

Outcome

Culture-confirmed bacterial sepsis was defined as a hospital discharge primary or secondary ICD-10 diagnostic code P36.0–P36.8 per the National Patient Register or the Cause of Death Register. These codes involve clinical infection together with bacterial growth in blood cultures. Distinguishing early from late-onset neonatal sepsis (LOS) requires the date of infection, but this information was unavailable. Therefore, we used the date of admission to a neonatal unit as proxy and defined EOS as admission within 72 hours from birth [3] with a discharge diagnosis of bacterial sepsis. The primary outcome was culture-confirmed EOS of any etiology. Secondary outcomes were EOS by specific bacteria (ICD-10 codes in Supplementary Table 1).

Covariates

Maternal age at delivery was the date of delivery minus the mother's birth date. Mothers' country of birth was categorized as Nordic vs non-Nordic. Maternal education was the highest level of schooling achieved. Information on whether the mother cohabited with a partner was obtained at the first prenatal visit. Parity was the number of births of each mother. Smoking was determined by self-report at either the first prenatal visit or in the third trimester; this has been validated with cotinine markers [22]. Gestational age in completed weeks was obtained by early second trimester ultrasound, date of the last menstrual period, or a postnatal assessment in 84.8%, 9.2%, and 6.0%, respectively. Birth weight for gestational age was defined using the ultrasound-based Swedish reference for fetal growth [23]. The Multigeneration Register allowed us to identify full siblings. ICD-10 codes for diseases in mothers and children are provided in Supplementary Table 1.

Statistical Analyses

We estimated adjusted hazard ratios (AHRs) of EOS with 95% confidence intervals (CIs) by categories of covariates from Cox proportional hazards models. Infants with EOS were censored at day of admission, and infants without EOS were censored at day 3 or on the day of death, whichever occurred first. The robust sandwich estimate of the covariance matrix was used to compute 95% CI accounting for the correlation of measures among women with more than 1 pregnancy in the dataset. Next, EOS risks were calculated in each BMI level and compared against women of normal BMI using AHRs, 95% CIs, and tests for trend. Adjustment covariates involved maternal age, country of origin, education level, cohabitation with a partner, parity, height, smoking during pregnancy, and year of delivery. We assessed whether the association between BMI and EOS was linear by testing linear and nonlinear spline terms [24] for BMI as continuous predictors (Supplementary Figure 1). None of the nonlinear terms offered a better fit than the linear term for BMI; thus, we estimated the HR per BMI unit difference with BMI as a continuous predictor. The proportional hazards assumption was verified by testing products of covariates and the log of follow-up time. We examined the associations of maternal BMI with risk of EOS by specific bacteria following an analogous approach.

To account for competing risks by early death, we conducted supplemental analyses with use of proportional subdistribution hazards models [25]. Nine percent of women had missing data on BMI and were excluded from the analyses. Therefore, we conducted further supplemental analyses to estimate missing values on BMI and covariates with a Markov chain Monte Carlo multiple imputation method before their inclusion in the multivariable models [26]. Results from 10 multiply-imputed datasets were combined with use of the PROC MIANALYZE routine of Statistical Analysis Software (SAS).

We assessed whether the associations between maternal BMI and EOS were mediated through consequences of maternal obesity that were also predictors of EOS (causal diagram in Supplementary Figure 2) under the assumptions of a counterfactual frame, as described in detail elsewhere [27–29]. Because the association of BMI with EOS was linear, we used BMI as a continuous exposure. We modeled the exposure-mediator and exposure-outcome relations with multivariable logistic and Cox regression, respectively, and considered interactions between BMI and the mediator.

Because gestational age was a strong effect modifier, we examined the association of BMI with EOS stratified by gestational age. The association was only apparent among term infants; thus, we repeated the bacteria-specific and mediation

analyses in this group only. Also in term infants, we conducted sibling-controlled analyses to enhance control for shared familial confounders using Cox models stratified by family. We introduced spline terms for BMI to account for nonlinearity of the association and birth order. All analyses were conducted with use of SAS version 9.4 (SAS Institute).

RESULTS

From 1997 through 2016, the Birth Register included information on 2 003 907 live singleton births. After excluding 30 124 and 1285 births with missing maternal and infant national registration numbers, respectively, and 1152 births with missing information on gestational age, 1 971 346 (98.4%) births were included in the study.

Perinatal Characteristics and Risk of EOS

There were 2913 cases of culture-confirmed EOS (risk per 1000 live births, 1.48). Maternal age, primiparity, height <165 cm, smoking during pregnancy, pregestational diabetes, pregestational hypertension, preeclampsia, infections, chorioamnionitis, and delivery before 2000 were positively associated with risk of EOS (Supplementary Table 2). Premature rupture of membranes and vaginal instrumental or cesarean section delivery were associated with increased risks of EOS. In term infants (≥37 weeks), only emergency cesarean section delivery was associated with increased EOS risk (AHR, 2.61; 95% CI, 2.24–3.05), whereas elective cesarean section was related to lower risk (AHR, 0.52; 95% CI, .37–.71). In preterm infants (<37 weeks), both elective (AHR, 2.76; 95% CI, 2.37–3.22) and emergency (AHR, 2.14; 95% CI, 1.81–2.52) cesarean section deliveries were related to increased EOS risk.

Gestational age was inversely related to EOS risk in a dose-response manner. EOS risk per 1000 in term and preterm infants was 0.76 and 15.52, respectively. Infant characteristics associated with increased risks included male sex, congenital malformations, macrosomia (birth weight ≥4000 g), low or high birth weight for gestational age (<3rd or >90th percentile), meconium aspiration, and Apgar score at 5 minutes <7.

Maternal BMI and Risk of EOS

Compared with infants of mothers with normal BMI, adjusted risks of EOS were 1.2, 1.7, 2.1, and 2.5 times higher for infants of mothers with overweight and obesity grades 1 through 3, respectively (Table 1). The association remained unchanged after accounting for competing risks (Supplementary Table 3). The 9% of women with missing data on BMI differed slightly from women with BMI information with respect to other maternal, pregnancy, and perinatal characteristics (Supplementary Table 4). Nevertheless, the association between maternal BMI and EOS did not change after accounting for missing data in multiple imputation analyses (Supplementary Table 5).

Maternal BMI and Risk of EOS by Specific Bacteria

Risk of EOS by GBS was 0.44 per 1000 live births (Supplementary Table 6). Maternal overweight and obesity were related to increased risks of EOS by GBS, *S. aureus*, other staphylococci, and *E. coli* in dose-response fashions (Table 2). Underweight was related to a 4.6 times higher risk of EOS by *E. coli*.

Table 1. Early Pregnancy Body Mass Index and Risk of Early-onset Neonatal Sepsis

Maternal Body Mass Index,[a] kg/m^2	No. of Infants[b]	Early-onset Neonatal Sepsis		Unadjusted HR (95% CI)[c]	Adjusted HR (95% CI)[d]
		No.	Risk/1000 Live Births		
<18.5	44 505	58	1.30	1.08 (.83–1.40)	1.07 (.83–1.40)
18.5–24.9	1 095 338	1327	1.21	1.00	1.00
25.0–29.9	445 478	636	1.43	1.18 (1.07–1.30)	1.19 (1.08–1.32)
30.0–34.9	148 002	305	2.06	1.70 (1.50–1.93)	1.70 (1.49–1.94)
35.0–39.9	45 151	110	2.44	2.01 (1.65–2.45)	2.11 (1.73–2.58)
≥40.0	15 806	45	2.85	2.35 (1.75–3.17)	2.50 (1.86–3.38)
Missing	177 066	432	2.44		
P, trend[e]				<.0001	<.0001
Per 1 kg/m^2				1.05 (1.04–1.05)	1.05 (1.04–1.06)
Per 10 kg/m^2 [f]				1.54 (1.43–1.65)	1.56 (1.45–1.69)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Body mass index calculated as weight in kilograms divided by height in meters squared.

[b]Live-born singleton infants in Sweden 1997–2016.

[c]From a Cox proportional hazards model with day of hospital admission for sepsis as the outcome.

[d]From a Cox proportional hazards model with day of hospital admission for sepsis as the outcome adjusted for maternal age, country of origin, education level, cohabitation with a partner, parity, height, smoking during pregnancy, and year of delivery. Complete case analyses including 2390 cases among 1 743 107 infants.

[e]Wald test when a variable representing ordinal categories of the predictor was introduced into the regression model as a continuous covariate.

[f]Ten units is the difference in median body mass index of women with obesity (32.8 kg/m^2) and without obesity (23.1 kg/m^2).

Table 2. Early Pregnancy Body Mass Index and Risk of Early-onset Neonatal Sepsis by Specific Bacteria

Bacteria	No. of Infants[a]	Early-onset Neonatal Sepsis		Unadjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
		No.	Risk/1000 Live Births		
Group B *Streptococcus*					
Maternal BMI,[d] kg/m^2					
<18.5	44 505	13	0.29	0.75 (.43–1.31)	0.73 (.41–1.31)
18.5–24.9	1 095 338	425	0.39	1.00	1.00
25.0–29.9	445 478	199	0.45	1.15 (.97–1.36)	1.21 (1.01–1.43)
30.0–34.9	148 002	90	0.61	1.57 (1.25–1.97)	1.71 (1.35–2.16)
35.0–39.9	45 151	39	0.86	2.23 (1.59–3.12)	2.41 (1.70–3.41)
≥40.0	15 806	14	0.89	2.29 (1.34–3.89)	2.56 (1.49–4.38)
Missing	177 066	86	0.49		
P, trend[e]				<.0001	<.0001
Per 1 kg/m^2				1.05 (1.03–1.06)	1.05 (1.04–1.07)
Per 10 kg/m^2 [f]				1.55 (1.37–1.77)	1.67 (1.46–1.90)
Staphylococcus aureus					
Maternal BMI, kg/m^2					
<18.5	44 505	7	0.16	1.17 (.55–2.50)	1.20 (.56–2.56)
18.5–24.9	1 095 338	147	0.13	1.00	1.00
25.0–29.9	445 478	74	0.17	1.24 (.94–1.64)	1.20 (.90–1.60)
30.0–34.9	148 002	38	0.26	1.91 (1.34–2.73)	1.95 (1.35–2.82)
35.0–39.9	45 151	14	0.31	2.31 (1.34–4.00)	2.40 (1.36–4.24)
≥40.0	15 806	8	0.51	3.78 (1.85–7.69)	3.96 (1.93–8.14)
Missing	177 066	62	0.35		
P, trend				<.0001	<.0001
Per 1 kg/m^2				1.06 (1.04–1.08)	1.06 (1.04–1.08)
Per 10 kg/m^2				1.74 (1.43–2.12)	1.76 (1.42–2.18)
Other staphylococci					
Maternal BMI, kg/m^2					
<18.5	44 505	20	0.45	1.27 (.81–1.98)	1.26 (.80–1.98)
18.5–24.9	1 095 338	389	0.36	1.00	1.00
25.0–29.9	445 478	190	0.43	1.20 (1.01–1.43)	1.20 (1.00–1.43)
30.0–34.9	148 002	92	0.62	1.75 (1.39–2.20)	1.56 (1.23–1.99)
35.0–39.9	45 151	23	0.51	1.43 (.94–2.18)	1.47 (.96–2.24)
≥40.0	15 806	12	0.76	2.14 (1.20–3.80)	2.19 (1.23–3.90)
Missing	177 066	190	1.07		
P, trend				<.0001	<.0001
Per 1 kg/m^2				1.04 (1.02–1.05)	1.03 (1.02–1.05)
Per 10 kg/m^2				1.43 (1.25–1.63)	1.37 (1.18–1.58)
Escherichia coli					
Maternal BMI, kg/m^2					
<18.5	44 505	8	0.18	4.38 (1.06–9.28)	4.62 (2.17–9.85)
18.5–24.9	1 095 338	45	0.04	1.00	1.00
25.0–29.9	445 478	27	0.06	1.48 (.92–2.38)	1.53 (.94–2.47)
≥30.0	208 959	17	0.11	2.56 (1.54–4.27)	2.47 (1.42–4.29)
Missing	177 066	17	0.10		
P, trend				.05	.10
Per 1 kg/m^2				1.04 (1.00–1.08)	1.03 (.99–1.08)
Per 10 kg/m^2				1.41 (.96–2.07)	1.37 (.91–2.08)

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

[a]Live-born singleton infants in Sweden 1997–2016.

[b]From Cox proportional hazards models with day of hospital admission for sepsis by each agent as the outcome.

[c]HRs and 95% CIs from Cox proportional hazards models with robust estimates of variance. The outcome was day of hospital admission for sepsis by each agent. Covariates included maternal age, country of origin, education level, cohabitation with a partner, parity, height, smoking during pregnancy, and year of delivery. Complete case analyses per etiologic agent included 758 infections by group B *Streptococcus*, 274 infections by *Staphylococcus aureus*, 689 infections by other staphylococci, and 100 infections by *Escherichia coli* among 1 743 107 live births.

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

[e]Wald test when a variable representing ordinal categories of BMI was introduced into a Cox proportional hazards model as a continuous predictor.

[f]Ten units is the difference in median BMI of women with obesity (32.8 kg/m^2) and without obesity (23.1 kg/m^2).

Mediation Analyses

Emergency cesarean section delivery, preeclampsia, preterm delivery, and elective cesarean section delivery mediated 18%, 14%, 12%, and 7% of the association between early pregnancy BMI and risk of EOS, respectively (Table 3). Experiencing any of these conditions explained 47% of the BMI–EOS associations.

Maternal BMI and Risk of EOS in Term Infants

There was a strong interaction between early pregnancy BMI and gestational age at delivery on EOS risk ($P < .0001$). Maternal overweight and obesity were consistently related to dose-response increases in EOS risk only among term infants (Table 4, Supplementary Figure 3). Compared with normal-weight women, AHR (95% CI) for overweight and obesity grades 1 through 3 were, respectively, 1.37 (1.20–1.56), 1.86 (1.55–2.22), 2.59 (1.99–3.37), and 2.82 (1.87–4.24). Most EOS cases among term infants were caused by GBS (Supplementary Table 7). Overweight and obesity were related to increased risks of EOS by GBS, staphylococci other than *S. aureus*, and *E. coli* (Supplementary Table 8). On the continuous scale, BMI was

Table 3. Mediation of Maternal Obesity Consequences on the Association Between Early Pregnancy Body Mass Index and Risk of Early-onset Neonatal Sepsis

Potential Mediator	BMI[a] Association in Levels of Mediator, HR (95% CI)	P Value for BMI–Mediator Interaction	HR (95% CI)			Percentage of BMI Association Mediated[d]
			Total BMI Association[b]	Direct BMI Association[c]	Indirect BMI Association Through Mediator	
Gestational diabetes						
No	1.55 (1.43–1.68)	.90	1.56 (1.44–1.68)	1.55 (1.43–1.67)	1.01 (1.00–1.01)	1.7
Yes	1.51 (1.00–2.27)					
Preeclampsia						
No	1.50 (1.38–1.63)	.0008	1.54 (1.42–1.66)	1.47 (1.35–1.59)	1.05 (1.04–1.06)	13.7
Yes	1.03 (.84–1.27)					
Maternal infections						
No	1.57 (1.45–1.70)	.57	1.56 (1.45–1.68)	1.56 (1.45–1.68)	1.00 (1.00–1.00)	0.0
Yes	1.45 (1.10–1.90)					
Premature rupture of membranes						
No	1.61 (1.48–1.74)	.001	1.57 (1.45–1.69)	1.55 (1.44–1.67)	1.01 (1.01–1.01)	2.8
Yes	1.10 (.89–1.37)					
Prolonged labor						
No	1.56 (1.45–1.68)	.68	1.56 (1.45–1.68)	1.56 (1.45–1.68)	1.00 (1.00–1.00)	0.0
Yes	1.83 (.86–3.89)					
Elective cesarean section						
No	1.58 (1.45–1.72)	.01	1.56 (1.45–1.69)	1.52 (1.41–1.65)	1.02 (1.02–1.03)	6.6
Yes	1.24 (1.05–1.48)					
Emergency cesarean section						
No	1.50 (1.37–1.64)	.05	1.55 (1.44–1.68)	1.45 (1.34–1.58)	1.07 (1.05–1.08)	17.9
Yes	1.26 (1.09–1.46)					
Preterm delivery						
No	1.74 (1.57–1.92)	<.0001	1.56 (1.45–1.68)	1.49 (1.39–1.61)	1.04 (1.04–1.05)	11.7
Yes	1.20 (1.07–1.34)					
Any congenital malformations						
No	1.57 (1.45–1.70)	.34	1.56 (1.44–1.68)	1.54 (1.43–1.67)	1.01 (1.01–1.01)	2.2
Yes	1.41 (1.15–1.73)					
Macrosomia (birth weight ≥4000 g)						
No	1.57 (1.44–1.71)	.77	1.55 (1.43–1.67)	1.55 (1.43–1.67)	1.00 (1.00–1.00)	0.0
Yes	1.61 (1.36–1.90)					
Meconium aspiration						
No	1.55 (1.43–1.67)	.49	1.56 (1.44–1.68)	1.54 (1.43–1.66)	1.01 (1.01–1.01)	2.6
Yes	1.30 (.81–2.10)					

HRs and 95% CIs from multivariable-adjusted Cox proportional hazards models. One model was fitted with each potential mediator. BMI–mediator associations were modeled with multivariable logistic regression. Covariates included maternal age, country of origin, education level, cohabitation with a partner, parity, height, year of delivery, smoking during pregnancy, and infant's sex. A BMI–mediator interaction term was tested and retained if statistically significant at $P < .05$. All effects on sepsis are estimated for a 10-kg/m^2 BMI difference from a baseline level of 23.1 kg/m^2 at the reference category of each covariate.

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

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

[b]Total effect estimates may vary between models for different mediators due to differences in the number of missing values for each mediator and exposure–mediator interactions. They may differ from estimates by levels of the mediator, even in the absence of interaction, due to noncollapsibility.

[c]Estimated at mediator level "no."

[d]Sum of percentages is not necessarily 100 because the effects of mediators are not mutually exclusive, mediators could interact with one another, and not all mediators may have been considered.

Table 4. Early Pregnancy Body Mass Index and Risk of Early-onset Neonatal Sepsis Stratified by Gestational Age at Delivery

Gestational Age at Delivery	No. of Infants[a]	Early-onset Neonatal Sepsis		Unadjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
		No.	Risk/1000 Live Births		
Term delivery (≥37 weeks)					
Maternal BMI,[d] kg/m^2					
<18.5	41 825	24	0.57	0.88 (.59–1.32)	0.87 (.57–1.32)
18.5–24.9	1 047 447	682	0.65	1.00	1.00
25.0–29.9	424 635	362	0.85	1.31 (1.15–1.49)	1.37 (1.20–1.56)
30.0–34.9	140 072	157	1.12	1.72 (1.45–2.05)	1.86 (1.55–2.22)
35.0–39.9	42 357	64	1.51	2.32 (1.79–3.01)	2.59 (1.99–3.37)
≥40.0	14 712	24	1.63	2.51 (1.67–3.77)	2.82 (1.87–4.24)
Missing	164 770	117	0.71		
P, trend[e]				<.0001	<.0001
Per 1 kg/m^2				1.06 (1.05–1.07)	1.06 (1.05–1.07)
Per 10 kg/m^2 [f]				1.68 (1.53–1.84)	1.79 (1.62–1.97)
Moderately preterm delivery (32–36 weeks)					
Maternal BMI, kg/m^2					
<18.5	2385	10	4.19	1.09 (.58–2.06)	1.13 (.59–2.14)
18.5–24.9	42 072	162	3.85	1.00	1.00
25.0–29.9	18 100	55	3.04	0.79 (.58–1.07)	0.81 (.59–1.10)
30.0–34.9	6733	26	3.86	1.00 (.66–1.52)	0.98 (.63–1.52)
35.0–39.9	2367	17	7.18	1.87 (1.13–3.07)	1.86 (1.10–3.15)
≥40.0	881	5	5.68	1.47 (.61–3.58)	1.60 (.66–3.92)
Missing	9630	45	4.67		
P, trend				.30	.32
Per 1 kg/m^2				1.01 (.99–1.04)	1.01 (.99–1.04)
Per 10 kg/m^2				1.11 (.87–1.41)	1.12 (.87–1.44)
Very preterm delivery (28–31 weeks)					
Maternal BMI, kg/m^2					
<18.5	212	12	56.60	1.16 (.66–2.04)	1.26 (.71–2.22)
18.5–24.9	4030	197	48.88	1.00	1.00
25.0–29.9	1853	79	42.63	0.87 (.68–1.13)	0.87 (.67–1.13)
30.0–34.9	799	43	53.82	1.10 (.80–1.52)	1.06 (.76–1.47)
35.0–39.9	283	11	38.87	0.80 (.44–1.44)	0.80 (.44–1.46)
≥40.0	138	6	43.48	0.89 (.40–1.97)	0.93 (.42–2.05)
Missing	1459	84	57.57		
P, trend				.56	.51
Per 1 kg/m^2				0.99 (.97–1.01)	0.99 (.97–1.01)
Per 10 kg/m^2				0.94 (.78–1.14)	0.92 (.76–1.13)
Extremely preterm delivery (22–27 weeks)					
Maternal BMI, kg/m^2					
<18.5	83	12	144.58	0.90 (.53–1.54)	1.00 (.59–1.70)
18.5–24.9	1789	286	159.87	1.00	1.00
25.0–29.9	890	140	157.30	0.98 (.82–1.19)	0.98 (.81–1.19)
30.0–34.9	398	79	198.49	1.24 (.99–1.56)	1.12 (.88–1.41)
35.0–39.9	144	18	125.00	0.78 (.50–1.22)	0.78 (.50–1.22)
≥40.0	75	10	133.33	0.83 (.46–1.50)	0.89 (.50–1.59)
Missing	1207	186	154.10		
P, trend				.87	.72
Per 1 kg/m^2				1.00 (.99–1.02)	1.00 (.98–1.01)
Per 10 kg/m^2				1.02 (.89–1.16)	0.98 (.85–1.13)

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

[a]Live-born singleton infants in Sweden 1997–2016.

[b]From Cox proportional hazards models with day of hospital admission for sepsis as the outcome.

[c]HRs and 95% CIs from Cox proportional hazards models with robust estimates of variance. The outcome was day of hospital admission for sepsis. Covariates included maternal age, country of origin, education level, cohabitation with a partner, parity, height, smoking during pregnancy, and year of delivery. Complete case analyses per category included 1277 cases among 1 662 647 full-term infants, 265 cases among 70 239 moderately preterm infants, 335 cases among 7015 very preterm infants, and 513 cases among 3206 extremely preterm infants.

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

[e]Wald test when a variable representing ordinal categories of BMI was introduced into a Cox proportional hazards model as a continuous predictor.

[f]Ten units is the difference in median BMI of women with obesity (32.8 kg/m^2) and without obesity (23.1 kg/m^2).

positively associated with EOS risk by GBS, *S. aureus*, other staphylococci, and *E. coli*. In term infants, emergency cesarean section and macrosomia mediated 20% and 18% of the BMI–EOS associations, respectively (Supplementary Table 9).

Sibling-controlled Analyses

Next, we examined the BMI–EOS association in a subcohort of 1 104 419 full siblings born at term, distributed in 496 332 families. In these analyses, there was a positive association between maternal BMI and EOS risk (Supplementary Figure 4). Every kilogram per meter squared interpregnancy BMI change was associated with a mean 8.3% increase in EOS risk (95% CI, 1.7%–15.3%; $P = .01$). The estimate remained unchanged after adjustment for time-varying characteristics, including cohabitation with a partner and smoking during pregnancy (8.1% risk increase per kilogram per meter squared change; 95% CI, 1.4%–15.2%; $P = .02$).

DISCUSSION

In this nationwide cohort study, maternal overweight and obesity severity in early pregnancy were related to risk of culture-confirmed EOS in a dose-response manner. Almost half of this association was explained through cesarean section delivery, preeclampsia, and preterm delivery. The association was consistently apparent only in infants born at term, in whom it was strongest for EOS caused by enteric bacteria and was partly mediated through emergency cesarean section delivery and macrosomia.

The association of maternal BMI with risk of EOS is consistent with preliminary observations from 2 studies in the United States [12, 13]. Our analyses extend these findings by focusing on early-onset neonatal sepsis, assessing microorganism-specific associations, identifying potential mediators, stratifying by gestational age, and implementing a family study in term infants.

The association between maternal obesity and EOS was partly mediated through conditions that may be interrelated, namely, preeclampsia, cesarean section, and preterm delivery. Neutropenia is a common finding among infants born to hypertensive mothers [30] and may increase risk of sepsis [31]. In addition, preeclampsia could prompt an emergency cesarean section, which carries the highest risk of maternal and neonatal infections of all modes of delivery [32]. EOS risk might be compounded if this chain of events resulted in preterm birth, since preterm infants may be more vulnerable to infection than term infants due to immunological immaturity. Of note, independent of mediation by cesarean section, maternal BMI increased EOS risk in infants delivered by vaginal birth and by cesarean section. Unexpectedly, we found increased risk of EOS by *E. coli* in women who were underweight. Maternal underweight is related to preterm delivery [33], and infants born preterm may be more susceptible to enterobacterial infections. This finding warrants confirmation in future studies.

The dose-response association between maternal BMI and EOS was only apparent among term infants, but statistical power was comparatively lower among preterm infants. Notwithstanding, the consistency of findings between the traditional cohort and the sibling-controlled approaches among term infants lends some support to causation. In term infants, the association between maternal obesity and EOS was partly mediated through macrosomia and emergency cesarean section delivery. Macrosomia could result in traumatic delivery, increasing the infant's exposure to enteric bacteria [34]. In addition, obesity is related to low gut microbial diversity [35], which might enhance the role of pathogenic bacteria. Emergency cesarean section is a strong risk factor for neonatal infection. Prophylactic administration of antibiotics to women who undergo emergency cesarean section was practiced in Sweden during the duration of the study, consisting of a single dose of a combination of 2 or 3 antibiotics [36]. In 2015, preoperatory intravenous administration of 1.5 g cefuroxime became a standard national recommendation. Clinical and pharmacokinetic studies suggest that women who are obese require a higher cephalosporin dose to achieve minimally inhibitory concentrations compared with women who are not obese [37]. In addition, obesity reduces transplacental passage of cefazolin [38], a commonly used prophylactic antibiotic. In the United States, compared with women who are not obese, prophylactic cefazolin for obese women is recommended at twice the dose (2 g) [39]. Thus, insufficient preoperatory antibiotic prophylaxis could explain, in part, a mediating effect of emergency cesarean section on the association of maternal obesity with EOS.

The study has several strengths. The population-based design with more than 1.9 million live births linked to nationwide registries reduced the possibility of selection bias. The relative homogeneity of the Swedish population and the existence of universal, standardized healthcare should further limit confounding by socioeconomic factors. Measurement error of exposure was minimized by the prospective collection of information and use of an early pregnancy assessment of BMI. The large sample size allowed analyses of pathogen-specific EOS, stratification by gestational age, and exploration of mediation pathways. Finally, the sibling comparisons offered a unique opportunity to enhance causal inference by controlling associations for confounders shared within families. Because full siblings share up to one-half of autosomal DNA, confounding by unmeasured genetic characteristics of the infants, for example, those related to immune fitness, is less likely when comparing siblings than when comparing unrelated infants. Sibling comparisons also control completely for genetic and all other time-invariant parental characteristics, including those that govern maternal susceptibility to infection and propensity to transmit bacteria to the infant.

Some limitations are also worth noting. Missing information on BMI could lead to selection bias; although multiple imputation analyses did not change the results. The validity of ICD codes for neonatal sepsis in Sweden has not been evaluated; however, specificity of ICD-coded sepsis during adult intensive care in the Swedish Patient Register is >92% [15]. Furthermore, the risk of culture-confirmed EOS per 1000 term live births in our study, 0.76, was within the range of figures reported in other population-based studies, 0.40 to 0.89 in the United States [40] and 0.70 in the United Kingdom [41]. Risk was higher in Sweden than in Norway, 0.54 per 1000 [42], because the Norwegian estimate excluded infections by coagulase-negative staphylococci. Coagulase-negative staphylococcal infections do not typically result from mother-to-infant transmission during delivery but often from postnatal care–related procedures. Yet, we found an association between maternal BMI and these infections. This might reflect an effect through different pathways. While the relative sociodemographic homogeneity of the Swedish population enhances the internal validity of the study, it may limit the generalizability of the findings to populations with different sociodemographic structures. The risk of EOS changed over the years of study, possibly owing to changes in Swedish legislation regarding the characterization of live births, enhanced detection, and increased active care of extremely preterm infants [43]. Nevertheless, adjustment for year of delivery had no impact on the estimates of association between maternal BMI and EOS. Finally, LOS cases may have been misclassified as EOS if the reason for hospitalization within the first 72 hours of life was unrelated to early sepsis but to late sepsis that ensued during the hospital stay due, for example, to nosocomial infection. This situation may have affected preferentially extremely or very preterm infants since they are routinely hospitalized immediately after birth and their risk of LOS is higher than that of moderately preterm [44] or term infants. Outcome misclassification is unlikely related to early pregnancy BMI; this nondifferential lack of specificity could attenuate the estimates of association. Misclassification of EOS as LOS is improbable when using early postnatal hospital admission as a proxy for the onset of infection and excluding late admissions.

In conclusion, there was a dose-response association between maternal overweight and obesity severity and risk of EOS, especially in term infants. Increasing awareness of obesity as a risk factor for EOS might result in reduced EOS risk.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. E. V. conceived the idea for the study. E. V., M. N., S. J., and S. C. designed the protocol. S. C. acquired the data. E. V. conducted the data analyses and drafted the manuscript. All authors provided critical revisions and approved the final version of the manuscript.

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