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Maternal body mass index and risk of intraventricular hemorrhage in preterm infants

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BACKGROUND: Intraventricular hemorrhage (IVH) and pre-pregnancy obesity and underweight have been linked to inflammatory states. We hypothesize that IVH in preterm infants is associated with pre-pregnancy obesity and underweight due to an inflammatory intrauterine environment.

METHODS: Population-based study of infants born between 22 and 32 weeks' gestation from 2007 to 2011. Data were extracted from vital statistics and the California Perinatal Quality Care Collaborative. Results were examined for all cases (any IVH) and for severe IVH.

RESULTS: Among 20,927 infants, 4,818 (23%) had any IVH and 1,514 (7%) had severe IVH. After adjustment for confounders, there was an increased risk of IVH associated with pre-pregnancy obesity, relative risk 1.14 (95% confidence interval (CI) 1.06, 1.32) for any IVH, and 1.25 (85% CI 1.10, 1.42) for severe IVH. The direct effect of pre-pregnancy obesity on any IVH was significant ($P < 0.001$) after controlling for antenatal inflammation-related conditions, but was not significant after controlling for gestational age ($P = 0.56$).

CONCLUSION: Pre-pregnancy obesity was found to be a risk factor for IVH in preterm infants; however, this relationship appeared to be largely mediated through the effect of BMI on gestational age at delivery. The etiology of IVH is complex and it is important to understand the contributing maternal factors.

High and low maternal body mass index (BMI) have been hypothesized to confer a wide range of negative impacts on fetal programming and neonatal outcomes (1–4). One notable risk of maternal obesity and underweight is preterm delivery, with an increase in the overall incidence of preterm birth associated with the extremes in maternal BMI (5–8). Independent of its associations with prematurity, maternal obesity has been shown to be an antenatal risk factor for certain adverse outcomes associated with prematurity, including bronchopulmonary dysplasia and necrotizing enterocolitis requiring surgery (9,10). Several studies have also shown that premature infants born to obese mothers are at increased risk of cognitive impairment at 24 months of age compared to those born to mothers with normal weight (11,12). Intraventricular hemorrhage (IVH) is a severe and important consequence of prematurity, and its relationship to maternal BMI has thus far not been well evaluated. We hypothesized that maternal BMI may be associated with IVH in preterm infants due to a heightened maternal inflammatory state while *in utero*.

Both maternal BMI and IVH have been independently linked to inflammation. Maternal obesity is associated with increased systemic inflammation, and has been shown to be a risk factor for certain pregnancy-related inflammatory conditions, such as preterm premature rupture of membranes (pPROM) and chorioamnionitis (13–17). In addition, preterm children of overweight and obese mothers have evidence of increased systemic inflammation (measured by serum concentrations of inflammatory proteins) compared to preterm infants born to women with lower BMI (18). Systemic inflammation with increased serum inflammatory cytokines has also been demonstrated in maternal underweight conditions, such as anorexia nervosa (19,20).

Pregnancies complicated by conditions associated with increased inflammation, such as chorioamnionitis, pPROM, and prolonged rupture of membranes (ROM), have been linked to an increased risk of IVH (21–24). It has been suggested that pro-inflammatory cytokines, in particular, may play a role in the development of IVH (25–27). The etiopathogenesis of IVH is complex, but evidence suggests that inflammatory processes may play a significant role.

There is a gap in our knowledge on the potential impact of maternal obesity or underweight status as an independent predisposing factor for IVH. Although the exact mechanism of IVH remains unknown, we hypothesized that the systemic inflammation that is observed in abnormal maternal weight may be a predisposing factor.

METHODS

Study Population and Data Source

The California Perinatal Quality Care Collaborative (CPQCC) collects data on infants admitted to 139 neonatal intensive care units (NICUs) in California. Standard definitions align with those used by the Vermont Oxford Network. This database represents over 95% of very low birthweight infants born in California and also includes information on maternal, fetal, and obstetrical complications. CPQCC data were previously linked to data sets from the

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Received 6 September 2017; accepted 27 February 2018; advance online publication 9 May 2018. doi:10.1038/pr.2018.47

California Office of Statewide Health Planning and Development (OSHPD) that include maternal delivery discharge records linked with birth certificates. The study was approved by the California Committee for the Protection of Human Subjects and the Stanford University Institutional Review Board.

The study period included births that occurred between 1 January 2007 and 31 December 2011. Infants born between 22 and 32 weeks' gestational age were included in the cohort. The study cohort was limited to this gestational age range, as this population of infants is at highest risk for IVH. Exclusion criteria included the following: birthweights at the extremes for their gestational age (<1st or >99th percentile), lack of neuroimaging, and major congenital anomalies. Details regarding major congenital anomalies are available in the CPQCC manual of definitions (28). We also excluded records of infants with missing maternal BMI.

Measures

CPQCC classifies IVH according to Papile *et al.* (29), with the most severe grade documented in the database according to any neuroimaging done during hospitalization. IVH was evaluated as an outcome in the following two ways: (1) any IVH (grades 1 to 4) and (2) severe IVH (grades 3 and 4).

Pre-pregnancy BMI (kg/m^2) was calculated from maternal self-reported weight and height recorded in the birth certificates, which were extracted from the OSHPD files. BMI was divided into the following four categories as defined by the World Health Organization (30): underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI >30). As a sensitivity analysis, we further divided Underweight into class I (17.0–18.4) and class II/III (<17.0), and Obesity into class I (30.0–34.9), class II (35.0–39.9), and class III (>40.0).

Covariates were selected *a priori* and evaluated from CPQCC and OSHPD data. Information on gestational age (weeks), birthweight (grams), infant sex (male or female), maternal non-intrauterine infection, antenatal steroids, and prolonged ROM or pPROM were retrieved from CPQCC. Maternal race/ethnicity (Non-Hispanic White, Hispanic, African-American, Asian/Pacific Islander, or other/unknown), age (years), education (less than high school, high school graduate or GED, college or graduate degree), principal source of payment (Medi-Cal, private, or other/unknown) were retrieved from birth record and OSHPD files. Chorioamnionitis and maternal pre-pregnancy diabetes and hypertension were obtained from either CPQCC or OSHPD data. Additional definitions of covariates are available in the CPQCC manual of definitions (28). Gestational age and antenatal inflammation-related conditions (defined as chorioamnionitis, maternal non-uterine infection, pPROM, or prolonged ROM) were evaluated as mediators and all other covariates were evaluated as confounders.

Statistical Analysis

The outcomes of IVH were compared according to demographic and maternal medical conditions. We compared infants with any IVH and those with severe IVH to infants without IVH. Risk ratios and 95% confidence intervals (CIs) for the association between pre-pregnancy BMI (four categories) and any IVH, and pre-pregnancy BMI and severe IVH, were estimated using log-binomial regression models. Modified Poisson regression models with robust standard errors were used in instances when the model did not converge (31). We conducted regression models unadjusted and adjusted for confounders. Results were considered statistically significant at $P<0.05$.

We performed assessments of whether gestational age or indicators of antenatal inflammation mediated the association between BMI and IVH. Given that gestational age and birthweight are strongly correlated, we only included gestational age in mediation analysis. To do so, we first estimated the total effect of BMI on IVH after adjustment for pre-pregnancy confounders. We then used a modified Poisson regression model to test the association between BMI and inflammation, and a linear regression model to test the association between BMI and gestational age. We tested the association between each mediator and IVH using modified Poisson regression models. Finally, we estimated the direct effect of BMI on IVH by including the mediator in the total effect regression model. The estimated indirect effect of BMI on IVH through the mediator was calculated as the difference between the total effect and the direct effect.

As a sensitivity analysis, we conducted all regression models using seven categories of pre-pregnancy BMI instead of four, to assess possible variation in results among subclasses of underweight and obesity. We examined whether there was any evidence for interaction of BMI with gestational age or BMI with antenatal inflammation, via product terms added to the models; *P*-values for interaction terms were >0.10 so we did not pursue interaction further.

RESULTS

During the study period, 30,403 infants born between 22 and 32 weeks' gestational age were cared for at CPQCC NICUs. After exclusions for birthweights at the extremes for their gestational age ($n=209$), lack of neuroimaging ($n=2,457$), major congenital anomalies ($n=3,256$), missing maternal BMI ($n=3,540$), and missing other data ($n=14$), 20,927 infants remained in the analytic cohort. The percentage of subjects with any or severe IVH was similar among the infants excluded for missing maternal BMI and the infants included in the analysis (data not shown).

There were baseline differences in demographics between infants with and without IVH (**Table 1**). Infants with IVH had lower gestational ages and birthweights than infants without IVH, and a higher proportion were male. Additionally, a higher proportion of mothers of infants with IVH identified as Hispanic or African-American, had chorioamnionitis, pPROM, or prolonged ROM, and a lower proportion had pre-pregnancy hypertension or received antenatal steroids.

The risk of any IVH in infants of mothers with pre-pregnancy obesity was 1.14 times (95% CI 1.06, 1.12) the risk in infants of mothers with pre-pregnancy normal weight, after adjustment for confounders (**Table 2**). The magnitude of these associations was larger for severe IVH, and confidence intervals excluded 1.0 for both pre-pregnancy obesity and overweight. In analyses to assess mediation, the estimated direct effect of pre-pregnancy obesity on any IVH after controlling for antenatal inflammation-related conditions (i.e., chorioamnionitis, maternal non-uterine infection, pPROM or prolonged ROM) was similar to the total effect. Therefore, the indirect effect of antenatal inflammation was not significant. In contrast, the estimated direct effect of pre-pregnancy overweight and obesity on any IVH after controlling for gestational age was not significant. The absolute risk difference associated with pre-pregnancy obesity was reduced from 0.13 to 0.02 with gestational age adjustment, which suggests that the indirect effect through gestational age explained 85% of the association between pre-pregnancy obesity and any IVH (data not shown). Mediation results were similar for pre-pregnancy overweight and for severe IVH (**Table 2**).

Sensitivity analyses that considered seven instead of four categories of BMI showed a similar pattern of results

Table 1. Descriptive characteristics of infants with and without IVH

	No IVH, *n* = 16,109 (77.0%)	Any IVH (grades1–4), *n* = 4,818 (23.0%)	Severe IVH (grades 3 and 4), *n* = 1,514 (7.2%)
GA at delivery (weeks), mean+SD	28.9+2.3	26.9+2.6	25.6+2.2
Birthweight (g), mean+SD	1,241.9+375.1	1,009.1+366.3	865.3+305.4
Male, *n* (%)	8,523 (52.9)	2,790 (57.9)	911 (60.2)
Maternal age (years), mean+SD	29.3+6.9	28.4+7.0	28.1+7.2
Maternal BMI (kg/m^2), mean+SD	26.5+6.4	26.9+6.6	27.0+6.6
Maternal Race/Ethnicity, *n* (%)			
Non-Hispanic White	4,312 (26.8)	1,166 (24.2)	366 (24.2)
Hispanic	7,551 (46.9)	2,367 (49.1)	778 (51.4)
African-American	1,807 (11.2)	624 (13.0)	206 (13.6)
Asian/Pacific Islander	1,266 (7.9)	339 (7.0)	79 (5.2)
Other/unknown	1,173 (7.3)	322 (6.7)	85 (5.6)
Maternal education, *n* (%)			
Less than High School/Unknown	4,307 (26.7)	1,421 (29.5)	486 (32.1)
High School Graduate or GED	4,081 (25.3)	1,293 (26.8)	429 (28.3)
College or Postgraduate Education	3,075 (19.1)	2,104 (43.7)	599 (39.6)
Principal source of payment, *n* (%)			
Medi-Cal	7,164 (44.5)	2,438 (50.6)	797 (52.6)
Private	7,995 (49.6)	2,059 (42.7)	613 (40.5)
Uninsured	387 (2.4)	173 (3.6)	55 (3.6)
Other/unknown	563 (3.5)	148 (3.1)	49 (3.2)
Maternal pre-pregnancy hypertension, *n* (%)	1,523 (9.5)	342 (7.1)	82 (5.4)
Maternal Pre-pregnancy diabetes, *n* (%)	467 (2.9)	149 (3.1)	41 (2.7)
Maternal chorioamnionitis, *n* (%)	1,639 (10.2)	797 (16.5)	280 (18.5)
Maternal non-intrauterine infection, *n* (%)	985 (6.1)	428 (8.9)	141 (9.3)
Antenatal steroids, *n* (%)	13,374 (83.0)	3,793 (78.7)	1,065 (70.3)
Preterm premature ROM or prolonged ROM, *n* (%)	5,643 (35.0)	2,016 (41.8)	693 (45.8)

(**Supplementary Table S1 online**). Risk of IVH was higher in mothers with greater BMIs and the magnitude of these associations was larger for severe IVH. Consistent with the analyses that collapsed obesity classes, there was a significant indirect effect of gestational age on the associations between pre-pregnancy obesity and IVH.

Mediation findings were supported by results of an inverse association between pre-pregnancy obesity and weeks' gestational age at delivery (adjusted regression coefficient −0.45 weeks, 95% CI -0.54, -0.36) compared to pre-pregnancy normal weight. Distribution of gestational age by maternal BMI status is displayed in **Supplementary Table S2 online**. The presence of antenatal inflammation-related conditions was associated with the risk of any IVH (aRR 1.33, 95% CI 1.26, 1.41), but not with pre-pregnancy obesity (aRR 1.05, 95% CI 0.99, 1.11).

DISCUSSION

We hypothesized that pre-pregnancy obesity and underweight would be associated with IVH in preterm infants due to a heightened inflammatory state *in utero*. Both underweight and obesity have been shown to be associated with systemic inflammation (13,14,19,20), and studies have linked the development of IVH to maternal inflammatory conditions (21–23). Our results demonstrated that pre-pregnancy obesity was associated with an increased risk of IVH; however, this effect appeared to be largely attributable to the relationship between obesity and earlier gestational age at delivery.

Maternal obesity and underweight are known risk factors for preterm delivery (5–8). In addition, early gestational age and low birthweight are the most significant risk factors for developing IVH, with the prevalence of IVH decreasing with increasing gestational age and birthweight (32,33). Our results confirmed that lower gestational age was significantly associated with both pre-pregnancy obesity and IVH. Mediation analysis subsequently revealed that much of the association between obesity and IVH was mediated by gestational age. This suggests that the association between maternal BMI and IVH is largely attributable to the existing relationship between obesity and earlier gestational age at

Table 2. Association of four categories of pre-pregnancy BMI with intraventricular hemorrhage in infants born between 22 and 32 weeks' gestation ($n = 20,927$)

	Any IVH (grades 1–4), $n = 4,818$					
Pre-pregnancy BMI[a]	No IVH, *n* (%)	Any IVH, *n* (%)	Unadjusted Model RR (95% CI)	Adjusted Model 1[b] RR (95% CI)	Adjusted Model 2[c] RR (95% CI)	Adjusted Model 3[d] RR (95% CI)
Underweight	695 (4.3)	200 (4.2)	1.01 (0.88–1.17)	0.97 (0.84–1.13)	0.98 (0.85, 1.13)	1.00 (0.87, 1.16)
Normal weight	7,267 (45.1)	2,055 (42.7)	Reference	Reference	Reference	Reference
Overweight	4,109 (25.5)	1,238 (25.7)	1.05 (0.98–1.13)	1.06 (0.98–1.13)	1.06 (0.98, 1.14)	0.99 (0.92, 1.06)
Obese	4,038 (25.1)	1,325 (27.5)	**1.12 (1.05–1.20)**	**1.14 (1.06–1.23)**	**1.14 (1.06, 1.22)**	1.02 (0.95, 1.10)
	Severe IVH (grades 3 and 4), $n = 1,514$					
Pre-pregnancy BMI	No IVH, *n* (%)	Severe IVH, *n* (%)	Unadjusted Model RR (95% CI)	Adjusted Model 1 RR (95% CI)	Adjusted Model 2 RR (95% CI)	Adjusted Model 3 RR (95% CI)
Underweight	695 (4.3)	70 (4.6)	1.17 (0.91–1.50)	1.10 (0.86–1.41)	1.12 (0.87, 1.43)	1.11 (0.86, 1.42)
Normal weight	7267 (45.1)	617 (40.8)	Reference	Reference	Reference	Reference
Overweight	4,109 (25.5)	401 (26.5)	1.14 (1.00–1.29)	**1.14 (1.01–1.30)**	**1.15 (1.01, 1.31)**	1.03 (0.91, 1.17)
Obese	4,038 (25.1)	426 (28.1)	**1.22 (1.08–1.38)**	**1.25 (1.10–1.42)**	**1.24 (1.09, 1.41)**	1.00 (0.88, 1.14)

BMI, body mass index; CI, confidence interval; IVH, intraventricular hemorrhage; RR, risk ratio

[a]Pre-pregnancy BMI categories: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2)

[b]Adjusted Model 1: total effect estimate adjusted for confounders: maternal age, race/ethnicity, education, insurance, antenatal steroids, pre-pregnancy diabetes mellitus, and hypertension.

[c]Adjusted Model 2: direct effect estimate, adjusted for confounders and mediation by antenatal inflammation (chorioamnionitis, non-uterine infection, pPROM, or prolonged ROM.

[d]Adjusted Model 3: direct effect estimate, adjusted for confounders and mediation by gestational age at delivery.

Values in bold represent significant risk ratios.

delivery, which is strongest at the extremes of obesity and the earliest gestational ages (2,34).

Among extremely preterm deliveries, pre-pregnancy obesity is associated with an increased risk of spontaneous delivery, which is defined as preterm delivery preceded by spontaneous onset of labor or rupture of membranes (35–37). In our cohort, medically indicated delivery was more likely among obese women, and this was true among infants with and without IVH (**Supplementary Table S2 online**). In addition, medically indicated delivery was somewhat more likely among infants without IVH than infants with IVH. However, in this sample of preterm deliveries, more than 90% of all deliveries were spontaneous; thus, it is unlikely that differences in indication between cases and controls or by BMI were driving our results. The increased risk of spontaneous preterm deliveries among women with pre-pregnancy obesity has been hypothesized to be due to an elevated inflammatory state, in addition to an increased risk of chorioamnionitis and pPROM (which are independent risk factors for IVH) (22,23,35,38). For this reason, we considered surrogates for antenatal inflammation as mediators in the relationship between pre-pregnancy BMI and IVH. In our cohort, antenatal inflammation-related conditions were significantly associated with IVH, but not with pre-pregnancy obesity which is likely why the indirect effect of antenatal inflammation on IVH was nonsignificant in mediation analysis. Although there was a significant association between pre-pregnancy obesity and IVH after controlling for antenatal inflammation-related conditions, our full analysis demonstrates that this relationship is mostly attributable to earlier gestational age at delivery.

A strength of this study was our large sample size. We utilized a population-based data set encompassing more than 20,000 infants from most NICUs in a large and diverse underlying study population. The CPQCC database encompasses more than 95% of very low birthweight infants in California, which is a significant strength of this analysis. One important limitation of this study is that we did not have neuroimaging and maternal BMI information for all eligible infants. The exclusion of 2,457 infants who did not have neuroimaging documented may have led to some selection bias; 1,119 of these infants died within 24 h of birth so were likely too ill to have had neuroimaging done before death. The remaining infants may have been too healthy and it is possible that they were not thought to be at risk. We excluded 3,540 infants due to missing maternal BMI information; however, these infants had similar rates of IVH as those included in the analysis, so we would not expect a significant impact on the results.

Another limitation is that there can be discordance in inter-reader agreement on neonatal head imaging results (39,40); however, we were unable to validate the diagnosis of IVH by head ultrasound in this study because the images were not available and the data were extracted from CPQCC records. We also evaluated IVH following the conventional grading system of Papile *et al.* (29). However, the heterogeneity of outcomes among different grades of IVH may bias toward the null, as intraventricular and intracerebral hemorrhage may differ in their risk profiles. Another limitation is that BMI was obtained through self-reported data; however, inaccuracies in self-reported height and weight have not been shown to

seriously bias the observed associations between pregnancy-related weight and birth outcomes (41). We used an effect decomposition approach to evaluate mediation of the BMI-IVH associations by gestational age and antenatal inflammation, which is limited by assumptions of no uncontrolled confounding between the mediator and outcome, and no unit-level interaction between the exposure and mediator, which is not possible to verify empirically (42). This study was observational and may have residual confounding; causal conclusions cannot be made.

In conclusion, although the development of IVH has been linked to maternal inflammatory conditions, we did not find that the extremes of maternal BMI independently contributed to an increased risk of IVH in preterm infants. These results demonstrate that the relationship between maternal BMI and IVH is complex and much of the causal pathway between the two appears to be mediated through the effect of BMI on gestational age at delivery.

STATEMENT OF FINANCIAL SUPPORT

This work was supported in part by the March of Dimes Prematurity Research Center at Stanford University and the Stanford Child Health Research Institute.

Disclosure: The authors declare no conflict of interest.

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