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The relationship between maternal body mass index and tobacco use on small for gestational age infants

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Abstract

Objective—To estimate the association between pre-pregnancy body mass index (BMI) and small for gestational age (SGA) neonates, and to determine if there is a synergistic effect of tobacco use on SGA across all BMI strata.

Study Design—Retrospective cohort study of 65,104 patients seen for second-trimester ultrasound. BMI was categorized into underweight, normal weight, overweight, and obese. SGA was defined as birth weight <10th percentile and <5th percentile. Univariable and multivariable logistic regression analyses were used to evaluate the association between BMI and SGA. Stratified analyses and tests for effect modification were performed to evaluate for a potential synergistic effect between tobacco use and abnormal pre-pregnancy BMI on SGA.

Results—After controlling for potential confounders, underweight BMI was significantly associated with an increased risk for SGA <10th percentile (aOR 1.8, 95% CI 1.5–2.1) while overweight (aOR 0.7, 95% CI 0.7–0.8) and obese BMI (aOR 0.6, 95% CI 0.5–0.7) were associated with a decreased risk of SGA. There was no effect modification of tobacco use on the risk of SGA across all BMI categories.

Conclusion—While both tobacco and underweight BMI are independently associated with SGA, there was no evidence of synergism. Continued emphasis on *both* smoking cessation and maintenance of normal pre-pregnancy BMI remain paramount to decreasing the incidence of SGA.

Keywords

body mass index; tobacco; small for gestational age; underweight

Introduction

Both tobacco exposure and low pre-pregnancy body mass index (BMI) are well-established, potentially modifiable risk factors for the birth of a small for gestational age (SGA) neonate.[1–4] Although the underlying mechanism of SGA is unclear, nutritional deficiency, utero-placental insufficiency, and vascular endothelial damage have each been hypothesized to play a role.[5,6] Despite these strong associations, not all infants born to smokers or underweight mothers are small for gestational age, suggesting that interactions between

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multiple factors are necessary in order for an effect on fetal growth to be observed. Aagaard-Tillery *et al.* proposed that in utero tobacco exposure may actually function as a "second hit" to the fetus to further attenuate fetal growth in the presence of other risk factors.[7]

On the other end of the spectrum, it has also previously been accepted that high pre-pregnancy maternal BMI decreases the risk of SGA and increases the risk of fetal macrosomia.[8,9] Alternatively, recent studies suggest that high maternal BMI actually may be associated with a decrease in birth weight; a decrease that may be even more substantial than that associated with low maternal BMI.[10]

Low birth weight remains a significant contributor to perinatal morbidity and mortality with consequences persisting into adult life. It has been demonstrated that growth-restricted fetuses have a 2–8 fold increased risk of for long-term health sequelae such as hypertension, cardiovascular disease, and diabetes mellitus as adults. Given both the significant short-term and long-term consequences of fetal growth restriction, efforts to further understand its causal pathways are warranted.[11,12] Previous studies are conflicting as to whether tobacco and low maternal BMI are independent, additive, or synergistic risk factors for SGA.[7,13] Understanding these relationships may affect how patients are counseled regarding the impact of these modifiable risk factors on pregnancy outcome. Our study aims to further define this relationship first by estimating the association between pre-pregnancy body mass index (BMI) and small for gestational age (SGA) neonates and then determining if there is a synergistic effect between tobacco use and maternal BMI on SGA.

Materials and Methods

This is a retrospective cohort study of 65,104 patients with singleton gestations and a documented BMI who were seen between 14 and 22 weeks' gestation in the Center for Ultrasound and Genetics at the Washington University Medical Center in St. Louis from 1990–2008. Approval from the institutional review board at our center was obtained. A computerized database was used to extract maternal characteristics including age, race, tobacco use, pre-pregnancy BMI, history of chronic hypertension, and history of pre-gestational diabetes mellitus. Our database also includes detailed information on medical and obstetrical history, pregnancy course, and delivery outcome. Outcome information is obtained by dedicated outcome coordinators at our center and is captured in an on-going manner. Multiple gestations, major fetal anomalies, chromosomal abnormalities, and cases of gestational diabetes were excluded from our analysis. Gestational diabetes was excluded based on its well-established association with both obesity and macrosomia.

Our primary exposure was pre-pregnancy BMI, and the primary outcome of interest was birth of a SGA neonate. Pre-pregnancy BMI was divided into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥30 kg/m^2), based on the World Health Organization BMI categorization. For the primary analysis, SGA was defined as birth weight <10^{th}%ile for gestational age, using national standards defined by the Alexander growth curve.[14] SGA <5^{th}%ile for gestational age was also evaluated as a secondary outcome of interest. Pre-pregnancy height, weight and smoking status were obtained from patient self-report on a routine health history questionnaire administered at the time of the ultrasound appointment. Tobacco use was coded as a dichotomous variable based on reported self-classification as a smoker or non-smoker at the time of ultrasound. Information on quantity of tobacco exposure was not available.

Baseline characteristics of the study groups were compared across BMI strata using one-way analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. Maternal pre-pregnancy BMI and tobacco use, along with other maternal

characteristics, were individually evaluated for association with SGA in a univariate analysis. The population was then stratified by tobacco use, and relative risks (RR) for SGA were again estimated for each BMI category, using normal weight as the reference group. These unadjusted RR were compared between smokers and non-smokers in each BMI category. Multivariable logistic regression models were then fit for the association between pre-pregnancy BMI and SGA, controlling for potential confounding factors identified in the univariable analysis. Non-significant variables were removed from the models in a backwards stepwise fashion. To further evaluate for synergism between tobacco and BMI, an interaction variable (BMI category* tobacco) was then added to the base model. The two models (with and without the interaction variable) were compared using the likelihood ratio (LR) test. This analytic technique allows for the evaluation of two or more factors and their impact on an outcome of interest that may be more or less than simply additive. All statistical analyses were performed using STATA version 10.0, Special Edition (College Station, TX). P-values <0.05 were considered statistically significant.

Results

Of 57,977 patients meeting inclusion criteria, complete outcome information was available for 50,563 (87.2%) patients. Of these patients, 3,811 (7.5%) gave birth to an SGA neonate <10^{th} %ile for gestational age and 1,606 (3.2%) gave birth to an SGA neonate <5^{th} %ile for gestational age. 5,551 (11%) patients in the cohort reported tobacco use. When dividing the study population into BMI categories, 1,174 (2.3%) were classified as underweight, 25,801 (51.1%) as normal weight, 13,008 (25.7%) as overweight, and 10,580 (20.9%) as obese. The rate of both SGA <10^{th} %ile (13.5%) and <5^{th} %ile (5.0%) was highest in the underweight mothers, and, although statistically significant, the rate of tobacco use did not vary considerably across BMI categories (10.3–12.2%). Table 1 shows descriptive data on maternal sociodemographics and pre-existing medical conditions across all BMI strata.

In a univariable analysis, both underweight BMI (RR 1.8, 95% CI 1.6–2.1) and tobacco use (RR 2.3, 95% CI 2.1–2.5) were associated with an increased risk of SGA <10^{th}%ile. Similarly, both underweight BMI (RR 1.6, 95% CI 1.2–2.1) and tobacco use (RR 2.9, 95% CI 2.6–3.3) were also associated with an increased risk for SGA <5^{th}%ile. While overweight BMI (RR 0.9, 95% CI 0.8–0.9) and obese BMI (RR 0.9, 95% CI 0.8–0.9) were associated with a decreased risk of SGA <10^{th}%ile, there was no statistically significant association between these BMI categories and SGA <5^{th} %ile. There was also no statistically significant association (either increased or decreased risk) between morbid obesity (BMI ≥40) and SGA <10^{th} or 5^{th} percentiles.

To evaluate for a possible synergistic effect of tobacco use on the association between maternal BMI and SGA, the population was first stratified by tobacco use. The incidence and RR of SGA was calculated for each BMI category in both the smoker and non-smoker strata. The association between tobacco use and SGA was consistent across all BMI categories, with approximately twice as many smokers giving birth to SGA neonates compared to non-smokers in each BMI category. (Tables 2 and 3) The RR of SGA was then compared between smokers and non-smokers in each BMI category. There was no statistically significant difference in the risk of SGA between the the smokers and non-smokers across all BMI categories, thereby indicating no evidence of synergism.

To further evaluate for synergism, a base logistic regression model was first created for the association of maternal BMI and SGA <10^{th} %ile adjusting for potential confounders. After adjusting for tobacco use, chronic hypertension, African American race, pre-eclampsia, and pre-gestational diabetes, underweight BMI (aOR 1.8, 95% CI 1.5–2.1) remained significantly associated with an increased risk of SGA while overweight BMI (aOR 0.7,

95% CI 0.7–0.8) and obese BMI (aOR 0.6, 95% CI 0.5–0.7) remained associated with a decreased risk of SGA<10th%ile. This base model was then compared to a second model containing the same potential confounders plus the interaction term (BMI category*tobacco). Results from this analysis are shown in Table 4. Adjusted odds ratios (aOR) for the association of maternal BMI and SGA are shown for both the base model and the model containing the interaction variable. There was minimal change in the aORs and surrounding confidence intervals with the addition of the interaction term to the model. When comparing the two models, the non-significant LR test (p=0.73) indicated that there was no significant effect modification of tobacco use on the association between maternal BMI and SGA across all BMI categories. A repeated analysis was then performed evaluating BMI as a continuous variable. Again, no significant effect modification was observed. (LR test p=0.72)

When evaluating the secondary outcome of SGA <5th%ile, underweight BMI remained significantly associated with an increased risk of SGA (aOR 1.5, 95% CI 1.2–2.0) after adjusting for tobacco use, chronic hypertension, African American race, pre-eclampsia and pre-gestational diabetes. While overweight and obese BMI were not significantly associated with SGA <5th%ile in the univariate analysis, these BMI categories were associated with a statistically significant decreased risk of SGA in the adjusted analysis. There was no evidence of significant effect modification when comparing the models with and without the interaction term. (LR test p=0.62)

Discussion

Data from our 18-year experience demonstrates no evidence of a synergistic effect between maternal BMI and tobacco use on the development of SGA across all BMI strata. Both underweight pre-pregnancy BMI and tobacco use were independently associated with an increased risk of SGA; whereas, overweight and obese BMI were associated with a decreased risk of SGA. In 2008, Aagaard-Tillery *et al.* performed a population-based retrospective analysis to determine if tobacco exposure was associated with a modification in birth weight and the incidence of SGA in the presence of other influential maternal factors including BMI. While that study demonstrated that tobacco use was both an independent and additive contributor to SGA, multiplicative interaction (i.e. synergy) was not assessed.[7] Results from a stratified analysis by Ness *et al.* demonstrated that smoking increased SGA risk among underweight women as well as overweight/obese women. In that same study, when synergism between BMI and tobacco use on SGA was evaluated by using an interaction variable (BMI category*tobacco), no significant synergistic effect was observed.[13] (p=0.11) Using two rigorous statistical methods, our study demonstrates no synergistic effect between tobacco use and abnormal pre-pregnancy BMI on the development of SGA. Although not observed in our population, previous reports have demonstrated a higher rate of tobacco use among underweight women.[15,16] While it is evident that both smoking cessation and maintenance of normal body weight are essential to one's general health status outside of pregnancy, our study also suggests that underweight, smokers should be counseled that elimination of only one of these risk factors does not alter the risk of SGA during pregnancy.

Our study again confirms the well-established association between low maternal BMI with SGA as well as the association between tobacco exposure and SGA, thereby validating our cohort. In our final model, low maternal pre-pregnancy BMI conveyed a 1.8 fold increased risk for SGA <10th%ile and a 1.5 fold increased risk for SGA <5th%ile after controlling for potential confounding factors including tobacco use. Our study also found a statistically significant decreased risk of SGA in both the overweight and obese pre-pregnancy BMI categories. These findings are similar to Cnattingius *et al.* who demonstrated a decreased

risk of delivering an SGA neonate with increasing body mass index.[8] Alternatively, Gardosi and Francis recently found a substantially negative effect of high maternal BMI on neonatal birth weight when deriving coefficients for creating customized fetal growth curves.[10] Even when evaluating those patients with the most severe obesity (BMI ≥40 and BMI ≥50), this phenomenon was not observed in our study population.

Strengths of our study include our large sample size obtained from our robust genetic database from which maternal sociodemographics and pregnancy outcome data were extracted. Since the initiation of the database, there have been dedicated nurse coordinators responsible for obtaining complete and accurate pregnancy and neonatal outcome data, thereby limiting the number of patients lost to follow up. Our study also used two well-validated methods, stratified analysis and effect modification analysis using interaction variables, to evaluate for synergism between tobacco exposure and BMI on the development of SGA, both yielding similar results. This lends strength to our argument that a synergistic effect between tobacco exposure and maternal BMI on SGA does not exist. In addition, an *a priori* definition of a single interaction variable was used to avoid potential α error. Finally, we obtained similar results using two different definitions of SGA (<10th and <5th %iles). While SGA <10th %ile is the most common threshold used in practice, the definition of SGA <5th %ile may be more representive of pathologic growth restriction as opposed to constitutionally small growth.

Our study is not without limitations, including its retrospective design. Data collection is certainly subject to misclassification and data entry errors; however, the follow-up system in our center has been well-validated in previous studies and the possibility of misclassification is minimal.[17,18] Although we controlled for known potential confounders in the adjusted analysis, the possibility of unknown or unmeasured confounders still exists. Maternal BMI was also recorded as pre-pregnancy BMI, and no information was available regarding gestational weight gain. It is possible that gestational weight gain above or below the recommendations from the Institute of Medicine may impact fetal growth. Tobacco exposure was also classified as a dichotomous variable in our database, and no information regarding the amount of tobacco use was available for analysis. Previous studies have demonstrated a positive dose-response relationship between tobacco use and SGA.[1,19] The potential remains that a synergistic effect between tobacco use and BMI may have been apparent if evaluating heavy smokers only. Our data also assumes that a positive self-report of tobacco use represents habitual use throughout pregnancy. In order to evaluate these potential discrepancies, a prospective study with detailed information on patient-reported tobacco use obtained at multiple time points throughout pregnancy would potentially be needed. Finally, our outcomes of SGA <10th%ile and <5th%ile for gestational age may not be entirely representative of pathologic growth restriction. While SGA <3rd %ile for gestational age may be a better surrogate for perinatal morbidity, the small number of patients in our cohort who would meet this criteria would limit any meaningful analysis.

In conclusion, our study demonstrated no synergistic effect between tobacco use and low maternal BMI on the development of SGA using two independent statistical approaches. Our study also confirms that low maternal BMI and tobacco exposure are independent risk factors for the development of SGA while high maternal BMI is associated with a decreased risk of SGA. While multiple mechanisms for the development of SGA have been proposed, the precise etiology still remains unclear. Continued patient counseling toward *both* smoking cessation and the maintenance of normal pre-pregnancy body weight remain paramount to decreasing the incidence of SGA and its associated neonatal and long-term morbidities.

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Table 1

Characteristics of the study group across body mass index categories

	Underweight n=1,174	Normal Weight n=25,801	Overweight n=13,008	Obese n=10,580
Mean Maternal Age (yrs)	28.3 ± 6.8	30.5 ± 6.2	30.3 ± 6.3	29.4 ± 6.3
Race				
White	60.1%	70.0%	63.9%	52.7%
African American	17.6%	13.0%	22.4%	37.5%
Other	22.3%	17.0%	13.7%	9.8%
SGA <10th %ile	13.5%	7.8%	6.9%	7.0%
SGA <5th %ile	5.0%	3.2%	3.0%	3.1%
Tobacco Use	11.9%	10.3%	11.1%	12.2%
Chronic HTN	0.5%	0.8%	1.8%	6.1%
Pre-eclampsia	2.8%	4.6%	8.4%	13.0%
Pre-gestational Diabetes	0.3%	0.8%	1.5%	3.9%

* All p values <0.001

SGA=small for gestational age; HTN=hypertension

Table 2

Incidence and Relative Risk of Small for Gestational Age (SGA) Neonates (<10th %ile) Across all BMI Categories Stratified by Tobacco Use

BMI Category	Smokers	Non-smokers
	Underweight (n=1,174)	
SGA	32 (22.9%)	127 (12.3%)
Non-SGA	108 (77.1%)	907 (87.7%)
RR (95% CI)	1.5 (1.1–2.1)	1.9 (1.6–2.2)
	p=0.22	
	Normal Weight (n=25,801) ***Reference Group*** *	
SGA	434 (16.3%)	1,581 (6.8%)
Non-SGA	2,235 (83.7%)	21,551 (93.2%)
	Overweight (n=13,008)	
SGA	210 (14.5%)	575 (6.2%)
Non-SGA	1,239 (85.5%)	10,874 (94.1%)
RR (95% CI)	0.9 (0.8–1.1)	0.9 (0.8–0.9)
	p=0.35	
	Obese (n=10,580)	
SGA	167 (12.9%)	575 (6.2%)
Non-SGA	1,126 (87.1)	8,712 (93.8%)
RR (95% CI)	0.8 (0.7–0.9)	0.9 (0.8–1.0)
	p=0.16	

* RR=relative risk; CI=confidence interval; BMI=body mass index

Table 3

Incidence and Relative Risk of Small for Gestational Age (SGA) Neonates (<5th %ile) Across all BMI Categories Stratified by Tobacco Use

BMI Category	Smokers	Non-smokers
	Underweight (n=1,174)	
SGA	14 (10%)	45 (4.4%)
Non-SGA	126 (90%)	989 (95.6%)
RR (95% CI)	1.3 (0.8–2.2)	1.7 (1.3–2.3)
	p=0.38	
	Normal Weight (n=25,801) ***Reference Group***	
SGA	221 (8.3%)	603 (2.6%)
Non-SGA	2,448 (91.7%)	22,529 (97.4%)
	Overweight (n=13,008)	
SGA	107 (7.4%)	285 (2.5%)
Non-SGA	1,342 (92.6%)	11,274 (97.5%)
RR (95% CI)	0.9 (0.7–1.2)	0.9 (0.8–1.0)
	p=0.89	
	Obese (n=10,580)	
SGA	87 (6.7%)	244 (2.6%)
Non-SGA	1,206 (93.3%)	9,043 (97.4%)
RR (95% CI)	0.8 (0.7–1.0)	1.0 (0.9–1.1)
	p=0.18	

Table 4

Effect modification of tobacco use and BMI on SGA

	SGA<10th %ile aOR* (95% CI) (Base Model)	SGA <10th %ile aOR¶ (95% CI) (+ Interaction Term)	SGA<5th %ile aOR* (95% CI) (Base Model)	SGA <5th%ile aOR¶ (95% CI) (+ Interaction Term)
Underweight	1.8 (1.5–2.1)	1.8 (1.5–2.2)	1.5 (1.2–2.0)	1.6 (1.2–2.2)
Overweight	0.7 (0.7–0.8)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)
Obese	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.7 (0.6–0.8)
LR test	0.73		0.62	

*Adjusted for tobacco use, chronic hypertension, pre-eclampsia, African American race, and pre-gestational diabetes

¶Adjusted for tobacco use, chronic hypertension, pre-eclampsia, African American race, and pre-gestational diabetes, and interaction term (BMI category*tobacco)

SGA=small for gestational age; BMI=body mass index