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In utero exposure to tobacco smoke, subsequent cardiometabolic risks, and metabolic syndrome among U.S. adolescents

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Abstract

Purpose: Maternal smoking during pregnancy increases risk of adverse pregnancy outcomes. However, little is known regarding *in utero* smoke exposure and offspring cardiometabolic risk. Thus, we examined the association between *in utero* smoke exposure and cardiometabolic risk factors and the metabolic syndrome (MetS) in adolescents.

Methods: Participants included 7464 adolescents aged 12–15 years identified from the National Health and Nutrition Examination Survey (1999–2014). Multiple logistic and linear regression analyses estimated sex-specific means and odds ratios (ORs) for the association between *in utero* smoke exposure and MetS and cardiometabolic risk factors.

Results: MetS prevalence was 9.0% in exposed versus 5.9% in unexposed adolescents. *In utero* smoke exposure was significantly associated with increased odds of MetS among males in models controlling for adolescent age, maternal age, and race/ethnicity (OR: 2.48, 95% confidence interval: 1.19, 5.20), with attenuation of this effect in subsequent models. *In utero* smoke exposure was associated with significantly elevated mean body mass index and waist circumference percentiles among female adolescents across most models in regression analyses.

Conclusions: *In utero* smoke exposure appears to be associated with an increased likelihood of high waist circumference and body mass index percentiles, especially among female adolescents. Our study demonstrates the long-term cardiometabolic impact in offspring, highlighting the importance of prepregnancy smoking cessation.

Keywords

Adolescent; Tobacco; Smoking; Pregnancy; Metabolic syndrome X; Waist circumference

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Introduction

Tobacco smoking during pregnancy has been shown to be directly associated with adverse pregnancy outcomes, including stillbirth, preterm birth, spontaneous abortion, and fetal growth restriction [1]. In addition, there is a growing body of research concerning associations of *in utero* maternal smoking and long-term health consequences for the offspring, including certain cancers and neurobehavioral disorders [2]. Although much is unknown about the mechanism underlying these associations, the developmental origins of health and disease hypothesis proposes that prenatal exposures cause fetal adaptations at the biologic and genetic level, resulting in changes to lifelong disease risk [3–5].

Of particular public health concern is the association between maternal smoking and increased cardiometabolic risks for offspring, characterized by metabolic syndrome (MetS). The MetS has been defined in various ways throughout years of research, particularly among adolescent populations [6]. Generally, the MetS is defined as a clustering of obesity, hypertension, dyslipidemia, and hyperglycemia and is known to increase the risk of cardiovascular disease (CVD) and type 2 diabetes (T2D) [7,8]. Prior studies have reported positive associations between *in utero* exposure to tobacco smoke and disorders such as hypertension, obesity, gestational diabetes mellitus, diabetes (type 1 and type 2), and the MetS in adulthood [9–11]. However, other studies have reported no association between these variables after adjustment for relevant confounders (maternal weight gain, maternal diabetes, socioeconomic status [SES], offspring smoking, offspring physical activity, etc.) [12]. Several reviews and meta-analyses have reported similarly conflicting results, with the overall conclusion that additional research is needed to examine the link between maternal smoking and risk of T2D and the MetS in offspring [13,14].

The prevalence of obesity, diabetes, and other cardiometabolic conditions in adolescents and children has increased rapidly during the last several decades, with childhood obesity more than tripling to reach 16.9% in 2012 [15]. These cardiometabolic conditions often track into adulthood, contributing to the increasing burden of CVD and other chronic diseases [16–19]. Furthermore, factors such as early age at menarche are thought to be predictive of adult body mass index (BMI) and CVD morbidity and mortality [20]. Therefore, it is imperative that determinants of childhood obesity and cardiometabolic well-being are understood and interventions for these determinants implemented.

The current research expands on the growing body of research by exploring the relationship between maternal smoking and components of MetS (abdominal adiposity, dyslipidemia, hypertension, etc.) in adolescents with nationally representative National Health and Nutrition Examination Survey (NHANES) data. As maternal smoking during pregnancy remains high, additional evidence supporting its long-term effects among offspring may help inform public health interventions to dissuade tobacco use among pregnant smokers [21]. This project aims to investigate the association between exposure to *in utero* smoking and cardiometabolic risk factors (MetS, MetS components, and age at menarche) among U.S. adolescents.

Materials and methods

Study design and data collection

Data from 7464 adolescents between the ages of 12 and 15 years were collected from eight cycles of the NHANES between 1999 and 2014. NHANES is designed by the National Center for Health Statistics at the Centers for Disease Control and Prevention to monitor the health and nutritional status of the U.S. population. NHANES uses a complex, stratified, multistage probability cluster sampling method to achieve a national representative sample of the noninstitutionalized U.S. population [22]. In-person, face-to-face interviews with adolescents and their parents/guardians were conducted for data collection. The Medical University of South Carolina institutional review board reviewed and declared this study to be nonhuman subjects research.

Outcome assessment

Physical examinations were conducted to assess blood pressure and anthropometry. Biospecimen collection and laboratory testing were conducted to assess lipids and fasting glucose levels. The methods for these assessments are described in-depth elsewhere [22].

MetS was defined using cardiometabolic cutoff points for obesity, dyslipidemia, fasting glucose levels, and elevated blood pressure. To be diagnosed, participants had to meet three of the following criteria based on modifications to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol: waist circumference above the 90th percentile for age and sex; systolic or diastolic blood pressure above the 90th percentile for age and height; high-density lipoprotein levels below or equal to 40 mg/dL; triglycerides levels above or equal to 110 mg/dL; and fasting glucose levels above 100 mg/dL [23,24]. BMI greater than or equal to 85th percentile for age and sex (overweight), BMI greater than or equal to 95th percentile for age and sex (obese), and age at menarche were also examined for associations with exposure to maternal smoking.

Exposure assessment

Maternal smoking during pregnancy was defined by a positive answer to the question: “Did biological mother smoke at any time while she was pregnant?” from the Early Childhood section of the Sample Personal Questionnaire (ECQ020).

Covariate assessment

Participant age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other), SES, age at menarche, early life factors (e.g., birth weight, maternal smoking during pregnancy), and environmental factors (e.g. household smoking) were self-reported by adolescent participants or their parents/guardians. Other race/ethnicity was defined as non-Hispanic persons reporting multiple races. SES is defined by the poverty index ratio and ranges from 0 to 5, with values less than one meaning that a family lives below the poverty threshold. Household smoking was defined as a positive answer to the question “Does anyone smoke inside home?” from the Household Smokers section of the Family Questionnaire (SMQFAM). Biospecimen collection and laboratory testing were conducted

to assess cotinine levels. The methods for these assessments are described in-depth elsewhere [22].

Statistical analyses

Proportions and 95% confidence intervals (CIs) were calculated for categorical variables. Means and standard deviations were calculated for continuous variables. All predictors were stratified by maternal smoking status during pregnancy to describe the prevalence of MetS and its various components among a sample of U.S. adolescents. Odds ratios (ORs) and 95% CIs for the association between the MetS and its components were calculated by multiple logistic regression models adjusted for the interaction of sex and maternal smoking in addition to other covariates. Covariates were chosen based on factors known to influence or interact with the maternal smoking during pregnancy and offspring cardiometabolic risk [13,14]. Interactions were assessed within models for significance, and models are reported stratified by interaction variables. Model 1 routinely adjusted for adolescent age, adolescent race/ ethnicity, maternal age, and poverty index ratio. In addition to the variables in model 1, model 2 subsequently included current household smoking. In addition to the variables in model 2, model 3 subsequently included birth weight. Model 4 included all variables in model 3 except for current household smoking, which was replaced with a measure of cotinine. Model 1 in the Supplementary Tables controlled for adolescent age, adolescent race/ethnicity, and maternal age. Adolescents with a BMI percentile indicating underweight (BMI $\leq 5^{th}$ percentile for age and sex; $n = 286$) were excluded from logistic regression analyses for overweight or obesity. Multiple linear regression analyses were performed to compare means between groups. As 438 female adolescents had not experienced menarche upon participation in the study, a multiple linear regression sensitivity analysis of the association between age at menarche and maternal smoking during pregnancy examined the impact of setting menarche to current age for this subset. Data were analyzed using SAS (version 9.3; SAS institute; Cary, NC). All analyses accounted for the clustered sampling design and oversampling.

Results

Missing data were common for the answers to individual survey questions as well as for some laboratory tests, so *Ns* for analyses do not consistently sum to 7464. Table 1 presents characteristics of the NHANES sample by maternal smoking status during pregnancy. Approximately 17% of adolescents were exposed to maternal smoking *in utero*. Adolescents with mothers who smoked while pregnant were more likely to be non-Hispanic white, have a lower birth weight, live in a smoking household, and have mothers who were slightly younger during their pregnancy than adolescents of mothers who did not smoke while pregnant. In addition, adolescents with mothers who smoked while pregnant were less likely to be Hispanic. The overall prevalence of MetS among adolescents was 6.5% (males: 7.9%; females: 4.9%). In females, the prevalence of MetS was 4.9% among unexposed and 4.8% among those exposed to *in utero* smoke. In males, the prevalence was 7.0% among unexposed and 13.1% among exposed but did not reach statistical significance (Table 2). In addition, components of the MetS differed in their prevalence between the exposed and unexposed within sexes. Significant differences in the prevalence of a high waist

circumference were observed for males exposed to *in utero* smoking (22.2% [95% CI: 17.2, 27.2]) compared to unexposed males (15.0% [95% CI: 13.3, 16.8]).

Linear regression of components of the MetS and age at menarche were conducted to further assess the relationship between these measures and maternal smoking (Table 3). Measures of anthropometry (BMI and waist circumference percentiles) were significantly elevated in the exposed group for males in model 1, and for females in models 2 and 3. BMI percentile was also significantly elevated for females in model 4. Among females not exposed to *in utero* smoke, high-density lipoprotein was significantly elevated in model 1 and model 2. Among males not exposed to *in utero* smoke, fasting glucose was significantly elevated in model 5. Age at menarche was significantly higher among unexposed female adolescents in models 1 through 3, although the magnitude of the observed difference was small. The sample size was inadequate for comparisons of age at menarche in model 4. Sensitivity analyses substituting current age for age at menarche among females who had not yet undergone menarche resulted in the same conclusions as the original analyses. Other components of the MetS were not significantly different by exposure status across all models. Systolic blood pressure, BMI, and waist circumference percentiles were significantly elevated in the exposed group for both males and females in model 1 as presented in Supplementary Table 1.

Logistic regression analyses results are reported in Table 4. Waist circumference greater than 90th percentile was significantly elevated among the exposed group for both sexes in model 1. Model 4 found that the odds of overweight (OR = 2.53, 95% CI: 1.09, 5.87) and obesity (OR = 2.38, 95% CI: 1.07, 5.28) were significantly higher among females exposed to *in utero* smoke exposures than unexposed female adolescents. Adjusting for adolescent age, maternal age, and race/ethnicity, the odds of having the MetS was 2.48 (95% CI: 1.19, 5.20) times higher among male adolescents exposed to *in utero* smoke exposure than unexposed male adolescents (see Supplementary Table 2). This association attenuated and became nonsignificant upon further adjustment. Similarly, the odds of obesity was 1.74 (95% CI: 1.10, 2.77) times higher among male adolescents exposed to *in utero* smoke exposure than unexposed male adolescents in model 1 (see Supplementary Table 2). This association attenuated and became nonsignificant upon further adjustment.

Discussion

This study demonstrates a trend toward the relationship between *in utero* exposure to tobacco and increased likelihood for MetS among adolescents in the U.S. The data used in this research come from a nationally representative sample and address various components of the MetS. After adjusting for adolescent age, adolescent race/ethnicity, and maternal age, adolescent males exposed to *in utero* smoke exposure had 2.48 times the odds of having the MetS as compared to unexposed adolescent males; female adolescents did not have a significant increase in their odds after exposure. The cardiometabolic component most significantly affected across sex was that of waist circumference. Interestingly, adjustment for birth weight did not attenuate the significant association between *in utero* tobacco smoke exposure and having waist circumference in the 90th percentile among male or female adolescents.

Studies have shown birth weight to be impacted by maternal smoking during pregnancy, and birth weight is a well-established predictor of one's later cardiometabolic well-being [10,25,26]. Our analyses suggest that *in utero* tobacco smoke exposure may have a direct effect on adolescent high weight circumference, although a more formal mediation analyses would be required to assess the controlled direct effect. Similarly, Cupul-Uicab et al. reported no changes in their observed associations between *in utero* tobacco smoke exposure and obesity, hypertension, or diabetes in a cohort of adult women following adjustment for current BMI and birth weight [10]. Multiple linear regression results suggest that male and female adolescents exposed to *in utero* tobacco smoke exposure may be more likely to have higher mean BMI and waist circumference percentile than unexposed adolescents. However, despite reaching statistical significance, some of the mean differences reported in multiple linear regression models may not be clinically significant.

The decision to include the interaction of sex and maternal smoking was made a priori due to previous studies suggesting that the programming effect of early life exposures on cardiometabolic risk of offspring may have differential effects by sex [27]. However, the interaction effect within our models was not statistically significant ($P \leq 0.2$) for the majority of our models (see Table 3). Despite not reaching statistical significance in all cases, we feel that presenting sex-specific results is appropriate, given our research question.

A 2013 meta-analysis found only two studies assessing the relationship between *in utero* exposure to tobacco smoke and the MetS [14]. These studies reported different results, which may be due to differences in the study sample sizes and ages of the participants. Power et al. reported a significant protective association between maternal smoking during pregnancy and offspring MetS risk among adults aged 45 years [14,28]. Huang et al. reported a significant increased risk of MetS among exposed children versus the unexposed children at 8 years of age [14,29]. Our study suggests that there is not a significant association between *in utero* tobacco exposure and the MetS among female adolescents or among male adolescents after adjustment for relevant confounders. However, we found consistent significant associations between in utero tobacco smoke exposure and offspring anthropometry, which is consistent with the findings of the 2013 meta-analysis [14].

We found that 16.8% of mothers in our sample self-reported smoking while pregnant, which is higher than the 8.4% national smoking prevalence reported by the National Vital Statistics Reports for the United States [30]. The mechanism behind the relationship between early life exposure to tobacco smoke and subsequent increased likelihood for cardiometabolic risk factors is not fully understood [31]. The hypothesis of developmental origins of health and disease proposes that the adaptations a fetus makes to intrauterine and maternal conditions affect the development of the structure and function of organs, which may lead to malfunction of body systems [32]. Some studies have applied this idea of "reprogramming" to demonstrate that the fetal adaptations could not only affect organ systems but also metabolism [13]. Active smoking by adolescents, and exposure to second-hand smoke by adolescents, increases the likelihood that an adolescent has the MetS, particularly among obese and overweight adolescents [33]. Cook et al. hypothesize a complex interaction between social, ethnic, environmental, and genetic factors leading to the development of cardiometabolic risks as a cluster in adolescents, with insulin resistance stemming from

obesity tying the components of the MetS together [34]. Cook et al. describe the MetS in adolescents as it begins with insulin resistance, made worse by obesity, dyslipidemia, and raised blood pressure [34]. If adolescents with MetS progress into adulthood with these metabolic disarrangements, they will have prolonged exposure to T2D, an illness typically occurring at the age of 50e60 years and its associated comorbidities, including depression, nephropathy, neuropathy, and CVD. Thus, the relationship between *in utero* tobacco smoke exposure, offspring adolescent adiposity, and other cardiometabolic outcomes may have profound public health implications.

Limitations of this study include the self-reporting of maternal smoking, which is typically underreported. However, this would bias our results toward the null. In the present study, we examined relationships by adolescent race/ethnicity but did not include these data in the results due to limited power. In addition, stratifying by race/ethnicity introduces certain limitations when measuring MetS, as the definition of MetS may be biased to underestimate associations within certain ethnic groups. In addition, we may have overadjusted in some models by including offspring birth weight, which is a recognized risk factor for adolescent obesity and a known outcome of maternal smoking during pregnancy [13]. Interestingly, other studies have found associations between adolescent adiposity and *in utero* tobacco smoke exposure, even after adjustment for possible mediating factors such as offspring birth weight [13]. This may suggest that the impact of tobacco smoke on the developing fetus may affect subsequent cardiometabolic risk through alternative pathways. Our study was also limited by the availability of data from NHANES; data related to dose and timing of smoke exposure would have been interesting to include in our analyses. NHANES data are cross-sectional in nature and thus cannot inform causality of this relationship; rather, this study is intended to be hypothesis generating. Furthermore, offspring cotinine was measured in a smaller subset of NHANES participants than current household smoking ($n = 2626$ adolescents had cotinine measurements, whereas $n = 6673$ adolescents had current household smoking in NHANES); thus, the results of model 4 should be interpreted with caution. We used $P \leq 0.05$ to determine statistical significance and did not make adjustments for multiple comparisons. As with other studies examining the link between maternal smoking during pregnancy and offspring cardiometabolic risk factors, we were unable to adjust for certain confounders that would have been interesting to include in our model, such as maternal weight gain during pregnancy, alcohol use during pregnancy, and maternal lifestyle factors (e.g., diet and physical activity) or offspring lifestyle factors [14].

This study adds to the public health importance of encouraging maternal smoking cessation before pregnancy and suggests that the health consequences of smoking may impact the offspring's cardiometabolic health from birth through adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Participant characteristics by mother's smoking status during pregnancy [percent (95% CI) or mean (±SD)]

Participant characteristics	Maternal smoking status during pregnancy	
	Non-smoker	Smoker
Male offspring (%)	51.1 (47.3, 50.6)	48.9 (45.3, 54.5)
Offspring Race/ethnicity (%)		
HISPANIC *	**21.2 (18.7, 23.7)**	**8.6 (6.0,11.2)**
Non-Hispanic black	14.6 (12.9, 16.4)	11.5 (9.2, 13.8)
Non-Hispanic white *	**56.4 (53.2, 59.6)**	**74.8 (71.0, 78.5)**
Other	7.7 (6.4, 9.1)	5.1 (3.2, 6.9)
Household smoking (%) *	**11.7 (10.2, 13.1)**	**52.5 (47.3, 57.7)**
Offspring cotinine (ng/mL)	0.05 ± 1.06	0.52 ± 1.23
Offspring birth weight (grams) *	**3401 ± 15**	**3303 ± 38**
Offspring age (y)	13.5 ± 0.02	13.5 ± 0.05
Maternal age at birth (y) *	**27.1 ± 0.16**	**25.6 ± 0.29**
PIR (0–5)	2.69 ± 0.05	2.17 ± 0.07

PIR = Poverty Income Ratio; SD = standard deviation.

* $P \leq .05$ for differences within component between maternal smoking status during pregnancy. The bold simply emphasized that these variables had significant differences.

Table 2

Prevalence [(percent (95% CI)] of metabolic syndrome and its components among U.S. adolescents aged 12–15 years by sex and smoking status of the mother during pregnancy

Cardiometabolic outcomes	Females		Males	
	Mom nonsmoker	Mom smoker	Mom nonsmoker	Mom smoker
Metabolic components (%)				
Waist circumference >90th percentile	20.1 (17.8, 22.4)	27.4 (21.9, 33.8)	**15.0* (13.3, 16.8)**	**22.2* (17.2, 27.2)**
Fasting glucose >100 mg/dL	10.8 (8.6, 13.0)	16.9 (10.0, 23.9)	24.3 (20.7, 28.0)	20.1 (12.8, 27.5)
Overweight (BMI > 85th percentile)	34.8 (32.0, 37.7)	43.0 (36.4, 49.6)	34.9 (32.1, 37.7)	40.4 (35.0, 45.8)
Obese (BMI > 95th percentile)	18.2 (16.0, 20.4)	24.9 (20.1, 29.7)	18.8 (16.8, 20.8)	23.2 (18.1, 28.4)
Blood pressure> 90th percentile	6.1 (4.8, 7.4)	4.2 (2.1, 6.4)	6.0 (4.9, 7.1)	7.6 (4.5, 10.6)
HDL cholesterol <40 mg/dL	13.5 (11.6, 15.5)	14.5 (10.3, 18.7)	19.6(17.4,21.9)	24.3 (18.5, 30.0)
Triglycerides > 110 mg/dL	16.9 (13.8, 19.9)	20.2 (13.8, 26.5)	18.7(15.6,21.8)	24.0(17.1,31.0)
MetS (%)	4.9 (3.2, 6.5)	4.8 (0.9, 8.8)	7.0 (4.8, 9.1)	13.1 (6.0, 20.1)
Age at menarche > 12 y (%)	35.7 (33.1, 38.3)	36.2 (30.7, 41.7)	—	—

HDL = high-density lipoprotein.

*Significance was determined by nonoverlapping 95% CIs comparing adolescents exposed to in utero smoke exposure to unexposed adolescents. The bold simply emphasized that these variables had significant differences.

Table 3

Least squares means for the association between *in utero* tobacco smoke exposure and MetS components in male and female adolescents [mean (95% CI)]

Cardiometabolic outcomes	Females		Males		Significance of interaction by sex
	Mom nonsmoker	Mom smoker	Mom nonsmoker	Mom smoker	
Model 1[†]					
BMI (percentile)	64.9 (63.2, 66.7)	67.9 (64.1, 71.7)	**64.3 (62.6, 66.1)***	**71.7 (68.3, 75.0)**	*P* = .13
WC (percentile)	78.5 (77.7, 79.3)	80.5 (78.7, 82.4)	**78.4 (77.6, 79.2)***	**81.1 (79.4, 82.7)**	*P* = .63
HDL (mg/dL)	**52 (51, 52)***	**50 (48, 52)**	51 (51,52)	52 (50, 53)	*P* = .15
Total TG (mg/dL)	73 (70, 75)	77 (70, 84)	74(71,77)	70 (64, 77)	*P* = .12
SBP (percentile)	42.7 (41.0, 44.4)	45.3 (40.8, 49.9)	42.6 (40.9, 44.3)	45.9 (42.3, 49.4)	*P* = .86
DBP (percentile)	37.4 (35.8, 39.1)	39.6 (36.2, 43.0)	37.7 (36.1, 39.4)	37.8 (34.5,41.1)	*P* = .42
Fasting glucose (mg/dL)	95 (93, 96)	93 (91, 96)	95 (94, 96)	95 (93, 96)	*P* = .45
Age at menarche (y)	**11.7 (11.7, 11.8)***	**11.5 (11.4, 11.7)**	—	—	
Model 2[‡]					
BMI (percentile)	**63.5 (61.5, 65.5)***	**70.3 (66.6, 74.0)**	64.3 (622.3, 66.3)	66.0 (61.9, 70.2)	*P* = .09
WC (percentile)	**78.2 (77.3, 79.1)***	**80.6 (78.9, 82.2)**	78.5 (77.3, 81.1)	79.3 (77.4, 81.1)	*P* = .28
HDL (mg/dL)	51 (51, 52)	52 (50, 53)	52 (51,52)	50 (48, 52)	*P* = .30
Total TG (mg/dL)	76 (72, 79)	72 (66, 80)	75 (72, 78)	78 (70, 86)	*P* = .19
SBP (percentile)	43.4 (41.5, 45.3)	44.7 (40.9, 48.4)	43.3 (41.3, 45.2)	45.2 (39.9, 50.4)	*P* = .87
DBP (percentile)	38.4 (36.5, 40.3)	36.7 (33.1,40.4)	38.3 (36.4, 40.2)	37.5 (33.8, 41.2)	*P* = .74
Fasting glucose (mg/dL)	95 (93, 96)	94 (92, 96)	95 (93, 96)	93 (90, 96)	*P* = .49
Age at menarche (y)	**11.7 (11.7, 11.8)***	**11.5 (11.3, 11.7)**	—	—	
Model 3[§]					
BMI (percentile)	**63.5 (61.4, 65.6)***	**70.2 (66.3, 74.1)**	64.2 (62.1, 66.3)	66.2 (62.1, 70.3)	*P* = .10
WC (percentile)	**78.2 (77.3, 79.1)***	**80.4 (78.6, 82.1)**	78.4 (77.4, 79.3)	79.3 (77.4, 81.1)	*P* = .34
HDL (mg/dL)	51 (51, 52)	52 (50, 53)	52 (51,52)	50 (48, 52)	*P* = .36
Total TG (mg/dL)	74 (68, 83)	74 (65, 84)	75 (68, 83)	78 (67, 91)	*P* = .32
SBP (percentile)	43.6 (41.7, 45.5)	44.3 (40.6, 47.9)	43.4 (41.4, 45.5)	45.1 (39.8, 50.4)	*P* = .78
DBP (percentile)	38.5 (36.5, 40.3)	36.9 (33.1,40.8)	38.5 (36.6, 40.3)	36.7 (32.9, 40.5)	*P* = .91

Cardiometabolic outcomes	Females		Males		Significance of interaction by sex
	Mom nonsmoker	Mom smoker	Mom nonsmoker	Mom smoker	
Fasting glucose (mg/dL)	95 (93, 96)	94 (92, 96)	95 (93, 96)	93 (90, 96)	$P = .62$
Age at menarche (y)	**11.7 (11.4, 12.1)** *	**11.5 (11.1, 11.8)**	—	—	
Model 4//					
BMI (percentile)	**64.9 (62.6, 67.2)** *	**69.4 (63.9, 74.9)**	65.0 (62.6, 67.4)	68.9 (63.2, 74.6)	$P = .88$
WC (percentile)	78.5 (77.5, 79.5)	81.2 (78.6, 83.7)	78.8 (77.7, 79.9)	79.6 (77.0, 82.2)	$P = .33$
HDL (mg/dL)	52 (51, 53)	52 (49, 55)	52 (51,53)	52 (49, 55)	$P = .87$
Total TG (mg/dL)	73 (62, 86)	70 (60, 82)	73 (62, 86)	69 (59,81)	$P = .85$
SBP (percentile)	44.6 (41.7, 47.5)	45.8 (39.1, 52.4)	44.2 (41.1, 47.3)	48.3 (41.3, 55.3)	$P = .62$
DBP (percentile)	38.0 (34.9, 41.1)	34.5 (29.2, 39.8)	37.7 (34.7, 40.7)	36.4 (30.3, 42.4)	$P = .60$
Fasting glucose (mg/dL)	96 (94, 97)	95 (91, 98)	**96 (94, 97)** *	**93 (91, 95)**	$P = .34$
Age at menarche (y)	—	—	—	—	

DBP = diastolic blood pressure; HDL = high-density lipoprotein; PIR = Poverty Income Ratio; SBP = systolic blood pressure; TG = total triglycerides; WC = waist circumference.

*$P \leq .05$ for mean difference comparing adolescents exposed to in utero smoke exposure to unexposed adolescents of the same sex. The bold simply emphasized that these variables had significant differences

†Adjusted for adolescent age, maternal age, race/ethnicity, and PIR

‡Adjusted for adolescent age, maternal age, race/ethnicity, PIR, and current household smoking

§Adjusted for adolescent age, maternal age, race/ethnicity, PIR, current household smoking, and birth weight

//Adjusted for adolescent age, maternal age, race/ethnicity, PIR, cotinine, and birth weight.

Table 4

Odds ratios (95% Cl) for the association between *in utero* tobacco smoke exposure and MetS components in male and female adolescents

Cardiometabolic outcomes	Model 1[†]		Model 2[‡]		Model 3[§]		Model 4[//]	
	Females OR (95% Cl)	Males OR (95% Cl)	Females OR (95% Cl)	Males OR (95% Cl)	Females OR (95% Cl)	Males OR (95% Cl)	Females OR (95% Cl)	Males OR (95% Cl)
MetS	0.96 (0.31, 2.97)	2.09 (0.94, 4.61)	1.12 (0.37, 3.48)	2.18 (0.93, 5.12)	1.27 (0.41, 3.89)	2.15 (0.90, 5.12)	1.00 (0.23, 4.36)	1.26 (0.36, 4.43)
Waist circumference >90th percentile	**1.50[*] (1.06, 2.13)**	**1.82[*] (1.29, 2.58)**	1.31 (0.68, 2.55)	1.39 (0.73, 2.64)	1.39 (0.69, 2.79)	1.29 (0.66, 2.53)	1.65 (0.71, 3.84)	1.09 (0.35, 3.45)
Weight Categories								
Overweight (BMI > 85th percentile)	1.44 (0.84, 2.47)	1.41 (0.83, 2.40)	1.56 (0.89, 2.76)	1.21 (0.73, 2.01)	1.70 (0.94, 3.08)	1.19 (0.70, 2.02)	**2.53[*] (1.09, 5.87)**	0.91 (0.38, 2.16)
Obese (BMI > 95th percentile)	1.53 (0.85, 2.78)	1.51 (0.84, 2.72)	1.61 (0.88, 2.98)	1.27 (0.68, 2.34)	1.75 (0.93, 3.28)	1.23 (0.65, 2.32)	**2.38[*] (1.07, 5.28)**	1.00 (0.36, 2.84)
HDL <40 mg/dL	0.87 (0.55, 1.40)	1.09 (0.73, 1.63)	0.69 (0.34, 1.42)	1.18 (0.66, 2.11)	0.74 (0.36, 1.52)	1.15 (0.64, 2.06)	0.78 (0.22, 2.76)	0.41 (0.13, 1.28)
Triglycerides >110 mg/dL	1.13 (0.64, 2.00)	1.13 (0.71, 1.80)	1.02 (0.55, 1.89)	1.07 (0.64, 1.79)	1.04 (0.56, 1.94)	1.02 (0.60, 1.71)	0.83 (0.38, 1.85)	0.74 (0.34, 1.64)
Systolic or diastolic BP>90th percentile	0.64 (0.33, 1.23)	1.34 (0.79, 2.28)	1.32 (0.48, 3.67)	0.92 (0.34, 2.47)	1.47 (0.52, 4.19)	1.00 (0.37, 2.69)	0.90 (0.15, 5.22)	1.09 (0.33, 3.68)
Fasting glucose >100 mg/dL	1.48 (0.79, 2.77)	0.65 (0.34, 1.23)	1.63 (0.78, 3.38)	0.65 (0.30, 1.42)	1.57 (0.72, 3.43)	0.66 (0.30, 1.44)	1.80 (0.74, 4.36)	0.57 (0.22, 1.50)

HDL = high-density lipoprotein; PIR = Poverty Income Ratio.

[*] $P \leq .05$ for OR comparing adolescents exposed to in utero smoke exposure to unexposed adolescents of the same sex. The bold simply emphasized that these variables had significant differences.

[†] Adjusted for adolescent age, maternal age, race/ethnicity, and PIR.

[‡] Adjusted for adolescent age, maternal age, race/ethnicity, PIR, and current household smoking.

[§] Adjusted for adolescent age, maternal age, race/ethnicity, PIR, current household smoking, and birth weight.

[//] Adjusted for adolescent age, maternal age, race/ethnicity, PIR, cotinine, and birth weight.