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Serum Cotinine and Adverse Cardiovascular Outcomes: A Cross-sectional Secondary Analysis of the nuMoM2b Heart Health Study

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Abstract

Objective—We aimed to (1) compare serum cotinine with self-report for ascertaining smoking status among reproductive-aged women; (2) estimate the relative odds of adverse cardiovascular (CV) outcomes among women by smoking status; (3) assess whether the association between adverse pregnancy outcomes (APOs) and CV outcomes varies by smoking status.

Study Design—We conducted a cross-sectional study of the nuMoM2b Heart Health Study. Women attended a study visit 2 to 7 years after their first pregnancy. The exposure was smoking status, determined by self-report and by serum cotinine. Outcomes included incident chronic hypertension (HTN), metabolic syndrome (MetS), and dyslipidemia. Multivariable logistic regression estimated odds ratios (ORs) for each outcome by smoking status.

Results—Of 4,392 women with serum cotinine measured, 3,610 were categorized as nonsmokers, 62 as secondhand smoke exposure, and 720 as smokers. Of 3,144 women who denied tobacco smoke exposure, serum cotinine was consistent with secondhand smoke exposure in 48 (1.5%) and current smoking in 131 (4.2%) After adjustment for APOs, smoking defined by serum cotinine was associated with MetS (adjusted OR [aOR]=1.52, 95% confidence interval [CI]: 1.21, 1.91) and dyslipidemia (aOR=1.28, 95% CI: 1.01, 1.62). When stratified by nicotine exposure, nonsmokers with an APO in their index pregnancy had higher odds of stage 1 (aOR=1.64, 95% CI: 1.32, 2.03) and stage 2 HTN (aOR=2.92, 95% CI: 2.17, 3.93), MetS (aOR=1.76, 95% CI: 1.42, 2.18), and dyslipidemia (aOR=1.55, 95% CI: 1.25, 1.91) relative to women with no APO. Results were similar when smoking exposure was defined by self-report.

Conclusion—Whether determined by serum cotinine or self-report, smoking is associated with subsequent CV outcomes in reproductive-aged women. APOs are also independently associated with CV outcomes in women.

Keywords

pregnancy; cross-sectional studies; tobacco smoke; nicotine; smokers; pregnancy outcome; cardiovascular diseases

Pregnancy has been described as a window to future health because women with certain pregnancy complications have found with increased risks for adverse health outcomes later in life.[1,2] Women with pregnancies complicated by hypertensive disorders of pregnancy, small for gestational age (SGA) neonates, preterm birth (PTB), and stillbirth, all have increased risk for cardiovascular (CV) disease, such as stroke and myocardial infarction, subsequent to their pregnancies.[3–9] In the Nulliparous Pregnancy Outcomes Study—Monitoring Mothers-to-Be Heart Health Study (nuMoM2b-HHS), women with any of

the above adverse pregnancy outcomes (APOs) had a two-fold increased risk of chronic hypertension (HTN) at a mean follow-up of 3.2 years, following the index pregnancy compared with women without these APOs.[10]

Tobacco use is a known confounder for the association between these pregnancy complications and later CV health.[11–15] Paradoxically, smoking is associated with reduced risk for hypertensive disorders of pregnancy,[16–18] yet increased risk for SGA, PTB, stillbirth, and CV disease. Several published studies demonstrating the association between APOs and CV disease lack data regarding tobacco exposure,[4,6,19] and others have ascertained smoking status through self-report.[3,9] Given the stigma associated with smoking, particularly among mothers, self-reported smoking may be unreliable for determining maternal smoking status and result in biased magnitudes of association.[20]

Cotinine, the primary metabolite of nicotine, is a highly reliable biomarker of short-term exposure to tobacco smoke and may more accurately identify women with recent exposure compared with ascertainment by self-report.[21–23] Measuring cotinine is preferable to measuring nicotine because cotinine has a relatively longer half-life of approximately 16 hours.[24]

We aimed to (1) determine how many additional pregnant women with nicotine exposure are identified using serum cotinine compared with self-reported exposure, (2) estimate the relative odds of adverse CV outcomes among reproductive-aged women categorized by smoking status, and (3) assess whether the association between APOs and CV outcomes varies according to smoking status.

Materials and Methods

Participants and Contact

We conducted a cross-sectional ancillary study of the nuMoM2b-HHS (NCT 02231398); complete methods have been previously described.[25] Briefly, nuMoM2b-HHS was a prospective observational cohort in which women were followed for 2 to 7 years (mean: 3.2 years) after their first pregnancy. The study was approved by all local governing institutional review boards, and all participants gave written informed consent. Women eligible for the nuMoM2b-HHS in-person study visit 2 to 7 years after their first pregnancy, if they participated in the nuMoM2b study (a prospective observational cohort of women recruited during the first trimester of their first pregnancy[26]), had obstetric delivery data available from the index pregnancy, agreed to be contacted for future studies, did not subsequently withdraw consent during interval contact, were at least 18 years of age, were at least 2 years beyond delivery of their index pregnancy, and were not currently pregnant.

In this analysis, we included the 4,392 nuMoM2b-HHS participants with first pregnancies carried to 20 weeks or more who attended an in-person study visit for CV assessment 2 to 7 years after the first pregnancy ended, provided a fasting blood specimen during that study visit, and had cotinine assay results. Blood collection used standard venipuncture into tiger top tubes that were held at room temperature for 30 minutes before centrifugation at 1,500 g for 10 minutes at 4°C. Specimens were aliquoted into cryovials and placed on wet ice until

storage at −75°C (within 90 minutes of aliquoting). These were then shipped on dry ice to the study biorepository for storage at −80°C. Aliquots were transferred on dry ice from the biorepository to the core laboratory at The Lundquist Institute and remained in storage at −80°C.

Women were excluded from this cross-sectional analysis if self-reported smoking status was missing. Similarly, women were excluded from analyses of the associations between cotinine-based nicotine exposure, APOs, and CV-related conditions, if they were missing data regarding the APOs or CV outcomes of interest.

Measures, Outcomes, and Definitions

The primary exposure of interest was smoking status at the time of the nuMoM2b-HHS in-person study visit. This was determined separately by self-report and by serum cotinine level. By self-report, women were classified as smokers if they reported having smoked within the last month. Women were classified as having secondhand smoke exposure if they did not report smoking during the last month and reported that they were exposed to cigarette smoke from others or that other people had smoked in their home during the last month. Women were classified as nonsmokers without secondhand smoke exposure if they described their smoking status as “never smoked” or “former smoker, quit more than 1 year ago,” or reported no smoking within the last month and also reported no secondhand exposure.

Serum cotinine was measured in a central laboratory (The Lundquist Institute) using a standard enzyme-linked immunosorbent assay with samples run in duplicates according to manufacturer instructions (Calbiotech no.: CO098D, El Cajon, CA). The interassay coefficient of variation was 8.4 and the minimal detectable concentration was 0.28mmol/L (0.05 ng/mL). Smoking status by serum cotinine level was designated according to previously defined cut-offs by race/ethnicity: cut points were 27.52, 33.60, 4.77, and 17.48mmol/L (4.85, 5.92, 0.84, and 3.08 ng/mL) for non-Hispanic white, non-Hispanic black, Hispanic, and other designations, respectively.[27] Women with serum cotinine concentrations below these cut-off points but with quantifiable serum cotinine levels (0.28mmol/L [0.05 ng/mL] or greater) were classified as having been exposed to secondhand smoke. Women with serum cotinine levels that were <0.28mmol/L (0.05 ng/mL) were classified as nonsmokers without secondhand smoke exposure.

Secondary exposures of interest included APOs during the woman’s first pregnancy. These were categorized as hypertensive disorders of pregnancy (HDP, including gestational HTN, preeclampsia, and eclampsia), SGA neonate (birth weight <5th percentile per Alexander’s curves[28]), spontaneous PTB (sPTB), and gestational diabetes mellitus (GDM). These outcomes were collected prospectively during the nuMoM2b study and verified using medical record abstraction.[26]

Additional characteristics were obtained during the early-pregnancy study visit and included as descriptive characteristics or model covariates. The methods of data collection have been previously published.[26] Demographic characteristics included early-pregnancy values of maternal age, maternal race, marital status, education, and family income. Behavioral

risk factors obtained during the early-pregnancy study visit included any previous substance use and self-reported smoking exposure in the previous month (defined as above). Body mass index (BMI, kg/m^2) was calculated using weights (balance-beam scale) and heights (stadiometer or measuring tape) taken using a standardized approach. Analysis of stored early-pregnancy blood specimens for total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides used spectrophotometric assays, and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation.[29]

Outcomes of interest included the following incident diagnoses (ascertained at the time of the nuMoM2b-HHS study visit 2 to 7 years following delivery of the first pregnancy): chronic HTN, defined by self-reported use of antihypertensive medication or measured blood pressures meeting criteria for elevated blood pressure, stage-1 or −2 HTN according to the 2017 American College of Cardiology/American Heart Association guideline[30]; metabolic syndrome (MetS), defined as meeting at least three of the following criteria: (1) waist circumference ≥ 88cm (35 inches) for non-Asian women and ≥ 80cm (31.5 inches) for Asian women; (2) triglycerides ≥ 1.70 mmol/L (150 mg/dL) or taking medication to lower triglycerides; (3) fasting glucose ≥ 5.55mmol/L (100mg/dL) or taking glucose-lowering medication; (4) systolic blood pressure ≥ 130mm Hg or diastolic blood pressure ≥ 85mm Hg or taking antihypertensive medication; (5) reduced HDL-C levels < 1.30mmol/L (50mg/dL) or taking medication to raise HDL-C; and (6) dyslipidemia, defined as having at least one of the following: total cholesterol ≥ 6.22mmol/L (240mg/dL), LDL-C ≥ 4.14mmol/L (160mg/dL), HDL-C < 0.91mmol/L (35mg/dL), triglycerides ≥ 2.26mmol/L (200mg/dL), or self-reported use of prescribed statin or other triglyceride-reducing medication.

Statistical Analysis

Univariate descriptive analyses assessed demographic characteristics among women overall and by serum cotinine–derived smoking status. Characteristics were summarized using mean and standard deviation for continuous measures and frequency and percentage for categorical measures.

We estimated the number of additional mothers with nicotine exposure identified using serum cotinine compared with self-reported exposure. Kendall’s tau correlation coefficient and the kappa statistic were calculated to estimate the correlation and agreement, respectively, between serum cotinine level and self-reported tobacco exposure for all participants and by race/ethnicity.

The prevalence of CV outcomes of interest was compared among women by serum cotinine–derived smoking status. Multivariable logistic regression was used to estimate odds ratios (ORs) for the outcomes of interest for smokers and those exposed to secondhand smoke with nonsmokers as the reference category, adjusting for age (years) at the time of enrollment in nuMoM2b, race/ethnicity (four categories), BMI (kg/m^2) at the time of enrollment into nuMoM2b, and history of APO (yes/no for each APO of interest). For the outcome of HTN, a generalized logit model was used to estimate the OR for elevated blood pressure, stage-1 HTN, and stage-2 HTN (versus normotension). For all OR, Wald’s 95% confidence intervals (CIs) were also computed.

To determine whether associations between APOs and CV outcomes varied according to smoking status, we tested for interaction between history of APO and serum cotinine–derived smoking status. We then used multivariable logistic regression models with APOs, smoking status at the time of the HHS study visit, and the APO-smoking interaction. The OR for the association between each APO of interest and CV outcomes was estimated directly within each category of smoking exposure based on the interaction model. Separate models were fit for each APO of interest, and all models were adjusted for baseline values of age, race/ethnicity, and BMI.

Because self-report is the method most commonly used to determine smoking status, in both clinically and previously published research in this field, we performed sensitivity analyses using self-reported smoking exposures instead of cotinine-based exposures. Data management and analyses were performed using SAS Version 9.4 (Cary, NC).

Results

Of 4,392 participants who were eligible for inclusion (►Fig. 1), 3,610 nonsmokers, 62 women with secondhand smoke exposure, and 720 smokers were included according to serum cotinine concentration at the time of their nuMoM2b-HHS visit (2–7 years after delivery of the first pregnancy). Among the 720 classified as smokers, 212 (29.4%) self-reported that they had also smoked during the month prior to the first trimester study visit during their index pregnancy. Among the 3,610 classified as nonsmokers, 25 (0.7%) self-reported that they had smoked during the month prior to the first trimester study visit during their index pregnancy. ►Table 1 describes the index pregnancy demographics and characteristics of women by cotinine-based nicotine exposure category. Smokers were more likely to be non-Hispanic black, younger, unpartnered, from a family with a lower income, obese, to have fewer years of education, or to have a history of substance use or any APO during their index pregnancy.

Of the 3,144 women who denied exposure to tobacco smoke, serum cotinine concentration was consistent with secondhand smoke exposure in 48 (1.5%), and current smoking in 131 (4.2%; ►Table 2). The estimated correlation between self-reported smoking status and cotinine-derived smoking status was 0.57 (95% CI: 0.54, 0.60), and the estimated agreement between the two measures of smoking exposure was 0.45 (95% CI: 0.42, 0.48). Generally, when comparing correlations and agreement between self-report and serum cotinine across race/ethnicity groups, correlations were similar and both measures showed a fair or moderate level of agreement.

►Table 3 reports the prevalence of the CV outcomes of interest at the time of the nuMoM2b-HHS visit by cotinine-based smoking status. Mean systolic and diastolic blood pressures were similar between groups, but elevated blood pressure, stage-1 and −2 HTN, dyslipidemia, and MetS diagnoses were all more common among smokers.

Results of the multivariable regression models are provided in ►Table 4. After adjusting for age, race/ethnicity, BMI, and history of any APO in the index nuMoM2b pregnancy, smoking was associated with increased odds of MetS and dyslipidemia. Although smoking

was associated with chronic HTN in the unadjusted model, adjusted ORs (aORs) were dramatically attenuated with CIs that crossed unity. Of the covariates included in multivariable models, BMI was noted to be the strongest attenuator of the association between smoking and hypertensive diagnoses. Because of the small number of women in the secondhand smoke-exposed group, estimates of the association with the CV outcomes for this group lacked precision and were considered unreliable. Results were similar when adjusting for each specific APO individually. In sensitivity analyses using self-reported smoking status instead of serum cotinine, the significant associations between self-reported smoking and outcomes of MetS (aOR=1.52, 95% CI: 1.16, 2.00) and dyslipidemia (aOR=1.33, 95% CI: 1.01, 1.75) were similar.

To assess whether associations between APOs and CV outcomes varied by smoking status, ►Table 5 shows the ORs for the association between APOs and CV outcomes within subgroups of participants defined by cotinine-derived smoking status. To allow efficient estimation of these ORs within cotinine exposure subgroups, these models included the APO-smoking interaction. Interaction between selected APOs and smoking status was statistically significant only for the outcome of HTN (interaction p=0.028 [any APO], p=0.02 [HDP], and p<0.001 [SGA]). Among nonsmokers, women with any APO in their index pregnancy had increased odds of stage-1 and −2 HTN, MetS, and dyslipidemia relative to women with no APO. Among smokers, women with any APO in their index pregnancy had higher odds of elevated blood pressure and stage-2 HTN relative to women with no APO; ORs for the other CV outcomes were >1, but with CIs crossing 1. Smokers and nonsmokers with GDM in their index pregnancy had higher odds of MetS (aOR=3.76, 95% CI: 1.59, 8.88 for smokers; aOR=2.30, 95% CI: 1.56, 3.38 for nonsmokers) and dyslipidemia (aOR=2.84, 95% CI: 1.29, 6.22 for smokers; aOR=1.62, 95% CI: 1.09, 2.40 for nonsmokers). Smokers and nonsmokers with HDP in their index pregnancy had higher odds of stage-2 HTN (aOR=2.67, 95% CI: 1.43, 4.97 for smokers; aOR=3.29, 95% CI: 2.36, 4.57 for nonsmokers). In sensitivity analyses using smoking status determined by self-report instead of serum cotinine, findings were similar.

Discussion

Of the 3,144 women in this population who denied tobacco smoke exposure (either secondhand smoke or smoking) within the prior month, serum cotinine levels identified 179 women with exposure (5.7%). Previous studies comparing self-reported smoking to cotinine in pregnant women indicate that self-report incorrectly classifies 2 to 25% of smokers as nonsmokers.[21–23] Our findings demonstrate a discrepancy at the lower end of this range. One previous publication reported that self-reported smoking status introduced bias into a study of smoking and pregnancy outcomes compared with cotinine-derived smoking status, yielding a 15% difference in the OR for SGA birth among cotinine-derived smokers compared with self-reported smokers.[20] In our study population, using self-reported smoking status compared with cotinine-derived smoking status did not yield consistently different ORs for the outcomes of interest.

In this population of young women (mean age: 27 years at index pregnancy), the prevalence of MetS and dyslipidemia 2 to 7 years after their index pregnancy was 25.2 and

18.3%, respectively, among smokers (compared with 15.2 and 14.5%, respectively, among nonsmokers). The association between smoking and CV outcomes persisted in models adjusting for confounders, including a history of any APO: smokers had increased odds of MetS (aOR=1.52, 95% CI: 1.21, 1.91) and dyslipidemia (aOR=1.28, 95% CI: 1.01, 1.62).

The APO-smoking interaction was significant for the outcome of HTN but not MetS or dyslipidemia. Among nonsmokers, APOs were positively associated with HTN, MetS, and dyslipidemia. The estimated ORs remained elevated among smokers, particularly for the associations between HDP or GDM and CV outcomes, but the relatively wide CIs encompassing 1.0 reflect a lack of precision due to the small counts within substrata formed by smoking status and APO occurrence. With additional years of follow-up, we may observe additional associations between APOs, smoking, and CV outcomes in this cohort.

Strengths of our study include the large sample size with an ethnically, racially, and geographically diverse population. Our primary outcomes of interest were the same as those for nuMoM2b-HHS; accordingly, detailed data regarding these outcomes were available for our secondary analysis. In addition, the exposure of interest, cotinine-derived nicotine exposure, was measured in a central laboratory using a standard assay protocol.

Limitations

Because we conducted a cross-sectional assessment of the association between nicotine exposure, as measured by serum cotinine, and adverse CV outcomes at the time of the nuMoM2b-HHS visit, we are unable to define the temporal relationship between nicotine exposure and the CV outcomes of interest.

Conclusion

Despite this limitation, our findings are meaningful from a public health perspective because up to 52% of reproductive-aged women in the United States do not undergo regular screening for MetS or dyslipidemia.[31] Whether self-report or serum cotinine is used to determine smoking status among mothers, women who smoke should be advised of the association between smoking and these precursors to CV events in an ongoing effort to reduce CV deaths among women.

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Conflict of Interest

H.N.S. reports grants from National Institutes of Health during the conduct of the study.

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Key Points

- Cotinine was detected in 5.7% of reported nonsmokers.
- Smoking and APOs were independently associated with CV health.
- Smoking was associated with MetS and dyslipidemia.

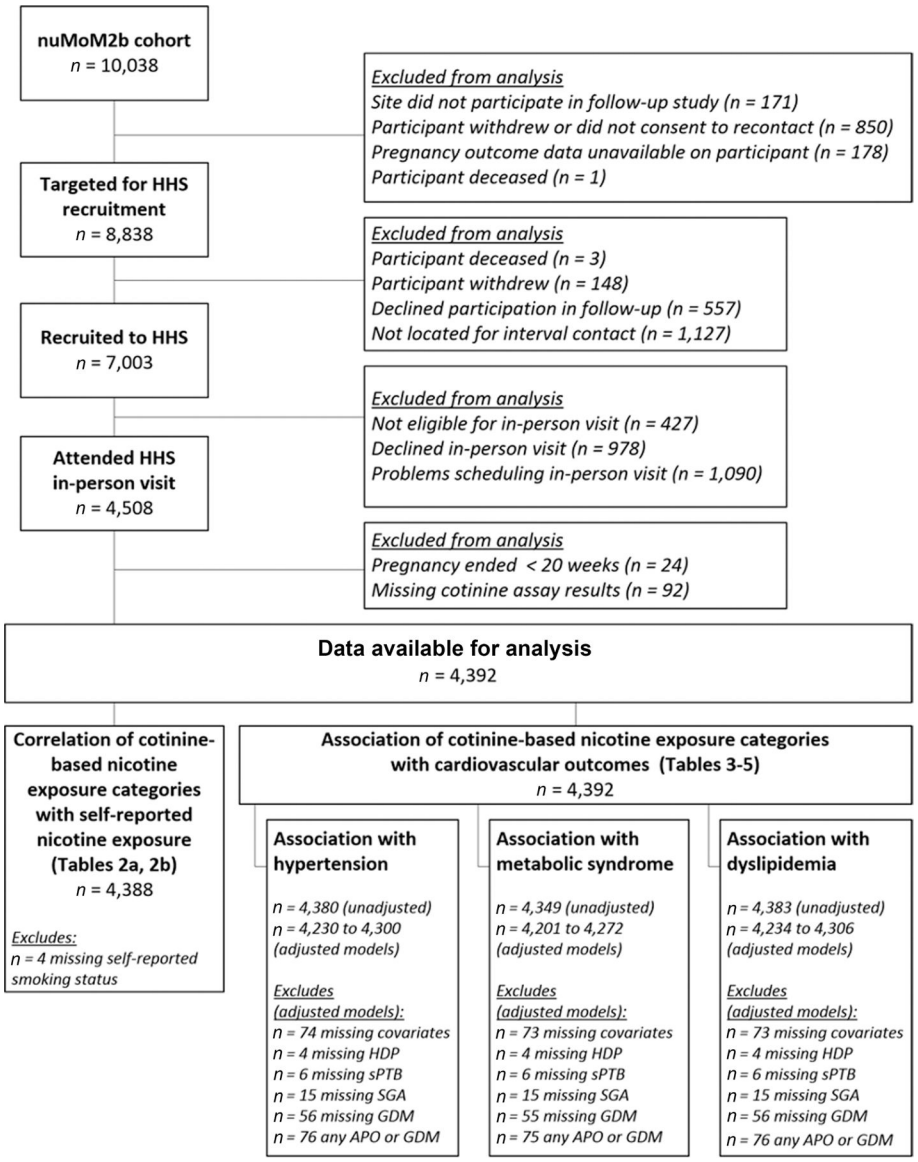

Fig. 1.

Flow chart for inclusion in analyses. APO, adverse pregnancy outcome; GDM, gestational diabetes; HDP, hypertensive disorders of pregnancy; HHS, Heart Health Study; nuMoM2b, Nulliparous Pregnancy Outcomes Study—Monitoring Mothers-to-Be; SGA, small for gestational age; sPTB, spontaneous preterm birth.

Table 1

Baseline characteristics and pregnancy outcomes from the index pregnancy by cotinine-based nicotine exposure at the 2-to-7-year follow-up visit

Baseline characteristics and pregnancy outcomes	**All participants (*n* = 4,392) Mean (SD) or *n* (%) or *n*/N (%)**	**Cotinine-based nicotine exposure category[a] Mean (SD) or *n* (%) or *n*/N (%)**		
		No exposure (*n* = 3,610)	**Secondhand (*n* = 62)**	**Smoker (*n* = 720)**
Maternal age (y)	27.0 (5.6)	27.6 (5.4)	27.8 (5.5)	23.8 (5.3)
Maternal race				
Non-Hispanic White	2,735 (62.3)	2,366 (65.5)	44 (71.0)	325 (45.1)
Non-Hispanic Black	598 (13.6)	353 (9.8)	10 (16.1)	235 (32.6)
Hispanic	724 (16.5)	621 (17.2)	4 (6.5)	99 (13.8)
Other	335 (7.6)	270 (7.5)	4 (6.5)	61 (8.5)
Marital status				
Married or living with partner	2,707 (61.7)	2,518 (69.8)	45 (72.6)	144 (20.0)
Widowed, divorced, or separated	45 (1.0)	36 (1.0)	0 (0.0)	9 (1.3)
Never married	1,635 (37.3)	1,051 (29.2)	17 (27.4)	567 (78.8)
Education				
Less than high school graduate	320 (7.3)	147 (4.1)	1 (1.6)	172 (23.9)
High school graduate or equivalency	501 (11.4)	319 (8.8)	4 (6.5)	178 (24.7)
Some college or college graduate	3,569 (81.3)	3,142 (87.1)	57 (91.9)	370 (51.4)
Family income as % of federal poverty level	414.7 (298.4)	440.4 (295.6)	521.1 (319.7)	227.6 (242.5)
Any previous substance abuse	1,436/4,388 (32.7)	1,021/3,607 (28.3)	20/62 (32.3)	395/719 (54.9)
BMI (kg/m^2)	26.6 (6.5)	26.2 (6.1)	26.7 (7.3)	28.3 (7.8)
Systolic blood pressure (mm Hg)	109.5 (10.9)	109.3 (10.5)	109.4 (11.0)	110.6 (12.2)
N with result	4,295	3,536	62	697
Diastolic blood pressure (mm Hg)	67.4 (8.4)	67.5 (8.2)	67.7 (8.2)	66.8 (9.0)
N with result	4,295	3,536	62	697
Total cholesterol (mmol/L)	4.8 (0.9)	4.9 (0.9)	5.0 (1.4)	4.6 (0.9)
N with result	4,285	3,528	61	696
HDL-C (mmol/L)	1.9 (0.4)	1.9 (0.4)	1.9 (0.4)	1.7 (0.4)
N with result	4,284	3,527	61	696
LDL-C (mmol/L)	2.3 (0.7)	2.3 (0.7)	2.4 (1.1)	2.2 (0.7)
N with result	4,276	3,520	61	695

Baseline characteristics and pregnancy outcomes	All participants (*n* = 4,392) Mean (SD) or *n* (%) or *n*/N (%)	Cotinine-based nicotine exposure category[a] Mean (SD) or *n* (%) or *n*/N (%)		
		No exposure (*n* = 3,610)	Secondhand (*n* = 62)	Smoker (*n* = 720)
HDL:LDL ratio	0.9 (0.4)	0.9 (0.4)	0.9 (0.4)	0.9 (0.4)
N with result	4,276	3,520	61	695
Triglycerides (mmol/L)	1.4 (0.6)	1.4 (0.6)	1.4 (0.7)	1.4 (0.6)
N with result	4,285	3,528	61	696
Chronic hypertension	121/4,388 (2.8)	81/3,607 (2.2)	1/62 (1.6)	39/719 (5.4)
Pre-gestational diabetes	56/4,390 (1.3)	34/3,610 (0.9)	0 (0.0)	22/718 (3.1)
Dyslipidemia	586/4,245 (13.8)	490/3,492 (14.0)	14/61 (23.0)	82/692 (11.8)
Self-reported smoking in the previous month	237/4,380 (5.4)	25/3,600 (0.7)	0 (0.0)	212/718 (29.5)
Adverse pregnancy outcome during index pregnancy				
None	3,275/4,316 (75.9)	2,742/3,563 (77.0)	51/62 (82.3)	482/691 (69.8)
Hypertensive disorders of pregnancy	600/4,388 (13.7)	474/3,607 (13.1)	5/62 (8.1)	121/719 (16.8)
Small for gestational age	182/4,377 (4.2)	138/3,601 (3.8)	2/62 (3.2)	42/714 (5.9)
Spontaneous preterm birth	216/4,386 (4.9)	168/3,605 (4.7)	3/62 (4.8)	45/719 (6.3)
Gestational diabetes	186/4,336 (4.3)	154/3,576 (4.3)	1/62 (1.6)	31/698 (4.4)
Any APO listed above	1,041/4,316 (24.1)	821/3,563 (23.0)	11/62 (17.7)	209/691 (30.2)

Abbreviations: APO, adverse pregnancy outcome; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; *n*, number in category; N, sample size; SD, standard deviation.

[a]Based on serum cotinine levels, smokers were defined as women with serum cotinine level greater than or equal to the following cut-offs: 27.52, 33.60, 4.77 and 17.48 mmol/L (4.85, 5.92, 0.84 and 3.08 ng/mL) for non-Hispanic white, non-Hispanic black, Hispanic, and other races, respectively. Women with serum cotinine concentrations below these cut points but with quantifiable serum cotinine (0.28 mmol/L [0.05 ng/mL] or greater) were classified as exposed to secondhand smoke. Women with serum cotinine levels that were < 0.28 mmol/L (0.05 ng/mL) or undetectable were classified as having no exposure.

Table 2

Cross-tabulation and estimated correlation and agreement of self-reported smoking exposure with cotinine-based nicotine exposure, both obtained at the 2-to-7-year follow-up visit

Self-reported smoking exposure category	**Cotinine-based nicotine exposure category**			
	None	**Secondhand**	**Smoker**	**Total**
None	2,965	48	131	3,144
Secondhand smoke	616	12	115	743
Smoker	27	2	472	501
Total	3,608	62	718	4,388
Kendall's tau correlation coefficient: 0.57 (95% CI: 0.54, 0.60)				
Kappa statistic: 0.45 (95% CI: 0.42, 0.48)				

Abbreviation: CI, confidence interval.

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Table 3

Hypertension, dyslipidemia, and metabolic syndrome 2 to 7 years after index pregnancy according to cotinine-based nicotine exposure at the 2-to-7-year follow-up visit

Cardiovascular outcomes 2–7 years after index pregnancy	**All participants (*n* = 4,392) Mean (SD) or *n* (%) or *n*/N (%)**	**Cotinine-based nicotine exposure category Mean (SD) or *n* (%) or *n*/N (%)**		
		No exposure (*n* = 3,610)	**Secondhand (*n* = 62)**	**Smoker (*n* = 720)**
Blood pressure (mm Hg)				
Systolic	111.5 (11.1)	111.2 (11.0)	113.4 (9.9)	112.7 (11.4)
Diastolic	72.1 (9.9)	72.0 (9.8)	73.5 (8.8)	72.8 (10.4)
Hypertension categories				
Normotensive: SBP < 120 and DBP < 80	3,136 (71.6)	2,612 (72.6)	41 (67.2)	483 (67.1)
Elevated: 120 ≤ SBP < 130 and 80 < DBP	290 (6.6)	233 (6.5)	7 (11.5)	50 (6.9)
Stage I: 130 ≤ SBP < 140 or 80 ≤ DBP < 90	658 (15.0)	527 (14.6)	8 (13.1)	123 (17.1)
Stage II: 140 ≤ SBP or 90 ≤ DBP, or antihypertensive medication	296 (6.8)	227 (6.3)	5 (8.2)	64 (8.9)
N with result	4,380	3,599	61	720
Total cholesterol (mmol/L)	4.7 (1.0)	4.7 (1.0)	4.8 (1.4)	4.4 (1.0)
N with result	4,387	3,605	62	720
HDL-C (mmol/L)	1.4 (0.3)	1.5 (0.3)	1.6 (0.4)	1.3 (0.3)
N with result	4,387	3,605	62	720
LDL-C (mmol/L)	2.8 (0.9)	2.8 (0.9)	2.7 (1.3)	2.6 (0.9)
N with result	4,369	3,589	62	718
Triglycerides (mmol/L)	1.1 (0.7)	1.1 (0.7)	1.0 (0.5)	1.1 (0.7)
N with result	4388	3606	62	720
Dyslipidemia	662/4,383 (15.1)	522/3,601 (14.5)	8/62 (12.9)	132/720 (18.3)
Metabolic syndrome	734/4,384 (16.7)	547/3,604 (15.2)	6/61 (9.8)	181/719 (25.2)

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; *n*, number in category; N, sample size; SBP, systolic blood pressure; SD, standard deviation.

Table 4

Association between cotinine-based nicotine exposure and cardiovascular outcomes at the 2-to-7-year follow-up visit

Cotinine-based nicotine exposure category	Hypertension category			Metabolic syndrome	Dyslipidemia
	Elevated blood pressure	Stage 1	Stage 2		
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unadjusted model results					
None	1.0	1.0	1.0	1.0	1.0
Secondhand smoke	1.91 (0.85, 4.31)	0.97 (0.45, 2.07)	1.40 (0.55, 3.59)	0.61 (0.26, 1.42)	0.87 (0.41, 1.85)
Smoker	1.16 (0.84, 1.60)	1.26 (1.01, 1.57)	1.52 (1.14, 2.05)	1.88 (1.55, 2.28)	1.32 (1.07, 1.63)
Model adjusted for age, race/ethnicity, BMI, and history of any adverse pregnancy outcome					
None	1.0	1.0	1.0	1.0	1.0
Secondhand smoke	1.90 (0.85, 4.32)	0.95 (0.44, 2.05)	1.53 (0.57, 4.11)	0.57 (0.23, 1.43)	0.88 (0.41, 1.89)
Smoker	1.01 (0.71, 1.44)	1.10 (0.87, 1.40)	1.18 (0.83, 1.67)	1.52 (1.21, 1.91)	1.32 (1.05, 1.67)

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

Table 5

Association between adverse pregnancy outcomes from the index pregnancy and cardiovascular outcomes at the 2-to-7-year follow-up visit, stratified by cotinine-based nicotine exposure at the 2-to-7-year follow-up visit, and adjusted for race/ethnicity, baseline age, and BMI

APO	Cotinine-based nicotine exposure category	Hypertension category			Metabolic syndrome	Dyslipidemia
		Elevated blood pressure	Stage 1	Stage 2		
		OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]
Any APO	None	1.25 (0.90, 1.72)	1.64 (1.32, 2.03)	2.92 (2.17, 3.93)	1.76 (1.42, 2.18)	1.55 (1.25, 1.91)
	Secondhand smoke	0.74 (0.08, 7.11)	1.54 (0.26, 9.24)	–	–	–
	Smoker	4.04 (2.17, 7.55)	1.39 (0.90, 2.16)	2.07 (1.15, 3.72)	1.45 (0.97, 2.18)	1.34 (0.88, 2.03)
		Interaction $p = 0.0280$			Interaction $p = 0.7068$	Interaction $p = 0.8327$
HDP	None	1.46 (0.98, 2.18)	2.17 (1.69, 2.79)	3.29 (2.36, 4.57)	1.71 (1.33, 2.19)	1.54 (1.20, 1.97)
	Secondhand smoke	–	4.69 (0.62, 35.36)	–	–	–
	Smoker	3.55 (1.85, 6.84)	0.98 (0.55, 1.74)	2.67 (1.43, 4.97)	1.13 (0.70, 1.83)	1.17 (0.72, 1.91)
		Interaction $p = 0.0197$			Interaction $p = 0.3235$	Interaction $p = 0.6220$
SGA	None	1.25 (1.23, 1.26)	1.66 (1.64, 1.67)	1.43 (1.41, 1.45)	1.08 (0.64, 1.81)	0.71 (0.40, 1.26)
	Secondhand smoke	–	–	–	–	–
	Smoker	2.57 (2.51, 2.63)	0.80 (0.78, 0.81)	0.23 (0.22, 0.24)	0.54 (0.21, 1.41)	1.01 (0.42, 2.40)
		Interaction $p < 0.0001$			Interaction $p = 0.4620$	Interaction $p = 0.8051$
sPTB	None	0.90 (0.46, 1.73)	0.71 (0.43, 1.17)	1.14 (0.61, 2.14)	1.57 (1.03, 2.38)	1.38 (0.91, 2.08)
	Secondhand smoke	–	–	–	–	–
	Smoker	1.93 (0.70, 5.27)	1.52 (0.69, 3.38)	0.62 (0.14, 2.85)	1.65 (0.77, 3.51)	0.98 (0.42, 2.31)
		Interaction $p = 0.5884$			Interaction $p = 0.9933$	Interaction $p = 0.7822$
GDM	None	1.24 (0.63, 2.43)	0.96 (0.59, 1.55)	2.26 (1.39, 3.68)	2.30 (1.56, 3.38)	1.62 (1.09, 2.40)
	Secondhand smoke	–	–	–	–	–
	Smoker	1.41 (0.31, 6.42)	1.65 (0.65, 4.18)	2.24 (0.75, 6.71)	3.76 (1.59, 8.88)	2.84 (1.29, 6.22)
		Interaction $p = 0.9767$			Interaction $p = 0.5881$	Interaction $p = 0.4487$

Abbreviations: APO, adverse pregnancy outcome; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes; HDP, hypertensive disorders of pregnancy (including mild, severe, and superimposed preeclampsia, eclampsia, and antepartum gestational hypertension); OR, odds ratio; SGA, small for gestational age (birth weight <5th percentile based on Alexander's norms); sPTB, spontaneous preterm birth <37 weeks.

[a]ORs for the association between APOs of interest (vs. no APO of interest) and cardiovascular outcomes are presented separately within subgroups defined by cotinine-based nicotine exposure category.