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Characterization of Tobacco Smoke Exposure and Associated Factors in an African American, Maternal Cohort in Atlanta, GA

By

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Master of Public Health

Global Environmental Health

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Dana Boyd Barr, Ph.D.

Committee Chair

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By

Victoria Rose Davidson

B.S., University of Georgia, 2018

Thesis Committee Chair: Dana Boyd Barr, Ph.D.

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ABSTRACT

Characterization of Tobacco Smoke Exposure and Associated Factors in an African American, Maternal Cohort in Atlanta, GA

By Victoria Rose Davidson

Background: African Americans (AA) have a greater tobacco smoke exposure burden compared to other races. AA pregnant women have greater exposure compared to White pregnant women, and research on active and passive tobacco smoke exposure and associated factors in AA maternal cohorts is needed. This study characterized tobacco smoke biomarkers in an AA maternal cohort and investigated associated demographic and behavioral factors.

Methods: Beginning January 2016, 3 urine samples from 104 pregnant women planning to deliver at Emory-affiliated Midtown and Grady Hospitals in Atlanta, GA were collected. Demographic, health, and environmental surveys collected covariates. Urine was analyzed for cotinine (COT), *trans*-3' hydroxycotinine (3HC), tetrahydrocannabinolic acid (THCA), and nicotine metabolite ratio (3HC/COT). Regressions were used to investigate associations.

Results: Geometric means for average COT, 3HC, and 3HC/COT across pregnancy were 10.19 (ug COT/g creatinine), 22.48 (ug 3HC/g creatinine), and 2.21, respectively. Surprisingly, COT and 3HC levels were highest and showed greatest variation at the third trimester. 3HC/COT was highest (2.39) and showed greatest variation at the 1st trimester and decreased to 2.17 at the third trimester. Based on a cut point of COT $\geq$ 50ng/mL to indicate active smoking, tobacco smoking prevalence during pregnancy was 32.7%, and cessation prevalence was 5.8%. Self-reported secondhand smoke exposure (SHS) prevalence was 43.3%. Tobacco smoking, quit ($\beta = 6.05$; 95% CI, 2.08-16.61; $p < .001$) and continued ($\beta = 51.41$; 95% CI, 30.27- 88.23 $p < .0001$), was the strongest predictor of average COT levels. SHS, income <100% FPL, alcohol use at first trimester, and smoking marijuana were determinants of increased COT levels across pregnancy, and education past high school or GED was protective. Increasing THCA levels ($\beta = 1.03$; 95% CI, 1.01-1.04; $p < .05$) predicted first trimester COT levels, and 24.0% of mothers co-used marijuana and tobacco at first trimester, indicated by COT and THCA levels.

Conclusions: COT and 3HC levels remained high through pregnancy. Future studies should investigate the interaction between COT and THCA and co-use in AA maternal cohorts. Alterations of NMR during pregnancy should be investigated to understand if changes in nicotine metabolism are uniquely contributing to COT burden in AA maternal cohorts.

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Conclusions: COT and 3HC levels remained high through pregnancy. Future studies should investigate the interaction between COT and THCA and co-use in AA maternal cohorts. Alterations of NMR during pregnancy should be investigated to understand if changes in nicotine metabolism are uniquely contributing to COT burden in AA maternal cohorts.

INTRODUCTION

Environmental Chemical Exposure among African Americans: Compared to Non-Hispanic Whites, African Americans have higher body burdens of environmental toxicants (e.g. lead, phthalates, parabens, cotinine (COT), etc.). A higher burden of toxicants is associated with adverse health effects and raises major concerns of environmental justice [1-4]. Research on the health effects of environmental toxicant exposure is an ongoing effort, with some effects such as cardiometabolic diseases or cancers more understood than others [5, 6]. African Americans are at increased risk of cardiovascular disease and related risk factors, cancers, and poor maternal-infant outcomes, and understanding the role that environmental toxicants may play in creating or perpetuating these health disparities is critical to reducing disparity [7-9].

Tobacco smoke exposure and COT levels among African Americans: The health effects of active tobacco smoke exposure are well known, some of which are increased risk for heart disease, stroke, lung cancer, and respiratory diseases such as chronic obstructive pulmonary disease. Prenatal active tobacco smoke exposure elevates risk for infant mortality, birth defects, low birthweight, and preterm birth [10, 11]. The U.S. Surgeon General reported in 2006 that there is no risk-free level of secondhand smoke (SHS) exposure. Infants and children can suffer from sudden infant death syndrome, respiratory infections, ear infections, and asthma, and exposed adults are at elevated risks for cardiovascular disease, stroke, and cancers- similar to the health risks of active smoking previously stated [12, 13].

COT, the most stable and primary metabolite of nicotine is a widely used biomarker for active and passive tobacco smoke exposure [4, 14, 15]. COT levels are highest in African American smokers compared to White smokers despite a similar smoking prevalence (19.3% vs 21.9%). In addition, African Americans have a higher risk of smoking-related illnesses [16-18]. Higher COT levels are also found in African American nonsmokers, compared to White nonsmokers and Mexican American nonsmokers, indicating a greater degree of environmental tobacco smoke exposure (ETS), or secondhand (SHS) and thirdhand smoke exposure [19]. Hypotheses for the higher COT burden in African Americans include slower rates of nicotine metabolism, difference in smoking topography, nicotine dependence at a lower number of cigarettes per day, and choice of cigarettes (menthol/nonmenthol) [20-23].

Literature indicates that COT levels concurrent with both active and passive tobacco smoke exposure remain higher in African American pregnant women compared to other pregnant women, especially White pregnant women, after adjusting for dose and frequency of exposure [24-28]. A COT body burden during pregnancy implies exposure to tobacco smoke, which contains thousands of toxic chemicals (e.g. polycyclic aromatic hydrocarbons) and known fetal toxicants such as carbon monoxide, metals, and nicotine that contribute to poor maternal and infant health outcomes [29, 30] Nicotine, the addictive substance in tobacco-smoke, indirectly causes vasoconstriction, jeopardizing blood flow to the placenta and is neurotoxic to the fetus. This blood flow restriction, in combination with the oxygen restrictive properties of carbon monoxide, are the predominant mechanisms behind adverse birth outcomes such as low birthweight, infant mortality, and placental abruption [8, 9]. Associations between active and ETS exposure and adverse birth outcomes, though weaker for ETS, have been well established [13, 17, 30-33].

Public health implications for African American mothers: According to the 2017 National Vistal Statics report, African American women have a greater risk of preterm birth compared to

White women (13.93% vs 9.05%), which contributes to African American infants' increased risk of low birthweight (<2500gm) compared to white infants (13.89% vs 7.00%) [9]. Preterm infants have higher mortality risk; and surviving infants are more likely to have neurodevelopmental deficiencies, hearing and visual impairment, behavioral impairment, and to develop chronic disease later in life [11]. Common confounders (socioeconomic status, maternal age) do not fully explain this black-white disparity; therefore, there is a great need to gain more understanding on the unique, biobehavioral and environmental risk factors that are experienced by pregnant African American women [34, 35]. Given the disparities in tobacco smoke exposure and disparities in maternal-infant outcomes within the African American community, research efforts directed towards characterizing the tobacco smoke exposure burden and understanding predictors of tobacco smoke exposure in African American maternal cohorts should be prioritized.

Urinary COT, 3'HydroxyCOT, and Nicotine Metabolite Ratio: The present study uses urinary COT, 3'hydroxycotinine (3HC), and the nicotine metabolite ratio (3HC/COT) to characterize tobacco smoke exposure. Nicotine is metabolized to COT by CYP2A6, and COT is a validated tool for predicting levels of environmental tobacco smoke (ETS) exposure and direct tobacco smoke exposure through plasma, saliva, and urine [15, 36]. Blood levels of COT are preferable, as they most resemble the dosage of nicotine, but plasma COT and urinary COT have been shown to be highly correlated [15, 37]. Urinary COT concentrations levels are higher than plasma and saliva, which make this biofluid preferable for detecting low levels of exposure indicative of SHS exposure [37, 38]. COT levels during pregnancy typically have within subject variation due to attempted cessation or behavior change [39]. CYP2A6 also metabolizes COT to trans-3'-hydroxycotinine (3HC), another biomarker of tobacco smoke exposure, which is found to be the more abundant metabolite of nicotine [40, 41]. The nicotine metabolite ratio (NMR) is indicative of CY2A6 activity, or how rapidly COT is converted to 3HC [42]. A higher 3HC/COT ratio, or faster nicotine metabolism, has been described as an indicator of higher nicotine

dependence [29]. Very few studies have examined NMR changes over pregnancy, but existing studies suggest that NMR increases during pregnancy. This could lead to more failed cessation attempts among pregnant women [43-46]

Self- report of smoking status and SHS exposure is a common method for measuring exposure, but it has been shown that many pregnant women underreport or misreport their smoking status and/or SHS exposure. For this reason, it common for prenatal tobacco smoke exposure studies to couple self-report measures with biological confirmation such as urinary COT, 3HC, and the NMR (3HC/COT), which was the approach selected for the present study [32, 39, 47-50].

Aims & Hypotheses:

Aim 1: The present study characterized active and passive tobacco smoke exposure across pregnancy via urinary COT, 3HC, and the nicotine metabolite ratio in the primary population of interest- an SES-diverse African American maternal cohort in Atlanta, GA. It was hypothesized that COT and 3HC concentrations at the first trimester would decrease as pregnancy progressed, and NMR would increase. Misclassification of smoking status due to self-report bias was also expected, especially pertinent to the final trimester.

Aim 2: The secondary aim investigated predictors of urinary COT and 3HC concentrations, tobacco smoke exposure, across pregnancy and at the first trimester in the African American maternal cohort in Atlanta, GA. Covariates considered for the models included: Age, income, educational attainment, marital status, relationship status, type of home, secondhand smoke exposure, tobacco use, alcohol use, marijuana use, tetrahydrocannabinolic acid (THCA) concentrations, and creatinine concentrations.

Aim 3: The final aim characterized COT, 3HC, and 3HC/COT, stratified by race in women of reproductive age in the 2015-2016 National Health and Nutrition Examination Survey. It was hypothesized that urinary COT and 3HC levels would be higher and the NMR would be lower

among Non-Hispanic Black, here referred to as African American women, compared to other races.

The present study sought to characterize active and passive prenatal tobacco smoke exposure and investigate exposure predictors in an African American maternal cohort in Atlanta, GA, via urinary COT, 3HC, and the nicotine metabolite ratio in order to better understand potential reasons for the existing disparity in COT burden.

METHODS

Center for Children's Health, the Environment, the Microbiome and Metabolomics (CCHEM^2):

Study Design: This project's dataset comes from an ongoing research project at CCHEM^2 which was reviewed and approved by the Internal Review Board at Emory University. Characterizing Exposures and Outcomes in an Urban Birth Cohort (CHERUB) is the first research effort in the Southeastern/Deep South in the United States to focus on exposures, particularly in a African American (AA) community.

Study Description: Beginning in January 2016, 364 pregnant, AA women were enrolled during their first trimester of pregnancy (i.e., 8-14 weeks gestation) at their routine prenatal visit at clinics affiliated with Emory Midtown and Grady Hospitals in Atlanta, Georgia. Inclusion criteria for enrollment include the following: AA women (self-identifying as Black and born in the U.S.); singleton pregnancy; between 8-14 weeks gestation; reached 20-24 weeks gestation without fetal loss or loss to followup; (verified by medical record); ability to understand written and spoken English; age 18-35 years old; no chronic medical conditions or chronic medications (verified by medical record).

Data Collection: Data were collected three times during pregnancy: (1) at a routine prenatal visit for enrollment at 8-14 weeks gestation; (2) at a home visit at 20-24 weeks gestation; and (3) at a

second routine prenatal visit at 24-30 weeks gestation. A series of demographic, health, and environmental surveys were administered at various data collection timepoints in the study. Demographic and health questionnaires were administered or updated at visits 1 and 3. These questionnaires collected data relevant for this analysis such as recent substance use using questions such as "During the last month: Have you smoked cigarettes or cigars?" For coding purposes, participants who reported no tobacco use at both visits were classified as tobacco "nonsmokers;" participants who reported use at the first visit but not at the second visit were classified as "quit smoking." Those who reported use at both trimesters were classified as tobacco "smokers." Marijuana use was assessed by the question, "During the last month: Have you smoked marijuana?" Marijuana smoking classification was coded identically to tobacco smoking. At 20-24 weeks (2^{nd}), a home environment questionnaire asked participants to describe the type of home lived in since becoming pregnant (single family home or multifamily home). The presence of smokers in the home was assessed by the question, "Does anyone living with you or present > 6 hr/day in your home smoke cigarettes, e-cigs, cigars, cigarillos, or use any other type of nicotine delivering product such as a patch or gum?" Participants who reported a smoker in the household (except for those who used vaporless or smokeless products) were classified as having secondhand smoke exposure. Other demographic and health data collected included age, educational attainment, income (as a % of poverty level), insurance (private vs. Medicaid), relationship and marital statuses, gravidity, and number of members of household.

Maternal urine was be collected at all three data collection time points. All samples were midstream, "clean-catch" spot or convenience samples. For samples collected at routine prenatal visits, residual urine remaining after clinical testing was collected, mixed, and transferred via pipette to a freezer safe Qorpak glass jar. For home visits, a urine sample was collected specifically for this study and was processed identically to the samples from prenatal clinic visits. All urine samples were labeled, inventoried, and stored at -80C until analysis.

Laboratory Analysis: Total (i.e., bound plus free) COT, 3HC and Tetrahydrocannabinolic acid (THCA; the primary metabolite of the marijuana active ingredient tetrahydrocannabinol) were measured in all urine samples collected longitudinally for each participant. 0.200 mL urine was aliquoted into a tube and spiked with an isotopically labeled analogue of the target chemicals and mixed. This urine solution was subjected to overnight enzymatic hydrolysis to liberate glucuronide- and sulfate-bound analytes. The hydrolysate was subjected to a solid phase extraction to isolate the target analytes and analyzed using liquid chromatography-tandem mass spectrometry. Two precursor → product ions were monitored for both the native and labeled analytes. Quantification was achieved using isotope dilution calibration. Quality control procedures included the inclusion of 2 spiked positive quality control materials, one reagent and one urine blank, NIST standard reference materials and 5% replicate analyses. The limits of detection (LODs) were 1.25 ng/mL (COT and 3HC) and 5.0 ng/mL (THCA).

National Health and Nutrition Survey (NHANES; 2015-2016).

***Study Description*:** NHANES is a nationally-representative sampling of the US, non-institutionalized population conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC) used to calculate population-based estimates of disease and other factors in the US population. Beginning in 1999, NHANES began annual, continuous field-based sampling with data released in 2-year cycles. Approximately 7500 US participants are sampled for each 2-year cycle. The National Center for Environmental Health at CDC uses NHANES as a vehicle to evaluate chemical exposures in the United States by measuring chemicals, their metabolites or reaction products in blood and urine samples collected in a random 1/3 subset of each cycle to maintain representativeness. To characterize both active and second-hand tobacco smoke exposure in women of reproductive age (18-40 years old) for comparison to our CCHEM2 cohort, we used data reported for the 2015-2016 cycle which was

closest in time to our cohort. In the NHANES 2015-2016 cycles, we evaluated n=1202 women aged 18-40 years collectively and by race/ethnicity.

The demographic and cotinine laboratory analysis data sets were downloaded from the online NHANES data archive at www.cdc.gov/nhanes. Available sociodemographic characteristics included age, sex, marital status, income, education, race/ethnicity. Data were pared to only retain individuals who had both cotinine measurements, were female and aged 18-40 years. Pregnancy status was only released for women ≥ 20 years old, and marital status for women <=20 years old (n=38) was coded as missing, to protect against disclosure. Race/ethnicity of participants were categorized (Non-Hispanic White, Non-Hispanic Black (referred to as African American under the criteria for the present study), Hispanic, and Other Race, including Multi-Racial), where Asian Americans are included in the "Other Race, including Multi-Racial" category.

Statistical Analysis

The CCHEM^2 cohort data were managed and deidentified with REDCap software by the CCHEM^2 team. Researchers exported the relevant, deidentified data to .xlsx files for the present study. All data were analyzed using SAS software, version 9.3. Urinary COT, 3HC, and THCA data were reported in ng/mL units (whole volume). Urinary concentrations below the LODs were replaced with an imputed valued equivalent to:

$$[Analyte]\left(\frac{ng}{mL}\right) = \frac{LOD\ (ng/mL)}{\sqrt{2}}$$

The 3HC/COT ratio was calculated for each trimester. Because spot samples collected in CCHEM2 and NHANES have variable dilution, creatinine was used to "correct" for this variability. Statistical analyses were conducted using both whole volume and creatinine-corrected COT, 3HC, THCA acid values. Urinary analyte values were creatinine-corrected using the following equation,

$$C_{adjusted} = \frac{C_{unadjusted}}{creatinine\ \left(\frac{mg}{mL}\right)} * 100$$

where $C_{unadjusted}$ is the whole volume analyte concentration. The units of $C_{adjusted}$ are ug analyte/g creatinine. Because creatinine excretion can vary considerably by age and during pregnancy with many physiological changes occurring, creatinine will also be used as an independent variable in models when using whole volume COT as the dependent variable [51].

Univariate analysis was used to evaluate distribution and to determine distributions and skewness. Due to an initial right tailed distribution, all urinary metabolites were log-transformed to satisfy normality assumptions, and geometric means and 95% CIs were used to describe and report respective concentrations. β coefficients for regression results were presented as exponentiated values of the log coefficients so that results remain interpretable as units of (ug analyte/g creatinine) or (ng/mL).

To account for behavior or physiological changes in the CCHEM^2 cohort during pregnancy, the intraclass correlation coefficients (ICCs) were calculated to confirm within-subject reliability of the urinary analyte, creatinine adjusted and adjusted, concentrations among 2 or more measurements. If the analyte's ICC $\geq$ 0.70, an average exposure concentration was created using 2 or more trimester measurements. Otherwise, the urinary analyte concentrations were only considered by trimester.

Women (n=105) missing demographic information and those (n=95) with only one urinary measurement were excluded. A subsample of women (n=104) had available behavior and home environment variables for inclusion in analyses.

The Kruskal-Wallis test was used to compare medians or ranks of transformed analyte concentrations among the race categories in NHANES sample. To assess for strong relationships or collinearity between and among predictors and exposure variables in the CCHEM^2 cohort,

correlation analyses were conducted. Simple linear regression was used to assess the relationship between average transformed urinary COT levels across pregnancy and demographic, home environment, and substance use variables. The univariate regression analysis was repeated with 1st and 3rd trimester specific transformed, urinary COT concentrations and respective predictors. Trimester specific regression analyses included transformed urinary THCA as a variable of interest. The analyses were replicated to examine the relationships of average, 1st trimester, and 3rd trimester transformed urinary 3HC with respective variables of interest. A multivariate linear regression model was fit to log transformed analyte concentrations with predictors that showed a strong, significant relationship. Given the present study's interest in prediction, final models were selected by automatic selection for best adjusted R^2 value. Significance was defined at alpha=0.05.

RESULTS

CCHEM^2 Maternal Cohort Demographic Data: *Table 1* presents demographic and select maternal characteristics of the CCHEM^2 maternal cohort. Most participants in the cohort were between 20-30 years old, with a mean age of (25.9, ± 4.7). Mothers were predominantly unmarried (88.8%) and living with a partner (41.4%). Most women (43.3%) reported a high school degree or a general education diploma (GED) or some college or technical school (22.1%) as their highest educational attainment. There was more variation for women with income ≥ 100% FPL, with 34.8% of women reporting 100% -199%FPL, 3.1% reporting 200% FPL- 299% FPL, and 13.41% reporting ≥ 300% FPL. Approximately half of the participants (48.1%) had incomes < 100% FPL, so only two income categories were presented. The majority of women were Medicaid recipients (85.6%) and reported receiving one or more of the following government benefits (71.2%): WIC nutrition program, county card, Healthy Start, Food Stamps (SNAP), Temporary Assistance for Needy Families (TANF or Government assistance), or Section 8.

CCHEM^2 Maternal Cohort Exposure Data: Creatinine concentrations (mg/mL) were normal at all 3 trimesters, with a change in mean levels across pregnancy, shown in *Figure 1*. This was further confirmed by within subject variation of creatinine concentrations across trimesters (ICC=0.3; 95% CI, 0.18-0.41). Mean concentrations were the highest at the first trimester (172.89 (mg/mL); 95% CI, 160.61-185.16), while 3rd trimester concentrations were lower (142.06 (units); 95% CI, 130.74-153.38). 2nd trimester levels were the lowest levels and showed the most variation, with a wider concentration range, but this trimester also had the least available creatinine measurements. Creatinine concentrations at 2nd and 3rd trimester had significant Pearson correlation coefficients with respective measurements of urinary COT (ng/mL) ($r=0.36$, $p<.01$; $r=0.25$, $p< .01$) and 3HC (ng/mL) ($r=0.41$, $p<.001$; $r=0.28$, $p<.001$).

Urinary COT and 3HC concentrations were adjusted for creatinine and geometric means presented by trimester in *Table 2*, along with the 3HC/COT ratios. Intraclass correlation coefficients for subjects with at least two measurements were calculated for COT (ug COT/g creatinine) (ICC=0.86; 95% CI, 0.82-0.89), 3HC (ug 3HC/g creatinine) (ICC=0.88; 95% CI, 0.85-0.91) and 3HC/COT (ICC=0.56; 95% CI, 0.47, 0.64). Average concentrations were calculated using two or more measurements for each analyte and presented as total pregnancy concentrations in *Table 2*. The average 3HC/COT ratio over pregnancy is presented but given the within subject variance of 3HC/COT (ICC<0.70), its average concentrations were not considered for models. The geometric mean for average COT across pregnancy was 10.19 (ug COT/g creatinine). COT levels were at highest concentrations and showed greatest variation, indicated by a wide range, at the third trimester. The geometric mean for average 3HC levels across pregnancy was 22.48 (ug 3HC/g creatinine). Third trimester 3HC concentrations showed the greatest variation and were the highest (24.21 ug 3HC/g creatinine), compared to other trimesters. 3HC/COT ratios were highest (2.39) and showed greatest variation at the 1st trimester. Across pregnancy, the geometric mean 3HC/COT ratio was 2.21.

Table 3 presents exposure distributions across pregnancy for demographic characteristics and other variables of interest. Self-reported drug use (0.61%) was at low prevalence in the sample and not included in analyses. Participants in the lower income category and those with low educational attainment had higher geometric mean concentrations of each analyte. Most participants lived in a multifamily home (56.7%). One participant reported having resided in a shelter and was included in the multifamily/apartment category without an impact on significance of associations. There was only a 5.8% prevalence of self-reported alcohol use at the first trimester, while only (0.7%) reported drinking through pregnancy The geometric means of analytes for those who quit drinking (4.9%) after 1st trimester were higher, with higher geometric standard errors, than never drinkers. Mothers who reported marijuana use (17.3%) at the first trimester only and those who reported continuing or beginning use after the 1st trimester (11.5%) had higher geometric mean concentrations of analytes. Most participants did not report tobacco use at either trimester (81.7%). Non-smokers who reported SHS exposure in their home had moderately higher geometric mean analyte concentrations compared to those who reported no SHS exposure. 13.5% of women reported cessation of tobacco smoking after the first trimester, and the self-reported prevalence of smoking tobacco through pregnancy was only 3.0%. The geometric mean levels of urinary analytes across pregnancy for those who smoked tobacco through pregnancy (3.0%) were higher than for those who quit (13.5%). The prevalence of self-reported co-use of marijuana and tobacco through pregnancy was 1.92%.

Linear regression analysis for total pregnancy: A common urinary COT cut-off point used for pregnant women, 50 ng/mL, was used to reclassify nonsmokers, quitters, and those who smoked through pregnancy (smokers) [52-54]. Those with COT<50ng/mL at the first, second, and/or third trimester were reclassified as nonsmokers. Those with COT ≥50 ng/mL at first trimester and COT<50 ng/mL at both the second and/or third trimester (if one trimester measurement was missing) were reclassified as quitters. This also applied to those who had COT≥50 ng/mL at first

and second trimester but <50 ng/mL at the third trimester. Smokers were classified as those with COT ≥50 ng/mL at all three trimesters, first and third trimester, or second and third trimester. Based on this criterion, (n=34) women were reclassified as smokers, who had self-reported quitting or never smoking at all. (n=3) women were reclassified as nonsmokers, who had originally self-reported tobacco use at the first trimester only (quit status). The prevalence of tobacco smoking through pregnancy was 32.7%, and the cessation prevalence was 5.8%. Models fit to whole weight (ng/mL) analyte concentrations across pregnancy can be found in *Appendix tables 1-2*.

Pearson correlation coefficients, univariate, and multivariate regression results are presented in *Tables 4-5* for average urinary COT and 3HC concentrations across pregnancy and predictors of interest. In *Table 4*, univariate analysis, shown in the unadjusted column, indicated marriage and education were associated with lower levels of COT, with graduating college or more having the most protective association (β= 0.04; 95% CI, 0.01-0.16; $p < .05$). Income <100 % FPL (β = 5.81; 95% CI, 2.41-14.15; $p < .0001$) affected exposure similarly to secondhand smoke exposure (β = 6.36; 95% CI, 2.61-15.49; $p < .0001$). Smoking marijuana, whether quit (β = 5.64; 95% CI, 1.73-18.54; $p < .001$) or continued (β = 78.26; 95% CI, 49.40-125.21; $p < .0001$), were associated with higher COT levels. Tobacco smoking, whether quit or continued, was the strongest determinant of average COT levels across pregnancy.

Variables showing significant associations and *a priori* covariates (age, income, educational attainment, alcohol use) were considered in the final multivariate model, shown in the adjusted column, for prediction of average COT levels. Tobacco smoking, quit (β = 6.05; 95% CI, 2.08-16.61; $p < .001$) and continued (β = 51.41; 95% CI, 30.27- 88.23 $p < .0001$), remained the strongest predictors of average COT levels across pregnancy. Secondhand smoke exposure and income <100% FPL also remained associated with increased COT levels, though associations were attenuated after adjustment for other covariates. Higher education such as some college or

technical school (β = 0.59; 95% CI, 0.34-1.02; p =.06) and graduating college or more (β = 0.54; 95% CI, 0.28-1.05; p =.07), remained protective for COT levels. Quitting alcohol (β = 1.93; 95% CI, 0.68-5.42; p =.28) and smoking marijuana (β = 1.60; 95% CI, 0.76-3.39; p=.12) were determinants of higher COT levels. The final model accounts for 79.0% of the variability of average COT levels during pregnancy (Adjusted R^2=0.79; p <.0001).

In *Table 5*, univariate regression results for 3HC levels across pregnancy were like those presented for COT levels, although regression coefficients appear larger due to the higher abundance of 3HC. Multivariate regression results show tobacco smoking, quit and continued, as the strongest predictor of average 3HC levels across pregnancy. Income <100% (β = 1.51; 95% CI, 0.83-2.77; p =.18) has attenuated effect of 3HC levels, compared to that observed on COT levels. Some college or technical school and graduating college or more remained protective for 3HC levels. Smoking marijuana, whether quit (β = 1.58; 95% CI, 0.76- 3.29; p =.21) or continued (β = 1.97; 95% CI, 0.79-4.85; p =.14), was associated with higher concentrations of 3HC. The final model accounts for 76.0% of the variability of average 3HC levels during pregnancy (Adjusted R^2=0.76; p <.0001).

Linear regression analysis at first trimester: Self-reported tobacco smoking prevalence in the first trimester was 14.6%. A common urinary COT cut-off point used for pregnant women, 50 ng/mL, was used to reclassify smoking status [52-54]. Of women who self-reported as non-smokers at the first trimester, (n=21) were reclassified as smokers due to urinary COT levels >50 ng/mL. Women (n=6) who self-reported smoking sand had COT levels <50 ng/mL were reclassified as nonsmokers. Those who self-reported smoking and had COT levels >50 ng/mL remained categorized as smokers. Tobacco smoking prevalence at the first trimester, based on COT levels was 32.7%, and the prevalence of tobacco and self-reported marijuana co-use at the first trimester was 14.4%. THCA levels were highly correlated with cotinine levels at each trimester. The geometric means of tetrahydrocannabinolic acid (THCA) across pregnancy (*Table*

8) remained similar for all participants, but the analyte showed large within subject variance (ICC=0.39; 95% CI, 0.28-0.49) across pregnancy. Therefore, THCA (ug THCA/g creatinine) was only considered for 1st trimester analysis. Self-reported marijuana-use and THCA levels at the first trimester did not have multicollinearity problems and were both investigated in models. Models fit to whole weight (ng/mL) analyte concentrations at the first trimester can be found in *Appendix tables 3-4*.

Tables 6-7 present the Pearson correlation coefficients, univariate, and multivariate regression results for first trimester urinary COT (ug COT/g creatinine) and 3HC (ug 3HC/g creatinine) concentrations and predictors of interest. In *Table 6*, univariate analysis, shown in the unadjusted column, indicated marriage and educational attainment past high school were strongly associated with lower levels of COT at first trimester. As expected, tobacco use and secondhand smoke exposure were the strongest determinants of increased COT levels at the 1st trimester. Univariate analysis showed that marijuana use (β = 6.05; 95% CI, 2.23-16.44; $p < .001$) and THCA levels (β = 1.08; 95% CI, 1.06-1.10; $p < .0001$) were associated with higher levels of COT. Variables showing significant associations and a priori covariates (age, income, educational attainment, alcohol use) were considered in the final multivariate model, shown in the adjusted column, for prediction of 1st trimester COT levels. Tobacco smoking (β = 24.53; 95% CI, 13.60-44.26; $p < .0001$) and secondhand smoke exposure (β = 1.67; 95% CI, 1.01-2.69; $p < .05$), remained the strong predictors. Alcohol use (β =2.08; 95% CI, 0.76-5.64; p=.15) was also associated with increased COT levels. Graduating college or more (β = 0.47; 95% CI, 0.23-0.98; p = .05) remained protective for COT levels. Income <100% FPL remained associated with increased COT levels. Increasing THCA levels (β = 1.03; 95% CI, 1.01-1.04; $p < .05$) were predictors of COT levels. This can be interpreted as a 3% increase in COT levels when THCA levels increase by 10%. The final model accounts for 76.0% of the variability of first trimester COT levels (Adjusted R^2=0.76; p <.0001).

Univariate analysis of 3HC levels at the first trimester (*Table 7*) show similar associations as for COT levels, with increased regression coefficients due to the higher abundance of 3HC levels. The final multivariate model for 3HC levels was almost exact to the model fit to COT. The fit model accounted for 80.0% of the variability of first trimester COT levels (Adjusted R^2=0.80; p <.0001) and offered slightly improved prediction plots than the COT prediction model.

Bivariate analyses: Based on regression results, it was of interest to further explore the relationship of marijuana use and tobacco smoke exposure at the first trimester with descriptive, bivariate analyses. The median level of THCA in self-reported marijuana users was 51.68 ng/mL and the 25th percentile at 10.73 (ng/mL). This is near a >10 ng/mL recommended previously [55]. While more participants were candid about marijuana use than tobacco use at the first trimester, there were (n=21) participants with levels of THCA above 10.73 ng/mL. Those participants were reclassified as marijuana smokers at for bivariate analyses, which increase of the prevalence of marijuana smoking at the first trimester to 40.4%. The prevalence of co-use at the first trimester, as indicated by COT and THCA levels, was 24.0%. 8.7% of participants were only tobacco smokers, and 16.4% were marijuana users only. Geometric mean levels of COT (ug COT/g creatinine) at the 1st trimester were significantly higher for marijuana only users compared to non-tobacco smokers (GM: 2.02; 95% CI 1.39-2.94, vs. GM 0.73; 95% CI 0.44-1.20; p=.007). Geometric mean levels of 3HC (ug COT/g creatinine) at the 1st trimester were significantly higher for marijuana only users compared to non-tobacco smokers (GM: 2.59; 95% CI 1.58-4.24, vs. GM 0.98; 95% CI 0.67-1.44; p=.004). Higher levels of COT and 3HC in marijuana-only users remained higher, after controlling for SHS exposure. There was no difference in NMR between marijuana only users and those who did not use either substance. Those that tobacco smoked only had higher COT levels than those who did not use either substance (GM: 5.18; 95% CI 4.15-6.46, vs. GM 0.73; 95% CI 0.44-1.20; p<.0001). A significant difference in the 3HC levels was also found, but little difference was found in nicotine metabolite ratio between tobacco only users and

those who did not use either substance (GM: 0.98; 95% CI 0.54-1.80, vs. GM 0.77; 95% CI 0.56-1.06; p=0.50). Co-users and tobacco only users had similar COT and 3HC levels and NMR. Co-users had higher COT levels than participants who did not use either substance (GM: 4.69; 95% CI 4.29-5.13, vs. GM 0.73; 95% CI 0.44-1.20; p<.0001), and 3HC levels followed the same trend. There was no difference found for the NMR.

NHANES Demographic Data: Demographic characteristics of women aged 18-40 years old from the NHANES 2015-2016 cycle are presented in *Table 9.* Mean age of women was 29 years old, ±6.5, and Non-Hispanic Black women were 3rd highest prevalence (18.9%) in the selected sample. Over half of the women were married (55.3%) and had educational attainment past high school (59.8%). The marital status of women (n=38) <=20 years old was not reported by NHANES to protect against disclosure. The 2016 Georgia Federal Poverty Level guidelines were used to calculate % FPL, with 24.8% of women <100 % FPL. Pregnancy status was only released by NHANES for women aged 20-44 years old, to protect against disclosure. 6.5% of women tested in this sample were pregnant.

NHANES Exposure Data: Geometric means for selected urinary biomarkers of tobacco-smoke exposure are shown in *Table 10***.** Analyte concentrations represent one biological sample and were adjusted for creatinine levels (units) at collection. The geometric mean values for adjusted, urinary COT, 3HC, and 3HC/COT were 2.2 ug COT/g creatinine, 3.5 ug HC/g creatinine, and 1.6.. *Table 11* shows geometric means for COT, 3HC, and 3HC/COT stratified by race. African American women consistently had higher geometric mean concentrations for each metabolite and the nicotine metabolite ratio. Urinary COT levels in African American women showed less variation than in other race categories, as indicated by a narrower range. African American women had a geometric mean 3HC concentration (GM, 15.6 ng/mL; 95% CI, 6.9-35.2) approximately twice that of Non-Hispanic White women (GM, 7.2 ng/mL; 95% CI, 3.6-14.2), with little difference in variation. The 3HC/COT ratio in African American women followed

trend, showing a difference in geometric mean >0.5 than women among other races. Given unequal variances among race categories, the Kruskal-Wallis test was used to detect significant difference of medians or ranks at $p<.05$ level.

DISCUSSION

Creatinine levels of this cohort decreased across pregnancy. This same trend has been found in other studies investigating toxicant exposures in maternal cohorts [56, 57]. Despite the variability of creatinine, creatinine adjusted COT and 3HC measurements in this cohort had low within subject variability, across pregnancy. This was unexpected as COT levels during pregnancy typically have within subject variation due to attempted cessation or behavior change [39]. The NMR did have within subject variation across pregnancy, which was also apparent in the slight decrease in geometric mean ratio from first to third trimester. This finding was unexpected, as previous studies found nicotine metabolism to increase during pregnancy [43-46]. Dempsey et al. found that an increased metabolism of cotinine during pregnancy resulted in lower, urinary COT levels. Within this cohort, we observed increasing 3HC and COT levels from 8-14 weeks gestation to 24-30 weeks gestation, with the highest concentrations found at 24-30 weeks gestation. The decrease in nicotine metabolism found in our maternal cohort could explain the increased burden of COT during pregnancy, which would align with literature that suggests Non-Hispanic Blacks have slower clearance of COT compared to Whites [21, 23]. However, our findings that the NMR was generally high within our cohort and within African American women of reproductive age within the NHANES cohort compared to other races contrast with the former hypothesis of slower nicotine metabolism. The present study's findings indicate there may be unique nicotine metabolism within African American women during pregnancy, and prior hypotheses on NMR and the COT burden in nonpregnant African American adults may not be generalizable to pregnant African American women.

Misreport of tobacco smoking status in this cohort was anticipated, and other maternal cohort studies have utilized biomarkers to discriminate smoking status that is in question [39, 49, 50]. After reclassification of smoking status based on COT ≥ 50ng/mL, the tobacco smoking prevalence during pregnancy was 32.7% and cessation prevalence was 5.8%. This tobacco smoking prevalence is high, compared to the U.S. prevalence in 2016, the year these data were collected, for all pregnant women (7.2%) and for African American pregnant women (6.0%) [58]. Similar smoking prevalence were found in a Southeastern U.S. maternal cohort of White and African American women in North Carolina and more recently, a racially diverse maternal cohort in Kentucky [32, 59]. To the best of our knowledge, this is the first study in the Southeastern U.S. to focus on tobacco smoke exposure in an African American maternal cohort.

Among demographic and maternal behavior factors, being married was inversely associated with COT and 3HC levels across pregnancy, but there was no association after adjusting for demographic and behavioral covariates. Income <100 % FPL was positively associated with average COT and 3HC levels, and this association remained after adjustment, although attenuated. Approximately half of women in this cohort reported incomes that were <100 % the federal poverty level and 71.2% of women reported receiving one or more government benefits such as the WIC nutrition program, Healthy Start, Food Stamps (SNAP), etc. Marriage has been shown to be slightly protective of tobacco smoke exposure in African American women and more so in other races, as it is sometimes an indicator of social support [60]. Low-income levels, as indicators of socioeconomic status, have been associated with increased active tobacco smoke exposure and passive smoke exposure [19, 61].

Maternal education past high school/GED was inversely associated with urinary COT and 3HC concentrations across pregnancy. This association was not attenuated after adjustment for demographic and behavioral covariates. Maternal education and income were not strongly correlated within this cohort, so both covariates offer interesting insight. Higher educational

attainment has been found to be protective of smoking behaviors and ETS in African American women [28, 62]. Self-reported secondhand smoke exposure was positively associated with average COT and 3HC levels across pregnancy. This association was attenuated but remained after adjustment for other covariates. The prevalence of self-reported secondhand smoke exposure (43.3%) was high compared to prevalence found in aforementioned maternal cohorts [32, 63]. Hawkins et al. found nonsmoking African American pregnant women from a maternal cohort in New York City to have a secondhand smoking prevalence of 63%, indicated by serum COT levels [28]. It is well established that African American nonsmokers are at a higher risk of secondhand smoke exposure compared to White and Hispanic non-smokers [19].

Self-reported alcohol use in only the first trimester did not have significant associations with average COT or 3HC levels but was fitted in the adjusted final model where it was positively associated. This is consistent with findings that tobacco use and alcohol use are co-morbid behaviors, although with the exception of (n=1) participant, mothers in the present cohort did not report alcohol use after the first trimester [64]. Self-reported marijuana use in only the first trimester and through pregnancy were positively associated with average COT and 3HC levels. After adjustment for demographic and other behavioral covariates, only smoking marijuana through pregnancy remained a determinant of increasing average COT levels. Although attenuated, self-reported marijuana use in only the first trimester and through pregnancy remained positively associated with 3HC levels. There is little research on the co-use of marijuana and tobacco in maternal cohorts, but the co-use of marijuana and tobacco has become more common than marijuana only use and less common than use of tobacco only, according to a nationally representative sample of women from 2005-2014. This study also found disparities in pregnant co-use, where co-users were more likely to be under 26 years old, Non-Hispanic Black, have lower educational attainment, and report lower incomes [65].

Upon investigation of COT and 3HC levels at the first trimester, we confirmed the positive associations of marijuana use with inclusion of log normal THCA levels in regression analyses. To the best of our knowledge this is the first study to examine the relationship between tobacco smoke exposure biomarkers and marijuana biomarkers in a maternal cohort. At the first trimester, THCA levels were positively associated with COT and 3HC levels, before and after adjustment for other covariates. Further exploration of marijuana and tobacco smoke biomarkers at the first trimester showed that smoking marijuana only was twice as prevalent than smoking only tobacco in this cohort, and 24% of participants were co-using, as indicated by COT and THCA levels.

The co-use of marijuana and tobacco has been associated with poorer cessation outcomes, which may help explain the low quit rate in this cohort [66, 67]. There was little difference in geometric mean COT and 3HC levels and 3HC/COT at the first trimester between of co-users and tobacco only users. Participants who only smoked marijuana at the first trimester, confirmed by THCA and COT levels, had significantly higher COT and 3HC levels compared to participants who used neither tobacco or marijuana. It is notable that this significant difference remained true even after controlling for self-reported SHS. This may be attributed to misreport of SHS or unknown ETS exposure among marijuana only users. An alternate reason for this finding may be due to a common practice in North America and Europe- smoking “blunts.” Blunts are made from splitting a cigar and replacing the tobacco filler with marijuana, but residual tobacco remains [68]. Pregnant women may perceive blunts as less risky, and the prevalence of marijuana blunt use is increasing in the U.S. for nonpregnant and pregnant women [69].

COT and 3HC levels at each trimester and across pregnancy within the CCHEM2 cohort, were higher than those described for women (of all races and of AA race) of reproductive age (18-40) from the 2015-2016 National Health and Nutrition Examination Survey. 3HC/COT for Non-Hispanic Black women from NHANES was higher than any other race, and similar high ratios were found within our African American maternal cohort [70]. This was a unique finding because

one of the hypotheses for the increased COT burden in African Americans compared to other races is a slower nicotine metabolism [21, 23].

The present study offers robust insight into active and passive tobacco smoke exposure during pregnancy, as average exposure was calculated with two or more urinary measurements during pregnancy. Tobacco smoke exposure was assessed using COT and 3HC, which were correlated through pregnancy. There were several limitations within the present study. Although the COT ≥50 ng/mL is a common cut point for distinguishing smokers and nonsmokers, COT levels below the cut point could be consistent with less frequent or intense smoking and nonsmokers who are heavily exposed to SHS [52-54]. This could have led to misclassification of nonsmokers, quitters, and smokers through pregnancy, and the high prevalence of self-reported secondhand smoke exposure within the present cohort makes this classification bias a possibility. There has not been consensus on cut-off points for urinary COT in pregnant women, and future research should aim to identify optimal cut-off points for urinary COT in African American women [48]. To establish optimal cut-off points, future studies should gather complete data on frequency of smoking, number of cigarettes smoked, and frequency of secondhand smoke exposure.

Another limitation of this study was that psychosocial data was not gathered for the cohort. Research on psychosocial risks and resources unique to African American pregnant women may be important in understanding exposure disparities. For instance, a review by Mickens et al. found that African American women who deal with stress from living in an urban and poor environment were more likely to tobacco smoke. The experiences of racism and discrimination are associated with higher risk for smoking behaviors. Other psychosocial factors such as social support and religion have been found to be protective against active tobacco smoke exposure in African American women [71]. To the best of our knowledge, there is not an established or commonly used THCA cut-point for pregnant women- only adolescents, so the cut-point we selected for bivariate analyses may have led to false negatives [55, 72].

The NHANES subsample described in the present study was small and may not be representative of COT and 3HC levels in the general population. Additionally, not all women were asked to complete a questionnaire on tobacco smoking behavior or SHS so we were unable to stratify results by exposure statuses. Finally, although the quality of prenatal care or education among mothers within the CCHEM2 cohort is unknown, participants were receiving prenatal care. These data may not be generalizable to African American mothers who are not able to attend prenatal care visits through pregnancy, due to lack of insurance or other reasons.

CONCLUSION

Levels of urinary biomarkers for tobacco smoke exposure within the CCHEM2 Cohort sample remained high through pregnancy. While tobacco smoking, quit or continued, and second smoke exposure were the strongest determinants of COT and 3HC levels, income <100 % FPL, quitting drinking after the first trimester, and smoking marijuana through pregnancy were associated with higher average COT and 3HC levels across pregnancy. Education past high school was protective for COT and 3HC levels. THCA levels at the 1st trimester were associated with increased COT and 3HC levels at the first trimester. The health effects of marijuana and tobacco co-use during pregnancy are not well known. Clinicians and health educators should inform expectant African American mothers on the impacts of co-use on tobacco smoking cessation. Future studies focusing on African American birth cohorts should investigate the interaction between biomarkers of marijuana and tobacco smoke and marijuana and tobacco co-practices in relation to COT levels. Furthermore, alterations of NMR during pregnancy should be investigated in African American maternal cohorts to better understand if the changes in nicotine metabolism are uniquely contributing to the disparity in COT levels for pregnant African American women.

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TABLES AND FIGURES

Table 1. Demographic and maternal characteristics of the CCHEM2 maternal cohort, Atlanta, Georgia (n=104)

	n	*Mean*	*SD*	*Range*
Age	104	25.9	4.7	18.0-39.0
	n			*%*
Marital Status				
Single	92			88.5
Married	12			11.5
Relationship Status				
Not in relationship	31			29.8
In relationship, not living together	30			28.9
In relationship, living together	43			41.4
Education level €				
Less than high school	17			16.4
Graduated high school/obtained GED	45			43.3
Some college or technical school	23			22.1
Graduated college or more	19			18.3
Income Ω				
< 100% FPL	50			48.1
≥ 100% FPL	54			51.9
Government Benefits*				
None	30			28.8
One or more	74			71.2
Insurance type during pregnancy				
Medicaid	89			85.6
Private through employer	14			13.5
Private through federal health insurance marketplace	1			0.9

€ GED=General Education Diploma

Ω FPL= Federal Poverty Level for 2016 State of Georgia

*Benefits= WIC nutrition program, county card, Healthy Start, Food Stamps (SNAP), Temporary Assistance for Needy Families (TANF or Government assistance), Section 8

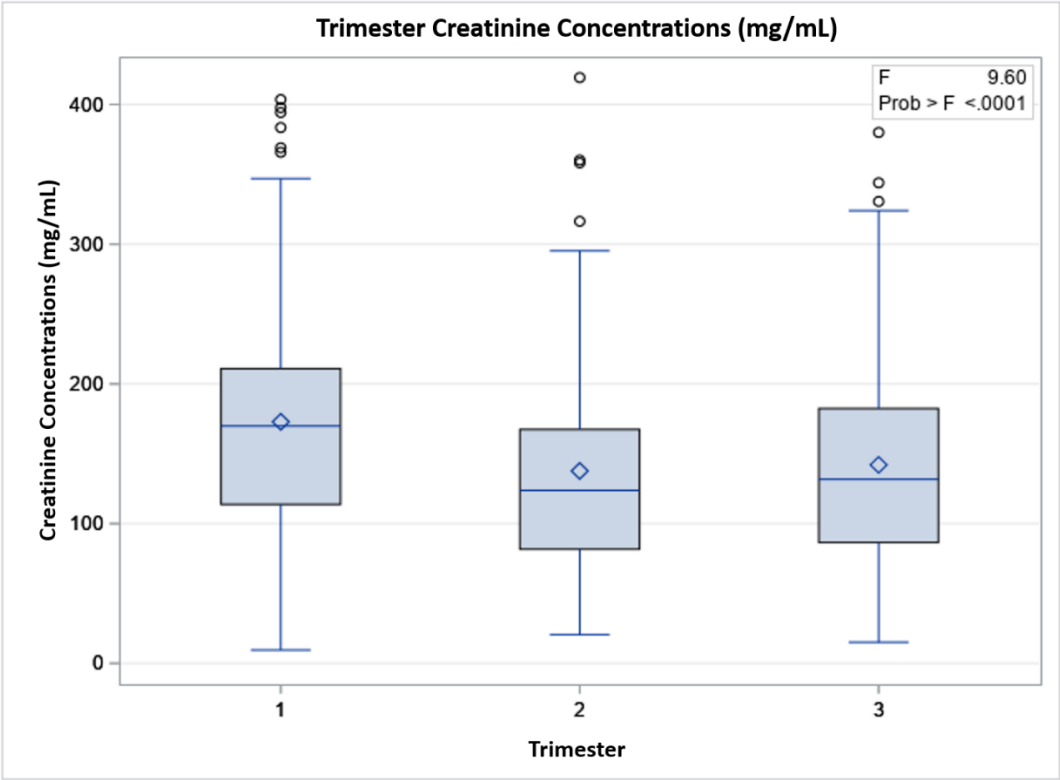

Figure 1. Creatinine concentrations (mg/mL) across pregnancy trimesters.

Table 2. Maternal tobacco smoke-exposure among CCHEM[2] maternal cohort assessed by adjusted geometric mean of metabolites (ug analyte/g creatinine)

Biomarker of exposure	*n*	*Value*	*95% CI*	*Range*
First trimester (8-14 weeks)				
Total cotinine (COT)	104	8.57	5.80, 12.68	0.24 – 3214.93
3-Hydroxycotinine (3HC)	104	20.49	13.40, 31.34	0.38 – 9426.36
3HC/COT	164	2.39	2.07, 2.77	0.34 – 39.40
Second trimester (20-24 weeks)				
Total cotinine (COT)	59	7.94	4.60, 13.68	0.36 – 4,329.89
3-Hydroxycotinine (3HC)	59	14.64	8.06, 26.59	0.51 – 4050.88

3HC/COT	59	1.84	1.52, 2.24	0.20 – 11.66
Third trimester (24-30 weeks)				
Total cotinine (COT)	102	11.17	7.29, 17.10	0.37 – 5,876.10
3-Hydroxycotinine (3HC)	102	24.21	15.13, 38.74	0.41 - 11,746.43
3HC/COT	102	2.17	1.88, 2.51	0.42 – 31.92
Total Pregnancy **Ω**				
Total cotinine (COT)	104	10.19	6.86, 15.15	0.42-4346.41
3-Hydroxycotinine (3HC)	104	22.48	14.49, 34.87	0.54-10522.65
3HC/COT	104	2.21	1.93, 2.52	0.35-28.31

Ω Urine measurements for ≥2 trimesters

Table 3. Active and Passive Exposure to tobacco-smoke in the CCHEM^2 Cohort. Geometric mean levels of average urinary metabolites (ng/mL) during pregnancy. (n=104)

		Biomarker of exposure, *GM (GSE)*		
	N (%)	Total cotinine (COT)	3' Hydroxycotinine (3HC)	3HC/COT
Total	104	7.7 (1.2)	15.8 (1.2)	2.0 (1.1)
Marital status				
Single	92 (88.5)	13.54 (1.29)	31.49 (1.32)	2.33 (1.09)
Married	12 (11.5)	1.16 (1.17)	1.69 (1.41)	1.46 (1.28)
Relationship Status				
Not in relationship	31 (29.8)	11.96 (1.58)	26.23 (1.57)	2.19 (1.16)
In relationship, not living together	30 (28.9)	9.49 (1.48)	22.55 (1.65)	2.38 (1.20)
In relationship, living together	43 (41.4)	9.69 (1.48)	20.21 (1.55)	2.09 (1.11)
Income **Ω**				

<100% FPL	50 (48.1)	25.47 (1.27)	60.83 (1.46)	2.38 (1.12)
≥100% FPL	54 (51.9)	4.37 (1.32)	8.94 (1.38)	2.05 (1.12)
Education level €				
Less than high school	17 (16.4)	45.23 (1.75)	105.14 (1.86)	2.32 (1.18)
Graduated high school/obtained GED	45 (43.3)	14.54 (1.44)	37.99 (1.48)	2.61 (1.15)
Some college or technical school	23 (22.1)	6.59 (1.62)	14.05 (1.69)	2.13 (1.17)
Graduated college or more	19 (18.3)	1.97 (1.43)	2.88 (1.54)	1.46 (1.15)
Type of Home				
Single family home	45 (43.3)	10.69 (1.43)	23.71 (1.53)	2.22 (1.14)
Multifamily home	59 (56.7)	9.83 (1.38)	21.58 (1.41)	2.20 (1.11)
Alcohol				
Never drink	97 (93.3)	9.69 (1.28)	21.22 (1.31)	2.19 (1.09)
Quit drinking	6 (5.8)	33.84 (3.03)	91.88 (3.62)	2.71 (1.31)
Drink	1 (0.9)	1.04 (-)	1.25 (-)	1.21 (-)
Marijuana				
Nonsmoker	74 (71.2)	5.75 (1.32)	11.21 (1.36)	1.95 (1.10)
Quit Smoking	18 (17.3)	32.55 (1.54)	102.50 (1.55)	3.15 (1.17)
Smoker	12 (11.5)	61.30 (1.80)	168.90 (1.98)	2.76 (1.25)
Tobacco				
Non-Smokers	85 (81.7)	5.11 (1.24)	10.71 (1.28)	2.10 (1.09)
No SHS	51 (49.0)	2.63 (1.29)	4.62 (1.32)	1.76 (1.09)
SHS exposure	34 (32.7)	13.86 (1.35)	37.81 (1.43)	2.73 (1.19)
Quit Smoking	14 (13.5)	152.37 (1.66)	446.49 (1.72)	2.93 (1.24)
No SHS	6 (35.3)	94.99 (2.23)	320.86 (2.51)	3.38 (1.49)
SHS exposure	8 (47.1)	217.18 (1.96)	572.10 (1.99)	2.63 (1.28)
Smoker	5 (3.0)	657.97 (1.61)	1543.90 (1.40)	2.35 (1.55)
No SHS	2 (40.0)	719.67 (4.33)	1319.94 (1.42)	1.83 (3.06)
SHS exposure	3 (60.0)	619.80 (1.21)	1713.94 (1.77)	2.77 (1.54)

€ GED=General Education Diploma

Ω FPL= Federal Poverty Level for 2016 State of Georgia
SHS=Secondhand smoke exposure

Table 4. Regression results for average urinary cotinine concentrations (ug COT/g creatinine) during pregnancy, corrected for misclassification (n=104).

		Total cotinine (COT)	
	r	$B_{unadjusted}$ *(95% CI)*	$B_{adjusted}$ *(95% CI)*
Age	-0.03	0.98 (0.89, 1.09)	
Married	-0.32**	0.09 (0.02, 0.35) **	
Relationship Status			
Not in relationship	---	Reference	---
In relationship, not living together	-0.02	1.54 (0.05, 52.46)	
In relationship, living together	-0.02	1.21 (0.03, 45.60)	
Income <100% FPL	0.36**	5.81 (2.41, 14.15) ***	1.67 (1.01, 2.77) *
Education			
Less than high school	---	Reference	---
Graduated high school/obtained GED	0.13	0.32 (0.09, 1.15)	
Some college or technical school	-0.10	0.14 (0.03, 0.61) *	0.59 (0.34, 1.02)
Graduated college or more	-0.32**	0.04 (0.01, 0.16) **	0.54 (0.28, 1.05)
Multifamily home	-0.02	0.92 (0.35, 0.99)	
Alcohol			
Never drink	--	Reference	---
Quit drinking	0.12	3.49 (0.46, 26.58)	1.93 (0.68, 5.42)
Drink	-0.09	0.11 (0.001, 13.60)	
Marijuana			
Nonsmoker	---	Reference	---
Quit smoking	0.22*	5.64 (1.73, 18.54) **	
Smoker	0.27*	10.70 (2.61, 43.4) ***	1.60 (0.76, 3.39)
Tobacco			

Nonsmoker	---	Reference	---
Quit smoking	0.17*	16.95 (7.46, 38.47) ***	6.05 (2.08, 16.61) **
Smoker	0.77***	78.26 (49.40, 125.21) ***	51.42 (30.27, 88.23) ***
Secondhand tobacco smoke exposure	0.38***	6.36 (2.61, 15.49) ***	1.86 (1.15, 2.97) *
R-squared			0.81
Adjusted R-squared			0.79
p-value			<.0001

Urinary cotinine (COT) levels (ug COT/g creatinine).
r = Pearson correlation coefficient.
$B_{unadjusted}$ & $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. Anti-log of coefficients.
Income % FPL= % Federal Poverty Level.
GED=General Education Diploma.
Multifamily home= apartment or multiunit residence.
Marijuana smoker= self-reported marijuana use in both 1st and 3rd trimester questionnaires.
Quit smoking marijuana= self-reported smoking marijuana in last month at 1st trimester and self-reported non-use in the past month at 3rd trimester.
Tobacco Smoker = smoked through pregnancy, as classified by COT (ng/mL) levels
Quit smoking tobacco= quit smoking tobacco by third trimester, as classified by COT (ng/mL) levels
Secondhand tobacco-smoke exposure=self-reported that someone living in their home or present in their home >6hrs/day uses home smoke cigarettes, e-cigs, cigars, cigarillos, or another nicotine delivering product.
*p-value <.05.
**p-value <.001
***p-value <.0001.

Table 5. Regression results for average urinary 3'-hydroxycotinine (3HC) concentrations (ug 3HC/g creatinine during pregnancy, corrected for misclassification (n=104).

		3'-hydroxycotinine (3HC)	
	r	$B_{unadjusted}$ *(95% CI)*	$B_{adjusted}$ *(95% CI)*
Age	-0.07	.96 (0.86, 1.07)	
Married	-0.35**	0.05 (0.01, 0.25) **	
Relationship Status			
Not in relationship	---	Reference	---
In relationship, not living together	0.0001	1.08 (0.02, 53.52)	
In relationship, living together	-0.03	0.98 (0.09, 52.46)	
<100% FPL	0.36**	6.82 (2.53, 18.17) **	1.51 (0.83, 2.77)
Education			

Less than high school	---	Reference	---
Graduated high school/obtained GED	0.17	0.36 (0.09, 1.46)	
Some college or technical school	-0.09	0.13 (0.03, 0.64) *	0.52 (0.27, 0.99) *
Graduated college or more	-0.36**	0.03 (0.01, 0.14) ***	0.31(0.14, 0.70) *
Multifamily home	-0.02	0.91 (0.32, 0.38)	
Alcohol			
Never drink	--	Reference	---
Quit drinking	0.13	4.31 (0.46, 40.44)	2.39 (0.70, 8.08)
Drink	-0.11	-2.83 (-8.18, 2.53)	
Marijuana			
Nonsmoker	---	Reference	---
Quit smoking	0.26*	9.12 (2.51, 33.45) **	1.58 (0.76, 3.29)
Smoker	0.27*	15.03 (3.25, 70.11) **	1.97 (0.79, 4.85)
Tobacco			
Nonsmoker	---	Reference	---
Quit smoking	0.15*	11.25 (3.22, 39.65) **	5.64 (1.71, 18.54) *
Smoker	0.74***	129.02 (69.41, 242.26) ***	51.94 (27.39, 97.51) ***
Secondhand tobacco smoke exposure	0.41***	9.21 (3.49, 24.29) ***	2.46 (1.40, 4.31) *
R-squared			0.78
Adjusted R-squared			0.76
p-value			<.0001

Urinary 3'-hydroxycotinine (3HC) levels (ug 3HC/g creatinine).
r = Pearson correlation coefficient.
$B_{unadjusted}$ & $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. Anti-log of coefficients.
Income % FPL= % Federal Poverty Level.
GED=General Education Diploma.
Multifamily home= apartment or multiunit residence.
Marijuana smoker= self-reported marijuana use in both 1st and 3rd trimester questionnaires.
Quit smoking marijuana= self-reported smoking marijuana in last month at 1st trimester and self-reported non-use in the past month at 3rd trimester.
Tobacco Smoker = smoked through pregnancy, as classified by COT (ng/mL) levels
Quit smoking tobacco= quit smoking tobacco by third trimester, as classified by COT (ng/mL) levels
Secondhand tobacco-smoke exposure=self-reported that someone living in their home or present in their home >6hrs/day uses home smoke cigarettes, e-cigs, cigars, cigarillos, or another nicotine delivering product.

*p-value <.05.
**p-value <.001
***p-value <.0001.

Table 6. Regression results for first trimester urinary cotinine concentrations, corrected for misclassfication (ug COT/g creatinine). (n=104)

		Total cotinine (COT)	
	r	$B_{unadjusted}$ *(95% CI)*	$B_{adjusted}$ *(95% CI)*
Age	-0.04	0.98 (0.89, 1.08)	
Married	-0.33**	0.08 (0.02, 0.33) **	
Relationship Status			
Not in relationship	---	Reference	---
In relationship, not living together	0.03	1.19 (0.04, 38.47)	
In relationship, living together	0.04	1.39 (0.04, 46.99)	
Income <100% FPL	0.35**	5.42 (2.25, 13.07) **	2.27 (1.36, 3.74) *
Education			
Less than high school	---	Reference	---
Graduated high school/obtained GED	0.08	0.34 (0.09, 1.22)	
Some college or technical school	-0.02	0.25 (0.06, 1.05)	
Graduated college or more	-0.32**	0.09 (0.01, 0.24) **	0.47 (0.23, 0.98) *
Multifamily home	-0.01	1.00 (0.39, 2.59)	
Alcohol users	0.08	2.39 (0.32, 17.81)	2.08 (0.76, 5.64) p=.15
Marijuana smokers	0.33**	6.05 (2.23, 16.44) **	
Tobacco smokers	0.82***	64.07 (35.87, 114.4) ***	24.53 (13.60, 44.26) ***
Secondhand smoke exposure	0.37***	6.11 (2.53, 14.73) ***	1.67 (1.01, 2.69) *
€ Tetrahydrocannabinolic acid (THCA)	0.58***	1.08 (1.06, 1.10) ***	1.03 (1.01, 1.04) **
R-squared			0.78
Adjusted R-squared			0.76
p-value			<0.0001

Urinary total cotinine (COT) (ug COT/g creatinine) at first trimester.
r = Pearson correlation coefficient.
$B_{unadjusted}$ & $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. Anti-log of coefficients.
€ $B_{unadjusted}$ & € $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. $1.10^{(coefficient)}$, interpretable for 10% increase in lognormal independent variable.
Income % FPL= Federal Poverty Level.
3HC/COT= lognormal ratio of 3'-hydroxycotinine (ug 3HC/g creatinine) to cotinine (ug COT/g creatinine).
Tetrahydrocannabinolic acid (THCA)= lognormal (ug THCA/g creatinine) at first trimester.
Multifamily home= apartment or multiunit residence.
Alcohol user=self-reported alcohol use in the past 30 days, at first trimester.
Tobacco smokers= participants with 1st trimester COT > 50 ng/mL.
Marijuana smoker= self-reported marijuana use in the past 30 days, at first trimester.
Secondhand tobacco-smoke exposure=self-reported that someone living in their home or present in their home >6hrs/day uses home smoke cigarettes, e-cigs, cigars, cigarillos, or another nicotine delivering product.
*p-value <.05.
**p-value <.001
***p-value <.0001.

Table 7. Regression results for first trimester urinary trans-3'-hydroxycotinine (3HC) concentrations, corrected for misclassification (ng/mL). (n=104)

		3'-hydroxycotinine (3HC)	
	r	$B_{unadjusted}$ *(95% CI)*	$B_{adjusted}$ *(95% CI)*
Age	-0.09	0.95 (0.85, 1.06)	
Married	-0.36**	0.05 (0.01, 0.23) **	
Relationship Status			
Not in relationship	---	Reference	---
In relationship, not living together	0.03	1.19 (2.25, 0.31)	
In relationship, living together	-0.02	0.97 (2.61, 0.28)	
<100% FPL	0.35**	6.30 (2.43, 16.44) **	2.08 (1.22, 3.49) *
Education			
Less than high school	---	Reference	---
Graduated high school/obtained GED	0.14	0.38 (0.10, 1.49)	
Some college or technical school	-0.02	0.23 (0.05, 1.03)	0.64 (0.35, 1.16) p=.07
Graduated college or more	-0.39***	0.03 (0.01, 0.15) ***	0.27 (0.13, 0.55) **
Multifamily home	0.02	1.04 (0.37, 2.92)	

Alcohol use	0.10	2.36 (0.26, 21.33)	2.56 (0.90, 7.24) p=.08
Marijuana use	0.38***	9.03 (3.13, 26.31) ***	
Tobacco use	0.79***	77.48 (39.65, 152.93) ***	18.17 (9.87, 33.45) ***
Secondhand smoke exposure	0.43***	9.30 (3.67, 23.81) ***	2.39 (1.43, 4.01) *
€ Tetrahydrocannabinolic acid (THCA)	0.62***	1.09 (1.07, 1.11) ***	1.04 (1.03, 1.06) ***
R-squared			0.80
Adjusted R-squared			0.78
p-value			<0.0001

Urinary 3'-hydroxycotinine (3HC) (ug 3HC/g creatinine) at first trimester.
r = Pearson correlation coefficient.
$B_{unadjusted}$ & $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. Anti-log of coefficients.
€ $B_{unadjusted}$ & € $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. $1.10^{(coefficient)}$, interpretable for 10% increase in lognormal independent variable.
Income % FPL= Federal Poverty Level.
3HC/COT= lognormal ratio of 3'-hydroxycotinine (ug 3HC/g creatinine) to cotinine (ug COT/g creatinine).
Tetrahydrocannabinolic acid (THCA)= lognormal (ug THCA/g creatinine) at first trimester.
Multifamily home= apartment or multiunit residence.
Alcohol user=self-reported alcohol use in the past 30 days, at first trimester.
Tobacco smokers= participants with 1st trimester COT > 50 ng/mL.
Marijuana smoker= self-reported marijuana use in the past 30 days, at first trimester.
Secondhand tobacco-smoke exposure=self-reported that someone living in their home or present in their home >6hrs/day uses home smoke cigarettes, e-cigs, cigars, cigarillos, or another nicotine delivering product.
*p-value <.05.
**p-value <.001
***p-value <.0001.

Table 8. Marijuana exposure among CCHEM[2] maternal cohort at trimesters assessed by geometric mean of tetrahydrocannabinolic acid (THCA) (ug THCA/g creatinine)

Tetrahydrocannabinolic acid (THCA)	*n*	*Value*	*95% CI*	*Range*
First trimester (8-14 weeks)	104	9.13	6.83, 12.20	0.92 – 967.79
Second trimester (20-24 weeks)	59	7.92	5.46, 11.48	0.98 – 835.69
Third trimester (24-30 weeks)	102	9.67	7.21, 12.96	0.93 – 1,524.22

Table 9. Demographic characteristics of women 18-40 years old from the NHANES, United States (n=358)

	n	*Mean*	*SD*	*Range*
Age	358	29.0	6.5	18.0-40.0

	n	*%*
Race-ethnicity		
Non-Hispanic White	104	29.1
African American	68	18.9
Hispanic	122	34.1
Other Race/ethnicities, including Multi-Racial	64	17.9
Marital Status		
Single	177	55.3
Married	143	44.7
Missing*	38	-
Education level		
Less than high school	82	22.9
Graduated high school/obtained GED	62	17.3
Some college or technical school	121	33.8
Graduated college or more	93	26.0
Income (FPL) Ω		
<100%	81	24.8
100%-199%	80	24.5
200%-299%	66	20.2
>=300%	100	30.6
Missing	31	-
Pregnancy Status**		
Not Pregnant	292	91.3
Pregnant	20	6.3
Undetermined	8	2.5
Missing	38	-

*Marital Status was for women ≤20 years old (n=38) was coded as missing, to protect against disclosure.

€ GED=General Education Diploma

Ω FPL=Federal Poverty Level for 2016 State of Georgia

**Pregnancy status was only released for women 20-44 years old, to protect against disclosure.

Table 10. Active and Passive Exposure to tobacco-smoke among women 18-40 years old from the 2015-2016 NHANES. Adjusted geometric mean of urinary analytes (ug analyte/g creatinine).

Biomarker of Exposure	*n*	*Value*	*95% CI*	*Range*

Total cotinine (COT)	358	2.2	1.6, 3.1	0.0-8400.0
3-Hydroxycotinine (3HC)	358	3.5	2.5, 4.8	0.0-17254.9
3HC/COT	358	1.6	1.5, 1.7	0.0-20.8

Table 11. Active and Passive Exposure to tobacco-smoke by race among women 18-40 years old from the 2015-2016 NHANES. Adjusted geometric means of urinary analytes (ug analyte/g creatinine)

			Total cotinine (COT)		
Race Category	*n*	*Value*	*95% CI*	*Range*	*p-value*
Non-Hispanic White	104	4.7	2.4, 9.0	0.0-6912.0	<0.05*
African American	68	7.3	3.3, 16.1	0.1-2739.7	
Hispanic	122	0.8	0.5, 1.2	0.0-5768.3	
Other Race, including Multi-Racial	64	1.4	0.7, 2.8	0.0-8400.0	
			3-Hydroxycotinine (3HC)		
	n	*Value*	*95% CI*	*Range*	*p-value*
Non-Hispanic White	104	7.2	3.6, 14.2	0.1-17254.9	<0.05*
African American	68	15.6	6.9, 35.2	0.1-17079.4	
Hispanic	122	1.2	0.8, 1.8	0.0-15000.0	
Other Race, including Multi-Racial	64	1.7	0.9, 3.4	0.0-9257.1	
			3HC/COT		
	n	*Value*	*95% CI*	*Range*	*p-value*
Non-Hispanic White	104	1.5	1.4, 1.7	0.3-8.3	<0.05*
African American	68	2.1	1.7, 2.6	0.0-17.8	
Hispanic	122	1.5	1.3, 1.6	0.0-6.0	
Other Race, including Multi-Racial	64	1.2	1.1, 1.4	0.1-20.8	

*significant at .05 significance level

APPENDICES

Whole weight biomarker concentrations, with inclusion of creatinine as independent variable.

Appendix Table 1. Regression results for average, whole weight cotinine concentrations (ng/mL) during pregnancy, with inclusion of creatinine levels in model, corrected for misclassification (n=100)

		Total cotinine (COT)	
	r	$B_{unadjusted}$ *(95% CI)*	$B_{adjusted}$ *(95% CI)*
Age	-0.04	0.93 (0.84, 1.04)	
Married	-0.35**	0.06 (0.01, 0.25) **	0.64 (0.28, 1.51)
Relationship Status			
Not in relationship	---	Reference	---
In relationship, not living together	-0.01	0.87 (0.02, 32.14)	
In relationship, living together	-0.02	0.99 (0.02, 40.04	
<100% FPL	0.39***	8.25 (3.29, 20.29) *	2.14 (1.28, 3.56) *
Education			
Less than high school	---	Reference	---
Graduated high school/obtained GED	0.12	0.31 (0.09, 1.13)	
Some college or technical school	-0.11	0.15 (0.03, 0.65) *	0.60 (0.34, 1.06)
Graduated college or more	-0.34**	0.03 (0.01, 0.12) ***	0.53 (0.24, 1.14)
Multifamily home	-0.03	0.79 (0.29, 2.16)	
Alcohol			
Never drink	--	Reference	---
Quit drinking	0.10	2.80 (0.35, 22.65)	1.95 (0.73, 5.26)
Drink	-0.11	0.07 (0.00, 10.59)	0.31 (0.03, 5.26)
Marijuana			
Nonsmoker	---	Reference	---
Quit smoking	0.25*	7.61 (2.27, 25.28) *	
Smoker	0.24*	12.43 (2.83, 54.60) *	
Tobacco			
Nonsmoker	---	Reference	---

Quit smoking	0.14	11.36 (4.01, 31.82) ***	8.41 (3.13, 22.65) ***
Smoker	0.83***	112.17 (66.02, 190.57) ***	54.05 (31.82, 92.76) ***
Secondhand tobacco smoke exposure	0.42***	6.23 (2.44, 15.96) **	1.67 (1.02, 2.69) *
Creatinine (units) at first trimester	0.01	1.00 (0.99, 1.01)	
Creatinine (units) at second trimester	0.17	1.00 (0.99, 1.01)	
Creatinine (units) at third trimester	0.26*	1.01 (1.00, 1.02) *	
R-squared			0.83
Adjusted R-squared			0.81
p-value			<.0001

Urinary cotinine (ng/mL) average concentration across pregnancy.
r = Pearson correlation coefficient.
$B_{unadjusted}$ & $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. Anti-log of coefficients.
Income % FPL= % Federal Poverty Level.
GED=General Education Diploma.
Multifamily home= apartment or multiunit residence.
Marijuana smoker= self-reported marijuana use in both 1st and 3rd trimester questionnaires.
Quit smoking marijuana= self-reported smoking marijuana in last month at 1st trimester and self-reported non-use in the past month at 3rd trimester.
Tobacco Smoker = smoked through pregnancy, as classified by COT (ng/mL) levels
Quit smoking tobacco= quit smoking tobacco by third trimester, as classified by COT (ng/mL) levels
Secondhand tobacco-smoke exposure=self-reported that someone living in their home or present in their home >6hrs/day uses home smoke cigarettes, e-cigs, cigars, cigarillos, or another nicotine delivering product.
*p-value <.05.
**p-value <.001
***p-value <.0001.

Appendix Table 2. Regression results for average, whole weight trans-3'-hydroxycotinine (3HC) (ng/mL) during pregnancy, with inclusion of creatinine levels in model, corrected for misclassification (n=100)

		Total cotinine (COT)	
	r	$B_{unadjusted}$ *(95% CI)*	$B_{adjusted}$ *(95% CI)*
Age	-0.12	0.90 (0.81, 1.02)	
Married	-0.38***	0.04 (0.01, 0.18) ***	
Relationship Status			
Not in relationship	---	Reference	---
In relationship, not living together	0.001	0.73 (0.01, 38.86)	
In relationship, living together	-0.07	0.79 (0.01, 46.06)	

<100% FPL	0.38***	9.03 (3.29, 24.78) ***	1.52 (0.81, 2.89)
Education			
Less than high school	---	Reference	---
Graduated high school/obtained GED	0.19*	0.33 (0.08, 1.34)	
Some college or technical school	-0.10	0.14 (0.03, 0.68) *	0.51 (0.26, 1.00)
Graduated college or more	-0.38***	0.02 (0.00, 0.09) ***	0.27 (0.12, 0.60) *
Multifamily home	-0.03	0.73 (0.24, 2.20)	
Alcohol			
Never drink	--	Reference	---
Quit drinking	0.10	3.56 (0.36, 35.16)	2.29 (0.67, 7.92)
Drink	-0.12	0.04 (0.00, 9.68)	
Marijuana			
Nonsmoker	---	Reference	---
Quit smoking	0.28*	12.55 (3.42, 46.53) **	1.88 (0.90, 3.90)
Smoker	0.24*	17.99 (3.63, 89.12) **	1.73 (0.66, 4.53)
Tobacco			
Nonsmoker	---	Reference	---
Quit smoking		14.88 (4.18, 53.52) ***	7.61, (2.32, 25.03) *
Smoker		145.47 (75.94, 278.66) ***	49.90 (25.53, 96.54) ***
Secondhand tobacco smoke exposure	0.41***	8.58 (3.10, 24.05) ***	2.36 (1.32, 4.18) *
Creatinine (units) at first trimester	0.06	1.00 (0.99, 1.01)	
Creatinine (units) at second trimester	0.20*	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)
Creatinine (units) at third trimester	0.32*	1.01 (1.00, 1.02) *	
R-squared			0.80
Adjusted R-squared			0.78
p-value			<.0001

Urinary 3'-hydroxycotinine (3HC) ng/mL average concentration across pregnancy.
r = Pearson correlation coefficient.
$B_{unadjusted}$ & $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. Anti-log of coefficients.
Income % FPL= % Federal Poverty Level.
GED=General Education Diploma.

Multifamily home= apartment or multiunit residence.
Marijuana smoker= self-reported marijuana use in both 1st and 3rd trimester questionnaires.
Quit smoking marijuana= self-reported smoking marijuana in last month at 1st trimester and self-reported non-use in the past month at 3rd trimester.
Tobacco Smoker = smoked through pregnancy, as classified by COT (ng/mL) levels
Quit smoking tobacco= quit smoking tobacco by third trimester, as classified by COT (ng/mL) levels
Secondhand tobacco-smoke exposure=self-reported that someone living in their home or present in their home >6hrs/day uses home smoke cigarettes, e-cigs, cigars, cigarillos, or another nicotine delivering product.
*p-value <.05.
**p-value <.001
***p-value <.0001.

Appendix Table 3. Regression results for first trimester, whole weight cotinine (COT) concentrations (ng/mL), with inclusion of creatinine levels in model, corrected for misclassification (n=104)

		Total cotinine (COT)	
	r	$B_{unadjusted}$ *(95% CI)*	$B_{adjusted}$ *(95% CI)*
Age	-0.05	0.96 (0.87, 1.05)	
Married	-0.36**	0.06 (0.02, 0.25) **	0.66 (0.29, 1.46)
Relationship Status			
Not in relationship	---	Reference	---
In relationship, not living together	0.03	1.18 (0.04, 36.97)	
In relationship, living together	-0.01	0.97 (0.03, 32.46)	
<100% FPL	0.37***	5.81 (2.44, 13.74) **	2.20 (1.40, 3.53) **
Education			
Less than high school	---	Reference	---
Graduated high school/obtained GED	0.06	0.38 (0.11, 1.34)	
Some college or technical school	-0.01	0.28 (0.07, 1.16)	
Graduated college or more	-0.34**	0.05 (0.01, 0.21) ***	0.62 (0.31, 1.23)
Multifamily home	-0.03	0.87 (0.34, 2.23)	
Alcohol use	0.07	1.86 (0.25, 13.59)	
Marijuana use	0.35**	6.82 (2.56, 17.99) **	1.45 (0.85, 2.44)
Tobacco use	0.60***	69.41 (40.45, 119.10) ***	27.11 (15.80, 46.53) ***

Secondhand smoke exposure	0.44***	7.09 (3.03, 16.78) ***	2.03 (1.28, 3.22) *
€ Tetrahydrocannabinolic acid (THCA)	0.53***	1.08 (1.05, 1.10) ***	1.02 (1.00, 1.03) *
Creatinine	0.06	1.00 (0.99, 1.01)	0.99 (0.99, 1.00)
R-squared			0.81
Adjusted R-squared			0.80
p-value			<0.0001

Urinary total cotinine (COT) ng/mL at first trimester.
r = Pearson correlation coefficient.
$B_{unadjusted}$ & $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. Anti-log of coefficients.
€ $B_{unadjusted}$ & € $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. $1.01^{(coefficient)}$, interpretable for 10% increase in lognormal independent variable.
Income % FPL= Federal Poverty Level.
Tetrahydrocannabinolic acid (THCA)= lognormal (ng/mL) at first trimester.
Creatinine (mg/mL) at first trimester.
Multifamily home= apartment or multiunit residence.
Alcohol user=self-reported alcohol use in the past 30 days, at first trimester.
Tobacco smokers= participants with 1st trimester COT > 50 ng/mL.
Marijuana smoker= self-reported marijuana use in the past 30 days, at first trimester.
Secondhand tobacco-smoke exposure=self-reported that someone living in their home or present in their home >6hrs/day uses home smoke cigarettes, e-cigs, cigars, cigarillos, or another nicotine delivering product.
*p-value <.05.
**p-value <.001
***p-value <.0001.

Appendix Table 4. Regression results for first trimester, whole weight trans-3'-hydroxycotinine (3HC) concentrations (ng/mL), with inclusion of creatinine levels in model, corrected for misclassification (n=104)

		3'-hydroxycotinine (3HC)	
	r	$B_{unadjusted}$ *(95% CI)*	$B_{adjusted}$ *(95% CI)*
Age	-0.10	0.92 (0.84, 1.03)	
Married	-0.38***	0.04 (0.01, 0.18) ***	
Relationship Status			
Not in relationship	---	Reference	---
In relationship, not living together	0.05	0.97 (0.25, 3.74)	
In relationship, living together	-0.05	0.68 (0.19, 2.34)	
<100% FPL	0.36***	6.75 (2.59, 17.64) **	2.01 (1.20, 3.39) *
Education			

Less than high school	---	Reference	---
Graduated high school/obtained GED	0.13	0.43 (0.11, 1.67)	1.38 (0.81. 2.32)
Some college or technical school	-0.02	0.26 (0.06, 1.17)	
Graduated college or more	-0.39**	0.03 (0.01, 0.14) ***	0.34 (0.16, 0.70) *
Multifamily home	-0.01	0.91 (0.32, 2.56)	
Alcohol use	0.09	2.36 (0.26, 21.33)	1.72 (0.60, 4.90)
Marijuana use	0.39**	10.07 (3.49, 29.37) ***	1.60 (0.87, 2.92)
Tobacco use	0.58***	83.93 (42.95, 164.02) ***	20.29 (11.13, 37.34) ***
Secondhand smoke exposure	0.48***	10.91 (4.31, 27.39) ***	2.77 (1.67, 4.62) **
Tetrahydrocannabinolic acid (THCA)	0.56***	1.09 (1.07, 1.12) ***	1.03 (1.02, 1.05) **
Creatinine	0.14	1.01 (0.99, 1.01)	
R-squared			0.81
Adjusted R-squared			0.79
p-value			<0.0001

Urinary 3'-hydroxycotinine (3HC) ng/mL at first trimester.
r = Pearson correlation coefficient.
$B_{unadjusted}$ & $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. Anti-log of coefficients.
€ $B_{unadjusted}$ & € $B_{adjusted}$ = univariate regression results, unadjusted & adjusted. $1.01^{(coefficient)}$, interpretable for 10% increase in lognormal independent variable.
Income % FPL= Federal Poverty Level.
Tetrahydrocannabinolic acid (THCA)= lognormal (ng/mL) at first trimester.
Creatinine (mg/mL) at first trimester.
Multifamily home= apartment or multiunit residence.
Alcohol user=self-reported alcohol use in the past 30 days, at first trimester.
Tobacco smokers= participants with 1st trimester COT > 50 ng/mL.
Marijuana smoker= self-reported marijuana use in the past 30 days, at first trimester.
Secondhand tobacco-smoke exposure=self-reported that someone living in their home or present in their home >6hrs/day uses home smoke cigarettes, e-cigs, cigars, cigarillos, or another nicotine delivering product.
*p-value <.05.
**p-value <.001
***p-value <.0001.