Levels of selected urinary metabolites of volatile organic compounds in a representative sample of US adolescents

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ABSTRACT
Data from National Health and Nutrition Examination Survey for the years 2011–2012 were used to evaluate the variability in the observed levels of 20 urinary metabolites of 16 parent volatile organic compounds by age, gender, race/ethnicity, and smoking status for adolescents aged 12–19 years. Smokers were found to have statistically significantly higher adjusted levels than nonsmokers for selected urinary metabolites of acrylonitrile ($p < 0.05$) and 1,3-butadiene ($p < 0.05$). For example, for N-Acetyl-S-(2-cyanoethyl)-L-cysteine, the adjusted levels for smokers were 29.2 ng/mL and 2.0 ng/mL for nonsmokers ($p < 0.05$). Females were found to have higher adjusted levels of selected metabolites of crotonaldehyde ($p < 0.05$), cyanide ($p < 0.05$), and tetrachloroethylene ($p < 0.05$) than males. For example, the adjusted levels of 2-Aminothiazoline-4-carboxylic acid or ATCA were 218.9 and 108.6 ng/mL for females and males, respectively ($p < 0.05$). Non-Hispanic whites (NHW) had higher adjusted levels than non-Hispanic blacks (NHB) for selected metabolites of N,N-dimethylformamide ($p < 0.05$) and ethylbenzene, styrene ($p < 0.05$). For example, for N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine or AMCC, the adjusted levels for NHW and NHB were 122.7 and 80.2 ng/mL, respectively ($p < 0.05$). The reverse was true for selected metabolites of carbon-disulfide and tetrachloroethylene. For example, for N-Acetyl-S-(benzyl)-L-cysteine or BMA, adjusted levels for NHW and NHB were 6.7 and 10.3 ng/mL, respectively ($p < 0.05$).

1. Introduction
Volatile organic compounds (VOCs) vaporize at room temperatures because of their low boiling points. Common sources of exposure to VOCs include paints, pesticides, deodorizers, cleaning and degreasing agents, personal care products, and solvents (Sexton et al. 2005). Humans can also be exposed to quite a few VOCs like benzene, toluene, xylenes, and others from environmental tobacco smoke (ETS) (Chambers et al. 2011). Protano et al. (2012a) reported the levels of urinary unmodified benzene (u-UB) among children living in a rural area of Italy. Those children who were exposed to ETS at home were found to have median u-UB levels of 359.5 ng/L and those who were not exposed to ETS at home were found to have median u-UB levels...
of 92.5 ng/L (Protano et al. 2012a). This study confirms that VOCs like benzene can be assumed by children who are exposed to ETS at home. Korte et al. (2000) reported benzene concentration to be about 45 µg/cigarette in the mainstream smoke and about 10 times of that in the sidestream smoke. Compared to nonsmokers, Jain (2015a) reported active smokers to have statistically significantly higher urinary levels of N-acetyl-S-(2-cyanoethyl)-L-cysteine (46.3 vs. 3.1 ng/mL), N-acetyl-S-(2-hydroxypropyl)-L-cysteine (88.4 vs. 57.6 ng/mL), mandelic acid (228.9 vs. 162.7 ng/mL), and 2-methylhippuric acid (73.6 vs. 31.6 ng/mL). Hence, active smokers can assume substantial levels of VOCs released by tobacco smoke. Other sources of exposure to VOCs include automobile exhausts and even office devices like printers and photocopiers (Kowalska, Szewczynska, and Posniani 2014).

Exposure to many VOCs has been associated with adverse health effects. For example, benzene may induce drowsiness, dizziness, rapid or irregular heartbeat, headaches, tremors, confusion, unconsciousness, and even death at very high levels of exposure (http://www.bt.cdc.gov/agent/benzene/basics/facts.asp). Similar symptoms may be caused by eating foods or drinking beverages which contain benzene (http://www.bt.cdc.gov/agent/benzene/basics/facts.asp). Anemia, leukemia, and excessive bleeding are some of the long-term health effects of exposure to benzene (http://www.bt.cdc.gov/agent/benzene/basics/facts.asp). Batteringman et al. (2014), Carwile et al. (2014), Cristofori, Sauer, and Trevisan (2015), Guyton et al. (2014), Lash et al. (2014), Lerner et al. (2014), Ruckart, Bove, and Maslia (2013, 2014), Singthong et al. (2014), Vlaanderen et al. (2014), and Yang et al. (2014) are some of the authors who have studied and reported adverse health risks associated with exposure to selected VOCs. Estimated cancer and non-cancer risk attributable to selected VOCs have been provided by Fowles and Dybing (2003), Burns et al. (2008), Cristofori, Sauer, and Trevisan (2015), and Vlaanderen et al. 2011. Elevated exposure to selected VOCs during prenatal period has also been associated with increased risk of stillbirth and placental abruption (Carwile et al. 2014), neural tube defects (Ruckart, Bove, and Maslia 2013), adverse immune status of the child (Lehmann et al. 2002), and wheezing during early infancy (Franck et al. 2014).

Data on selected VOCs in blood and/or air have been reported among others by Ashley et al. (1994), Bonanno et al. (2001), Chambers et al. (2011), Churchill, Ashley, and Kaye (2001), Jia, Yu, and Masiak (2012), Kim et al. (2006), Lin, Egeghy, and Rappaport (2008), Sexton et al. (2005), and Su, Mukherjee, and Batteringman (2013). Levels of VOCs and their metabolites and/or the analytical methods to detect them in urine have been reported among others by Alwis et al. (2012), Barbieri et al. (2004), Carmela et al. 2009, Ding et al. (2009), Protano et al. (2012b), Reska et al. (2010), and Schettgen et al. (2008, 2009). Wilson (2015) reported on the use of electronic nose technologies to detect the presence of certain VOCs in human breath.

US National Health and Nutrition Examination Survey (NHANES) released data in public domain for the years 2011–2012 for the first time for 28 metabolites of urinary VOCs as listed in Alwis et al. (2012) for a representative sample of US population. Thus, the objective of this study was to use data from 2011–2012 NHANES to evaluate the variability in the concentration levels of selected VOC metabolites by age, gender, race/ethnicity, and smoking status for adolescents aged 12–19 years. This is a sister publication to two other recent publications by this author (Jain 2015a, 2015b).
2. Materials and methods

NHANES data on demographics, body measures, and urinary VOC files for the years 2011–2012 (http://wwwn.cdc.gov/nchs/nhanes/search/nhanes11_12.aspx) for those aged 12–19 years were downloaded and match merged. The laboratory methods used to measure VOCs in urine, as previously mentioned, are provided in Alwis et al. (2012) and at http://wwwn.cdc.gov/nchs/nhanes/2011-2012/UVOCS_G.htm#Description_of_Laboratory_Methodology. The sampling plan for NHANES is a complex, stratified, multistage, probability cluster designed to be representative of the civilian, non-institutionalized US population. NHANES provides sampling weights to account for the complex survey design, including oversampling, survey non-response, and post-stratification. All analyses incorporated information on sampling design variables.

Data were available for 28 metabolites of 18 parent VOCs. Specifically, parents and their metabolites for which data were available are listed in Supplementary Table S1 as well as in Alwis et al. (2012). Percentage values at or above the limit of detection (LOD) varied from <1% for N-Acetyl-S-(1,2-dichlorovinyl)-L-cysteine (1,2DCVMA) to 100% for N-Acetyl-S-(2-carbamoyl methyl)-L-cysteine (AAMA) (Supplementary Table S1). There were eight metabolites for which percentage observations ≥ LOD were <60%. These metabolites were N-Acetyl-S-(phenyl)-L-cysteine (PMA), N-Acetyl-S-(1-hydroxymethyl-2-propenyl)-L-cysteine (MHBMA1), N-Acetyl-S-(2-hydroxy-3-butenyl)-L-cysteine (MHBMA2), N-Acetyl-S-(1-phenyl-2-hydroxyethyl)-L-cysteine + N-Acetyl-S-(2-phenyl-2-hydroxyethyl)-L-cysteine (PEMA), N-Acetyl-S-(trichlorovinyl)-L-cysteine (TCVMA), 1,2DCVMA, N-Acetyl-S-(2,2-dichlorovinyl)-L-cysteine (2,2DCVMA), and N-Acetyl-S-(2,4-dimethylphenyl)-L-cysteine + N-Acetyl-S-(2,5-dimethylphenyl)-L-cysteine + N-Acetyl-S-(3,4-dimethylphenyl)-L-cysteine (DPM). Since, in my opinion, a reliable statistical analysis cannot be done unless at least 60% observations are ≥ LOD; these eight metabolites were not analyzed. Thus, this study was limited to analyzing 20 metabolites, namely, N-Acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA), N-Acetyl-S-(3-hydroxypropyl)-L-cysteine (3HPMA), AAMA, N-Acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (GAMA), N-Acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA), N-Acetyl-S-(2-hydroxyethyl)-L-cysteine (HEMA), trans, trans-Muconic acid (MU), N-Acetyl-S-(n-propyl)-L-cysteine (BPMA), N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMMA), N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine (MHBMA3), 2-Thioxothiazolidine-4-carboxylic acid (TTCA), N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine (HPMMA), 2-Aminothiazoline-4-carboxylic acid (ATCA), N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine (AMCC), Phenylglyoxylic acid (PGA), N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (2HPMA), Mandelic acid (MA), N-Acetyl-S-(benzyl)-L-cysteine (BMA), 2-methylhippuric acid (2MHA), and 3-methylhippuric acid + 4-methylhippuric acid (3MHA + 4MHA). All values below the LOD were imputed as LOD/Sqrt(2). Data were available for a total of 402 participants. Details are given in Table 1.

Distributions of all 20 metabolites were found to be non-normal as determined by Shapiro–Wilk test of normality. Consequently, log10 transformations were used to normalize the data before using them in regression models. However, log10 transformed data were not always found to be normally distributed as determined by Shapiro–Wilk test of normality, but the skewnesses were substantially reduced. Since regression analysis is robust to certain levels of departures from normality, we proceeded to use log10 transformed data for building regression models. Thus, regression models were fitted with log10
transformed values of each of the 20 metabolites listed earlier as dependent variables. The independent variables included in all models were gender (male, female), race/ethnicity (non-Hispanic white (NHW), non-Hispanic black (NHB), all other race/ethnicities including Hispanics and Non-Hispanic Asians (OTH)), smoking status (nonsmokers defined as those with serum cotinine values of $<10$ ng/mL, smokers defined as those with serum cotinine values of $\geq 10$ ng/mL), age, body mass index (BMI), poverty income ratio, total number of rooms in the house, total number of smokers smoking inside the house, number of days that the tobacco products were used during the last five days, and urine creatinine. First-order interaction terms between gender, race/ethnicity, and smoking status were also considered but were included in the final models if they were found to be statistically significant at $\alpha = 0.05$. It should be noted that there were very few smokers for Hispanics and non-Hispanic Asians and as such they were collapsed with other unclassified race/ethnicities.

All analyses were done using SAS version 9.3 (www.sas.com). Specifically, SAS Proc SURVEYMENS was used to do all univariate analyses including computations of unadjusted geometric means (UGMs) and SAS Proc SURVEYREG was used to fit regression models including computations of adjusted geometric means (AGMs). Actual sample sizes used in regression models were smaller because of missing values for independent variables, for example, poverty income ratio, BMI, etc. Sample sizes used in regression models are given in Table 1.

### 3. Results

#### 3.1. Univariate analysis

Females were found to have statistically significantly higher UGMs than males ($p < 0.05$) for HEMA, MHBMA3, HPMMA, PGA, and MA or for 6 of the 20 metabolites (Supplementary Table S2, $p < 0.05$) for which data were analyzed. 2HPMA was the only metabolite for which males had higher levels than females, but the differences were not statistically significant (Table S2).

Smokers were found to have statistically significantly higher UGMs than nonsmokers for CEMA, 3HPMA, AAMA, GAMA, CYMA, HEMA, DHBMA, MHBMA3, HPMMA,
AMCC, PGA, 2HPMA, MA, 2MHA, and 3MHA + 4MHA (Table S2, \( p < 0.05 \)). For CYMA, UGMs for smokers were as much as more than 30-fold higher than for non-smokers (58.8 vs. 1.8 ng/mg creatinine, Table S2).

NHW had the higher UGMs than NHB \( ( p < 0.05) \) for AAMA, GAMA, DHBMA, HPMMA, ATCA, AMCC, PGA, and 2MHA (Table S3). However, the reverse was true for BMA (Table S3). NHW had the higher UGMs than OTH \( ( p < 0.05) \) for AAMA, GAMA, CYMA, HEMA, AMCC, PGA, and 3MHA + 4MHA (Table S3). NHB had lower UGMs than OTH for 3HPMA, MU, DHBMA, and ATCA, but the reverse was true for BMA and 3MHA + 4MHA (Table S3).

### 3.2. Multivariate analysis

Sample sizes used in regression models were about 10% lower than that of the univariate analysis (Table 1) because of missing values for various independent variables. \( R^2 \) varied from a very low of 13.8% for BPMA to a high of 74.6% for CYMA. Interactions between race/ethnicity and smoking status were found to be statistically significant at \( \alpha = 0.05 \) for 2HPMA only. AGMs are presented in Tables 2–4. Regression slopes along with \( p \)-values for the association between log10 transformed values of VOC metabolites and continuous variables and model \( R^2 \) are listed in Table 5.

#### 3.2.1. Effect of smoking

Smokers were found to have statistically significantly higher AGMs than nonsmokers for the following urinary VOCs (metabolites): acrylonitrile (CYMA, Table 2) and 1,3-butadiene (MHBMA3, Table 2). AGMs were about 15-fold higher for smokers as compared to nonsmokers. For example, for CYMA, AGMs were 2.0 and 29.2 ng/mL for nonsmokers and smokers, respectively (Table 2). For other metabolites, while smokers did have higher geometric means than nonsmokers, for example, for 3HPMA, AAMA, GAMA, DHBMA, HPMMA, and MA, the differences were not statistically significant (Table 3).

#### 3.2.2. Effect of gender

For 4 of the 20 metabolites, namely, HEMA, HPMMA, ATCA, and BMA, females had statistically significantly higher AGMs than males (Table 2, \( p < 0.05 \)). DHBMA, 2HPMA, and 2MHA were the only metabolites for which males had higher AGMs than females, but the differences were not statistically significant (Table 2).

#### 3.2.3. Effect of race/ethnicity

NHW were found to have statistically significantly lower AGMs (Table S3) than NHB for TTCA \( ( p = 0.02, \) Table 3) and BMA \( ( p = 0.01, \) Table 3), but the reverse was true for AMCC \( ( p = <0.01) \) and PGA \( ( p = 0.02, \) Table 3). NHB had statistically significantly lower AGMs than OTH for MU \( ( p = 0.01) \), HPMMA \( ( p = 0.03) \), and AMCC \( ( p < 0.01) \). NHW smokers had statistically significantly lower levels of 2HPMA than OTH smokers \( ( p < 0.05, \) Table 4).

#### 3.2.4. Associations between the levels of metabolites and other continuous variables

There was a statistically significant negative association between age and the levels of ATCA, BMA, and 3MHA + 4MHA (Table 5). Poverty income ratio did not affect the
Table 2. Adjusted geometric means with 95% confidence intervals in ng/mL for selected volatile organic compounds metabolites for those aged 12–19 years by gender and smoking status. Data from National Health and Nutrition Examination Survey 2011–2012.

| Parent VOC | Abbreviated name | Gender | Smoking status |
|------------|------------------|--------|----------------|
|            |                  | Males  | Females        |
|            |                  |        | Nonsmoker | Smoker    |
| Acrolein   | CEMA             | 96.3 (73.6 – 126) | 96.8 (67.6 – 138.5) | 99.1 (84.4 – 116.4) | 94 (483.3 – 183.1) |
|            | 3HPMA            | 298.7 (230.4 – 387.4) | 338 (258.3 – 442.3) | 282.5 (240 – 332.4) | 357.5 (209.4 – 610.3) |
| Acrylamide | AAMA             | 74.2 (58.7 – 93.7) | 74.3 (59.4 – 92.9) | 53.8 (44.3 – 65.2) | 102.5 (59.5 – 176.4) |
|            | GAMA             | 20.5 (15.7 – 26.8) | 21.6 (16.9 – 27.7) | 16.2 (14.1 – 18.5) | 27.5 (16.1 – 46.8) |
| Acrylonitrile | CYMA             | 7 (4.6 – 10.8) | 8.5 (5.6 – 13) | 2 (1.7 – 2.4) | 29.2 (12.5 – 68.2) |
| Acrylonitrile, vinyl chloride, ethylene oxide | HEMA | 1 (0.8 – 1.4) | 1.5 (1 – 2.1) | 1 (0.9 – 1.1) | 1.5 (0.8 – 3) |
| Benzene    | MU               | 75.4 (60.7 – 93.6) | 80.8 (63 – 103.7) | 78.2 (64.1 – 95.3) | 77.9 (502.2 – 120.9) |
|            | BPMA             | 2.9 (2.2 – 4) | 3.1 (2.1 – 4.7) | 3.9 (2.9 – 5.1) | 2.4 (1.2 – 4.7) |
| 1,3-Butadiene | DHBMA            | 294 (253.2 – 341.2) | 284.2 (236.6 – 341.5) | 283.2 (253.2 – 316.6) | 295.1 (200.6 – 431.4) |
|            | MHBMA3           | 11.5 (8.7 – 15.2) | 13.5 (9.8 – 18.6) | 8.3 (6.9 – 10.1) | 18.5 (9.9 – 34.8) |
| Carbon-disulfide | TTCA        | 5.9 (4.6 – 7.6) | 6.5 (4.4 – 9.6) | 8.6 (7.3 – 10.1) | 4.5 (2.4 – 8.4) |
| Crotonaldehyde | HPMMA           | 369.8 (293.9 – 465.3) | 428.8 (343.1 – 535.9) | 378.2 (325.7 – 439.2) | 419.3 (268.5 – 654.7) |
|            | ATCA             | 1086 (82.8 – 142.4) | 218.9 (162.8 – 294.3) | 127.2 (109.4 – 147.3) | 186.8 (112.5 – 310.3) |
|            | AMCC             | 95.5 (70.5 – 129.4) | 100.8 (74.2 – 137.1) | 75.5 (64.4 – 88.6) | 127.5 (64.9 – 250.7) |
| Ethylbenzene, styrene | PGA          | 193.9 (169.4 – 221.9) | 215 (174.9 – 264.2) | 178.8 (160.5 – 199.3) | 233.1 (155.1 – 350.4) |
| Propylene oxide | 2HPMA          | 57.2 (45.5 – 71.8) | 55 (43.9 – 69.1) | 50.9 (44.9 – 57.8) | 61.8 (38.4 – 99.4) |
| Styrene    | MA               | 1569 (127.5 – 193) | 168.7 (135.7 – 209.8) | 143.9 (127.7 – 162.2) | 183.9 (122.3 – 276.5) |
| Tetrachloroethene | BMA           | 6.9 (5.2 – 9.3) | 9.3 (7 – 12.3) | 7.8 (6.9 – 8.8) | 8.3 (4.9 – 14) |
| Xylene     | 2MHA             | 44.9 (33.1 – 60.8) | 41.5 (31.6 – 54.5) | 32.5 (27.7 – 38.2) | 57.3 (30.6 – 107.3) |
|            | 3MHA + 4MHA      | 269.3 (193.3 – 375.1) | 274.6 (203.9 – 369.8) | 232.3 (202.8 – 266.2) | 318.3 (167.1 – 606.1) |

*aFemales had statistically significantly higher levels than males (p < 0.05).
*bThere was a statistically significant interaction between race/ethnicity and smoking status.
*cCEMA = N-Acetyl-S-(2-carboxyethyl)-L-cysteine, 3HPMA = N-Acetyl-S-(3-hydroxypropyl)-L-cysteine, AAMA = N-Acetyl-S-(2-carbamoyl)-2-hydroxypyrrol-1-yl-L-cysteine, CYMA = N-Acetyl-S-(3-cyanoethyl)-L-cysteine, MU = trans, trans-Muconic acid, BPMA = N-Acetyl-S-(propyl)-L-cysteine, DHBMA = N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine, MHBMA3 = N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine, TTCA = 2-Thioxothiazolidine-4-carboxylic acid, HPMMA = N-Acetyl-S-(3-hydroxypropyl)1-methyl-L-cysteine, ATCA = 2-Aminothiazoline-4-carboxylic acid, AMCC = N-Acetyl-S-(methylcarbamoyl)-L-cysteine, PGA = Phenylglyoxylic acid, 2HPMA = N-Acetyl-S-(2-hydroxypropyl)-L-cysteine, MA = Mandelic acid, BMA = N-Acetyl-S-(benzyl)-L-cysteine, 2MHA = 2-methylhippuric acid, 3MHA+4MHA = 3-methylhippuric acid + 4-methylhippuric acid.

*dSmokers had statistically significantly higher levels than nonsmokers (p < 0.05).
### Table 3. Adjusted geometric means with 95% confidence intervals in ng/mL for selected volatile organic compounds metabolites for those aged 12–19 years by race/ethnicity. Data from National Health and Nutrition Examination Survey 2011–2012.

| Parent VOC | Abbreviated name<sup>a</sup> | Non-Hispanic white (NHW) | Non-Hispanic black (NHB) | Other race/ethnicities (OTH) | Statistically significant differences |
|------------|--------------------------------|--------------------------|--------------------------|-----------------------------|-------------------------------------|
| Acrolein   | CEMA                           | 85.8 (63.9–115.1)        | 105.9 (76.3–146.9)       | 99.1 (69.6–141.1)           |                                     |
|            | 3HPMA                          | 295.1 (216–403.3)        | 295.1 (219.4–396.9)      | 368.4 (280.4–484.1)         |                                     |
| Acrylamide | AAMA                           | 79.3 (62.8–100.2)        | 73.3 (55.9–95.9)         | 70.4 (49.8–99.5)            |                                     |
|            | GAMA                           | 23.3 (18.3–29.6)         | 18.9 (14.3–25.2)         | 21.2 (15.5–29.2)            |                                     |
| Acrylonitrite | CYMA                          | 7.8 (5.1–11.9)          | 8.7 (5.7–13.3)           | 6.8 (4.4–10.6)              |                                     |
| Acrylonitrite, vinyl chloride, ethylene oxide | HEMA                         | 1.2 (0.8–1.7)           | 1.4 (1–1.9)               | 1.2 (0.8–1.6)               |                                     |
| Benzene    | MU                             | 79.2 (63.7–98.4)         | 62.2 (42.8–90.5)         | 96.5 (73.4–126.8)           | NHB < OTH (p = 0.01)                |
| 1-Bromopropene | BPMA                          | 2.4 (1.4–4.1)           | 3.5 (2.4–5)              | 3.4 (2.2–5.2)               |                                     |
| 1,3-Butadene | DHBMA                         | 296.2 (255.1–344)       | 271.7 (220.6–334.7)     | 300.1 (246.5–365.3)         |                                     |
| Carbon-disulfide | TTCMA                       | 5.3 (3.9–7.4)           | 7.7 (5.5–10.7)           | 5.9 (4.2–8.2)               | NHB < NHW (p = 0.02)                |
| Crotonaldehyde | HPMMA                        | 427.9 (336.6–543.9)     | 339.8 (249.1–463.6)     | 434.3 (342.8–550.2)         | NHB < OTH (p = 0.03)                |
| Cyanide    | ATCA                           | 161.9 (111–236.2)       | 135.4 (100.4–182.5)     | 167.2 (126.3–221.2)         |                                     |
| N,N-Dimethylformamide | AMCC                    | 122.7 (90.2–166.7)     | 80.2 (57.9–111)          | 96.1 (69.2–133.4)           | NHW > NHW (<0.01), NHW < OTH (p = 0.01) |
| Ethylbenzene, styrene | PGA                          | 233 (208.1–260.9)      | 189.2 (150.8–237.4)     | 193 (152.5–244.4)           | NHW > NHW (p = 0.02)                |
| Propylene oxide | 2HPMA<sup>b</sup>             | 68.1 (54–86)            | 52 (35.9–75.2)           | 49.9 (40.2–61.8)            | NHW > OTH (p = 0.02)                |
| Styrene    | MA                             | 157.5 (127.8–194)       | 160.1 (122.4–209.5)     | 170.8 (137.3–212.4)         |                                     |
| Tetrachloroethylene | BMA                          | 6.7 (4.9–9.1)           | 10.3 (7.2–14.9)          | 7.5 (5.9–9.5)               | NHW < NHW (p = 0.01), NHW > OTH (p = 0.03) |
| Xylene     | 2MHA                           | 44.2 (34.8–56.2)        | 42.6 (31.5–57.7)         | 42.7 (29.7–61.4)            |                                     |
|            | 3MHA + 4MHA                    | 294.1 (210.6–410.6)     | 285.7 (208.2–392.1)     | 239.3 (174.1–329.1)         |                                     |

<sup>a</sup>CEMA = N-Acetyl-S-(2-carboxyethyl)-L-cysteine, 3HPMA = N-Acetyl-S-(3-hydroxypropyl)-L-cysteine, AAMA = N-Acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine, GAMA = N-Acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine, CYMA = N-Acetyl-S-(2-cyanoethyl)-L-cysteine, MU = trans- trans-Muconic acid, BPMA = N-Acetyl-S-(n-propyl)-L-cysteine, DHBMA = N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine, MHBMA3 = N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine, TTCA = 2-Thioxothiazolidine-4-carboxylic acid, HPMMA = N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine, ATCA = 2-Aminothiazoline-4-carboxylic acid, AMCC = N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine, PGA = Phenylglyoxylic acid, 2HPMA = N-Acetyl-S-(2-hydroxypropyl)-L-cysteine, MA = Mandelic acid, BMA = N-Acetyl-S-(benzyl)-L-cysteine, 2MHA = 2-methylhippuric acid, 3MHA + 4MHA = 3-methylhippuric acid + 4-methylhippuric acid.

<sup>b</sup>There was a statistically significant interaction between race/ethnicity and smoking status.
levels of any of the 20 VOC metabolites. Levels of HEMA and 3MHA + 4MHA decreased with increase in BMI (Table 5). Number of rooms in the house was positively associated with the levels of MU ($p < 0.01$, Table 5). Increase in the number of smokers in the house was associated with increased levels of CYMA and AMCC ($p \leq 0.03$, Table 5). Increase in number of days the tobacco products were used during the last five days was associated with increased levels of almost all metabolites ($p \leq 0.01$, Table 5) except HEMA, BPMA, and ATCA. Urine creatinine was positively associated with the levels of every metabolite (Table 5).

### 3.2.5. Comparison with nonsmoking adults aged $\geq 20$ years

Adolescents had statistically significantly higher UGMs than nonsmoking adults aged $\geq 20$ years for AAMA, HEMA, and CYMA, but the reverse was true for CEMA, BPMA, DHBMA, TTCA, AMCC, PGA, 2HPMA, and MA (Table 6).

### 4. Discussion

This study was undertaken to evaluate the variability attributable to gender, race/ethnicity, and smoking status in the observed levels of 20 urinary metabolites of VOCs among adolescents aged 12–19 years. Smoking was found to be associated with higher adjusted levels of two metabolites as compared to nonsmokers. Female adolescents were found to have higher adjusted levels of four metabolites than male adolescents. NHW had lower adjusted levels of two metabolites than NHB, and NHB had lower adjusted levels of three metabolites than NHW.

#### 4.1. Impact of smoking

It was for CYMA and MHBMA3 only that smokers were found to have statistically significantly higher adjusted levels than nonsmokers. And, smokers were not found to have higher adjusted levels than nonsmokers for benzene (trans, trans-Muconic acid, or MU) and certain other metabolites which was a surprise because Alwis et al. (2012) found unadjusted levels of MU and other metabolites to be higher among smokers than nonsmokers. In comparison, Jain (2015a) found smokers to have higher levels than nonsmokers among adults for 15 metabolites. It is a possibility that relatively small unweighted proportion of smokers in the data for adolescents (12%, Table 2) as compared to 41.2% (Jain 2015a) among adults may be responsible for statistically insignificant
Table 5. Regression slopes with $p$-values for various volatile organic compound metabolites for models fitted for children aged 12–19 years. All dependent variables were log10 transformed with VOC values in $\mu$g/mL.

| Parent VOC | Independent variable | \( R^2 \) in % | Age | Poverty-income ratio | Body mass index | No. of rooms in house | No. of smokers in house | No. of days smoked during the last five days | Urine creatinine |
|------------|----------------------|----------------|-----|----------------------|----------------|-----------------------|------------------------|----------------------------------------------|----------------|
| Acrolein   | CEMA (57.1)          | −0.0213 (0.05)| 0.0178 (0.3) | −0.001 (0.77) | −0.0145 (0.17) | 0.0539 (0.49) | 0.1139 (<0.01) | 0.0034 (<0.01) |
| 3HPMA (56.8)| −0.0059 (0.6)       | 0.0042 (0.82) | −0.0032 (0.38) | −0.0018 (0.9) | 0.0674 (0.26) | 0.1106 (<0.01) | 0.0032 (<0.01) |
| Acrylamide | AAMA (54.5)          | −0.0141 (0.37)| 0.0014 (0.92) | −0.0075 (0.14) | −0.0119 (0.37) | −0.0186 (0.76) | 0.0711 (<0.01) | 0.0032 (<0.01) |
| GA (58.9)  | −0.0142 (0.16)       | 0.0044 (0.69) | −0.0012 (0.7) | −0.0038 (0.72) | 0.0131 (0.73) | 0.055 (0.01) | 0.027 (<0.01) |
| Acrylonitrile | CYMA (74.6)       | 0.0032 (0.84) | −0.0078 (0.6) | −0.0072 (0.1) | 0.0085 (0.52) | 0.2677 (<0.01) | 0.1091 (<0.01) | 0.0026 (<0.01) |
| Acrylonitrile, vinyl chloride, ethylene oxide | HEMA (45.4) | −0.0108 (0.26) | 0.0053 (0.71) | −0.0099 (0.01) | −0.0053 (0.6) | 0.1159 (0.12) | 0.0694 (0.05) | 0.0019 (<0.01) |
| Benzene    | MU (27.4)            | −0.0005 (0.98)| −0.0301 (0.29) | 0.0008 (0.85) | 0.0324 (0.01) | 0.0657 (0.18) | 0.0683 (0.01) | 0.0028 (<0.01) |
| 1-Bromopropane | BPMA (13.8)   | 0.0078 (0.55) | 0.0266 (0.4) | −0.0049 (0.29) | −0.0028 (0.91) | −0.0612 (0.16) | 0.0504 (0.14) | 0.0002 (0.02) |
| 1,3-Butadiene | DHBMA (65.7)          | −0.0162 (0.06)| 0.0073 (0.56) | −0.0019 (0.4) | −0.0109 (0.21) | −0.0045 (0.9) | 0.0515 (<0.01) | 0.0032 (<0.01) |
| MHBMA (58.5)| −0.0242 (0.14)       | 0.0169 (0.54) | −0.0063 (0.17) | 0.0042 (0.77) | 0.0908 (0.22) | 0.1386 (<0.01) | 0.0036 (<0.01) |
| Carbon-disulfide | TTCA (19.3) | 0.0002 (0.99) | 0.0389 (0.19) | 0.0022 (0.74) | −0.0255 (0.18) | 0.255 (0.68) | 0.0823 (<0.01) | 0.0021 (<0.01) |
| Crotonaldehyde | HPMMA (59.1)         | −0.0018 (0.87)| −0.0087 (0.68) | −0.0072 (0.08) | −0.0001 (0.99) | 0.1041 (0.1) | 0.1311 (<0.01) | 0.0034 (<0.01) |
| Cyanide    | ATCA (34.5)          | −0.0521 (<0.01)| 0.0184 (0.52) | 0.0002 (0.95) | −0.0308 (0.09) | −0.0229 (0.71) | 0.0146 (0.62) | 0.0024 (<0.01) |
| N,N-Dimethylformamide | AMCC (68.0) | −0.0049 (0.67) | 0.0006 (0.96) | −0.0038 (0.2) | −0.0022 (0.81) | 0.1023 (0.03) | 0.0976 (<0.01) | 0.0033 (<0.01) |
| Ethylbenzene, styrene | PGA (63.0) | −0.0149 (0.1) | 0.0146 (0.37) | −0.0038 (0.05) | −0.0001 (0.99) | 0.0448 (0.34) | 0.0558 (0.01) | 0.0034 (<0.01) |
| Propylene oxide | 2HPMA (52.1)         | −0.0155 (0.09)| 0.0116 (0.57) | −0.0034 (0.18) | −0.0217 (0.16) | 0.0048 (0.92) | 0.0689 (0.02) | 0.003 (<0.01) |
| Styrene    | MA (60.2)            | −0.0021 (0.75)| 0.006 (0.68) | −0.0014 (0.46) | −0.0015 (0.89) | 0.0342 (0.35) | 0.0567 (0.02) | 0.0029 (<0.01) |
| Toluene    | BMA (47.5)           | −0.0328 (<0.01)| 0.01 (0.62) | 0.0028 (0.33) | −0.0152 (0.2) | −0.0724 (0.1) | 0.029 (0.33) | 0.0033 (<0.01) |
| Xylene     | 2MHA (35.5)          | −0.022 (0.07) | 0.0004 (0.99) | −0.0065 (0.1) | 0.0263 (0.13) | 0.0316 (0.58) | 0.0898 (0.01) | 0.0024 (<0.01) |
| 3MHA + 4MHA (45.2) | −0.0321 (<0.01)| −0.0054 (0.77) | −0.0086 (0.01) | 0.0207 (0.15) | 0.0058 (0.9) | 0.123 (0.01) | 0.0033 (<0.01) |
differences among smokers and nonsmokers for VOC metabolites among adolescents. It should also be noted that even among adults, (Jain 2015a) smokers were not found to have higher MU levels than nonsmokers.

However, the frequency of the use of tobacco products during the last five days was found to be associated with increased levels of not only MU ($\beta = 0.0683$, $p = 0.01$, Table 5) but also for 15 of 19 other metabolites (Table 5). In addition, for 2 (CYMA, AMCC) of the 20 metabolites, even the exposure to ETS, which, for the purpose of this study is defined as the total exposure to both secondhand and thirdhand smoke as per descriptions provided elsewhere (Matt et al. 2011), at home indicated by the number of smokers smoking inside home was associated with increased levels of these metabolites (Table 5).

### 4.2. Effect of gender

For all four metabolites (MU, HPMMMA, ATCA, BMA, Table 2) for which statistically significant gender differences were observed, females had higher AGMs than males. Higher levels of all of these four metabolites are associated with smoking. Based on NHANES data for the years 1999–2010, on the average, daily female smokers smoke 15.62 cigarettes per day as compared to 18.31 cigarettes per day smoked by daily male smokers and this is reflected in their serum cotinine levels of 202.83 and 222.44 ng/mL, respectively (Jain 2014). Consequently, simply speaking, female smokers’ exposure to these VOCs from

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**Table 6.** Comparison of unadjusted geometric means with 95% confidence intervals in ng/mg creatinine for selected urinary metabolites of volatile organic compounds between those aged 12–19 years old and nonsmoking adults aged $\geq 20$ years. Data from National Health and Nutrition Examination Survey 2011–2012.

| Parent VOC | Urinary metabolite | 12–19 | $\geq 20$ | $p$ |
|------------|-------------------|-------|-----------|-----|
| Acrolein | CEMA | 79.6(71 – 89.3)$^a$ | 93.1(87.1 – 99.6)$^a$ | 0.01 |
| | 3HPMA | 245.6(212.6 – 283.8) | 259.2(242 – 277.6) | 0.35 |
| Acrylamide | AAMA | 52.1(46.3 – 58.7)$^b$ | 42.5(40.2 – 44.8)$^b$ | <0.01 |
| | GAMA | 16.2(14.2 – 18.4) | 15(14.2 – 15.9) | 0.26 |
| Acrylonitrile | CYMA | 2.6(2.1 – 3.2)$^b$ | 1.7(1.6 – 1.9)$^b$ | <0.01 |
| Acrylonitrile, vinyl chloride, ethylene oxide | HEMA | 0.9(0.9 – 1)$^b$ | 0.8(0.7 – 0.8)$^b$ | 0.01 |
| Benzene | MU | 69.5(60.2 – 80.1) | 73.8(66.7 – 81.6) | 0.42 |
| 1-Bromopropane | BPMA | 3.1(2.3 – 4.1)$^a$ | 5.7(5 – 6.4)$^a$ | <0.01 |
| 1,3-Butadene | DHBMA | 249.2(232.1 – 267.6)$^a$ | 268.4(256.6 – 280.7)$^a$ | 0.04 |
| | MHBNBA3 | 7.8(6.6 – 9.3) | 8(7.3 – 8.8) | 0.74 |
| Carbon-disulfide | TTCA | 7(5.8 – 8.6)$^a$ | 10.3(9.1 – 11.6)$^a$ | <0.01 |
| Crotonaldehyde | HPMMMA | 341.2(299.8 – 388.3) | 387.2(360.8 – 415.6) | 0.06 |
| Cyanide | ATCA | 115(101.2 – 130.6) | 111.4(101.4 – 122.4) | 0.69 |
| | AMMC | 75.6(66.7 – 85.8)$^a$ | 127(119.7 – 134.7)$^a$ | <0.01 |
| Ethylbenzene, styrene | PGA | 168.5(149.9 – 189.4)$^a$ | 184(170.2 – 198.6)$^a$ | 0.04 |
| Propylene oxide | 2HPMA | 45.8(41.3 – 50.9)$^a$ | 61.4(55.1 – 68.3)$^a$ | <0.01 |
| Styrene | MA | 126.8(115.5 – 139.2)$^a$ | 149.9(140.3 – 160.3)$^a$ | <0.01 |
| Toluene | BMA | 6.3(5.5 – 7.3) | 7.5(6.9 – 8.2) | 0.07 |
| Xylene | 2MHA | 30.2(25.4 – 35.9) | 30.2(27 – 33.9) | 0.99 |
| | 3MHA + 4MHA | 208.4(178 – 244.1) | 200.6(187.1 – 215.2) | 0.57 |

$^a$Adults had statistically significantly higher levels than adolescents.

$^b$Adolescents had statistically significantly higher levels than adults.
tobacco smoke should be at a level lower than that of male smokers and for this reason, females should have lower levels of these VOC metabolites than males, not otherwise. However, there may be constituents in tobacco smoke other than VOCs, for example, polycyclic aromatic hydrocarbons, that may be inducing enzymes that inhibit or decelerate metabolism of these VOCs to a higher degree among female smokers than among male smokers. Alternatively, females may be excreting parent VOCs associated with these metabolites more slowly than males. More work will be needed to explain these observations. Among adults, for eight VOC metabolites, while female smokers were found to have higher levels of a few metabolites than male smokers, the reverse was true for non-smokers (Jain 2015a). Thus, for these metabolites smoking was found to confound metabolism of VOC metabolites among males and females.

4.3. Effect of race/ethnicity

Racial/ethnic differences in the observed levels of various metabolites may be due to racial/ethnic differences in the exposure levels to various VOCs and/or the racial/ethnic differences in metabolism of these VOCs. Since, NHW had lower levels of TTCA and BMA than NHB, it is a possibility that NHW excrete parent VOCs associated with these metabolites at a rate faster than NHB do. The direction of metabolism may be reversed among NHW and NHB for AMCC and PGA because for these metabolites, NHW were found to have higher levels than NHB. For AMCC and PGA, similar results were reported for adults also (Jain 2015a). More work will be needed to explain these observations.

4.4. Limitations of the study

Some of the breakdown products or metabolites of VOC may have their origin in compounds other than VOC parents. For example, as specified by Alwis et al. (2012), BMA, in addition to being a breakdown product of toluene, may also be formed by multiple other sources, for example, benzyl alcohol. Similarly, MU, a metabolite of benzene, may also be formed by sorbic acid (Aprea et al. 2008; Protano et al. 2010). Thus, detection of certain metabolites of VOCs in urine does not necessarily guarantee their source in one of the VOCs. Consequently, at times, one or more VOCs may falsely be interpreted as a source of exposure. In addition, there may be metabolites other than BMA and MU which may have their origin in yet unidentified sources other than VOCs.

Analysis of this study was based on cross-sectional data. Neither the data on timing nor the levels of VOC exposure were available. Consequently, any and all conclusions based on observed levels of VOCs must be made with caution. It is quite a possibility that some of the observed differences in the levels of VOCs among different genders and race/ethnicities may be primarily attributable to differences in the levels of exposure to the associated VOCs and not necessarily to the metabolic differences.

5. Conclusion

For the first time, data on variability in the levels of 20 urinary metabolites of 16 parent VOCs by age, gender, race/ethnicity, and smoking status for a nationally representative
sample of US adolescents were presented. The most significant findings of the study were (1) smoking was associated with relatively higher levels of selected metabolites of acrylonitrile and 1,3-butadiene, (2) female adolescents were found to have higher adjusted levels of selected metabolites of benzene, crotonaldehyde, cyanide, and tetrachloroethylene, (3) NHW had lower adjusted levels of selected metabolites of carbon-disulfide, N,N-dimethylformamide, tetrachloroethylene than NHB, and (4) adolescents had higher adjusted levels of selected metabolites of acrylamide and acrylonitrile than nonsmoker adults.

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Author declares that he received no funds to conduct this research and that he has no financial or other conflicts that could have affected the conclusions arrived at in this communication. All data used in this research are available free of cost from www.cdc.gov/nchs/nhanes.html.

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