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Hand nicotine as an independent marker of thirdhand smoke pollution in children's environments

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Abstract

Background: Hand nicotine (HN) levels measure children's exposure to tobacco smoke pollutants from thirdhand and secondhand smoke. HN is associated with urinary and salivary cotinine, but the associations of HN with other tobacco smoke exposure (TSE) markers remain unknown.

Objectives: We compared levels of HN and four urinary TSE biomarkers: cotinine, *trans*-3′-hydroxycotinine (3HC), nicotelline N-oxides, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and children's sociodemographic and TSE patterns. We also examined if HN is a plausible pathway for children's exposure to active smoking.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

E. MelindaMahabee-Gittens: Conceptualization, Methodology, Investigation, Data curation, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition. **Ashley L. Merianos:** Methodology, Investigation, Validation, Formal analysis, Visualization, Writing – review & editing. **Lara Stone:** Methodology, Data curation, Writing – review & editing. **Chase A. Wullenweber:** Methodology, Data curation, Writing – review & editing. **PenelopeJ.E.Quintana:** Methodology, Writing – review & editing. **Eunha Hoh:** Methodology, Writing – review & editing. **Nathan G. Dodder:** Methodology, Writing – review & editing. **Nicolas Lopez-Galvez:** Writing – review & editing. **Georg E. Matt:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – review & editing, Funding acquisition.

Appendix A. Supplementary data

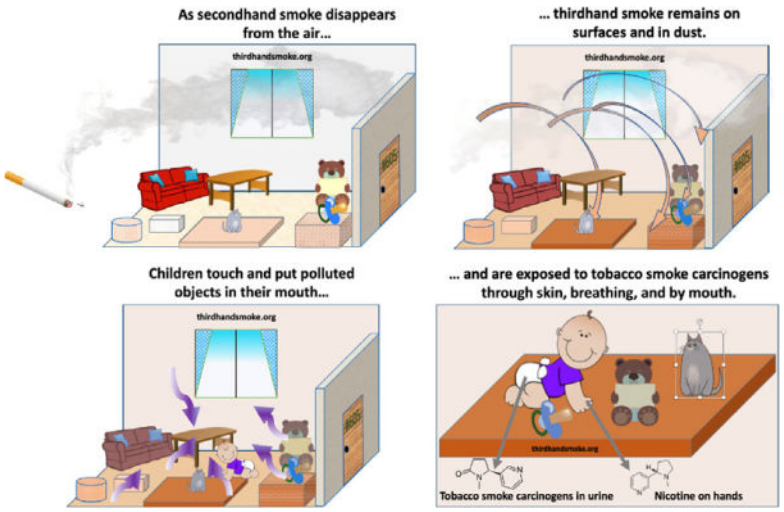
Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.157914.

Methods: Data were collected from 175 non-smoking patients (Mean (SD) age = 5.4 (3.4) years) who lived with ≥1 cigarette smoker(s). HN and TSE biomarker levels were determined using LC-MS/MS. Multivariate and multivariable regression analyses were conducted to examine associations between TSE markers and parent-reported measures, controlling for sociodemographics.

Results: Of the five markers of TSE, cotinine ($R^2 = 0.221$; $p = 0.003$) and HN ($R^2 = 0.247$; $p = 0.001$) showed the strongest overall associations. Of the five markers, only cotinine showed significantly higher levels among Black children ($\hat{\beta} = 0.307$, $p < 0.05$) independent of age, reported exposure, and home smoking bans. Cotinine ($\hat{\beta} = 0.010$, $p < 0.05$), NNAL ($\hat{\beta} = 0.012$, $p < 0.05$), and HN ($\hat{\beta} = 0.011$, $p < 0.05$) showed significant positive associations with reported exposure independent of race, age, and home smoking bans. NNAL ($\hat{\beta} = -0.285$, $p < 0.05$) and HN ($\hat{\beta} = -0.336$, $p < 0.05$), but not cotinine, 3HC, and N-oxides, showed significantly lower levels among children who lived in homes with smoking bans. Child age, hand surface area, home smoking ban, and reported exposure independently accounted for 21 % of the variance in HN levels ($p = 0.002$). HN accounted for 30 % of the variance in cotinine independent of child race and child age.

Discussion: HN levels were associated with modifiable tobacco-related behaviors and shows promise as a marker of sources of THS pollution in a child's environment not captured by measurement of urinary cotinine alone. HN levels provide additional information about TSE, complementing other biomarkers when assessing children's overall TSE.

Graphical Abstract



Keywords

Thirdhand smoke; Secondhand smoke; Tobacco smoke pollution; Cotinine; Hand wipes; Nicotine; TSNAs

1. Introduction

Thirdhand smoke (THS) is the nearly ubiquitous chemical residue that remains in environments in which tobacco products have been previously smoked (Jacob et al., 2017; Diez-Izquierdo et al., 2018). THS residue deposits in the dust and adsorbs to surfaces, creating accessible home reservoirs through which children can be exposed via dermal transfer, ingestion, and inhalation (Jacob et al., 2017; Diez-Izquierdo et al., 2018). Exposure to THS pollutants found in these reservoirs are potentially neurotoxic, cytotoxic, and genotoxic to children as they include nicotine, tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), heavy metals, and other compounds associated with pediatric morbidity and mortality (Jacob et al., 2017; Diez-Izquierdo et al., 2018; Hang et al., 2020). Children who live with smokers who do not smoke in their presence and children who live with nonsmokers who have strict smoking bans can still be exposed to THS pollution long after tobacco products have been used (Matt et al., 2022; Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2021b; Mahabee-Gittens et al., 2019; Mahabee-Gittens et al., 2018). Children who live with smokers who actively smoke in their presence are exposed to secondhand smoke (SHS) while lit tobacco products are being smoked, and they are also exposed to THS for days, weeks, or even years after tobacco products were used (Jacob et al., 2017). Given the potential for smokers' children to be exposed to both THS and SHS, personal measures of THS and SHS exposure must be assessed to accurately measure levels of children's overall tobacco smoke exposure (TSE) (Mahabee-Gittens et al., 2021a).

Traditional TSE markers such as urinary cotinine, a metabolite of nicotine which measures children's recent TSE (i.e., past 1–2 days) (Benowitz et al., 2009), provide information on children's overall combined SHS and THS exposure. In contrast, the assessment of levels of nicotine on the hands of children who live with smokers provides a way to examine non-inhalation exposure to nicotine that may be transferred to the hands of children from SHS via the air and through dermal or oral contact with THS-polluted dust and objects (e.g., clothes, toys, furniture, parents' hands) (Matt et al., 2022; Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2021b; Mahabee-Gittens et al., 2019; Mahabee-Gittens et al., 2018). Thus, in combination with other TSE biomarkers such as cotinine, hand nicotine levels may provide a measure of how THS exposure pathways contribute to children's overall TSE (Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2021b; Mahabee-Gittens et al., 2018).

Previous research with children of smokers and nonsmokers has successfully used hand nicotine levels as a proxy of THS exposure (Matt et al., 2022; Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2021b; Mahabee-Gittens et al., 2019; Mahabee-Gittens et al., 2018). This work demonstrated that smokers' children have elevated hand nicotine levels up to two times higher than levels observed in adult nonsmokers who lived in homes of former smokers, and over three times higher than finger wipe levels of adult nonsmokers who live with smokers (Matt et al., 2022; Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2021b; Mahabee-Gittens et al., 2019; Mahabee-Gittens et al., 2018; Matt et al., 2016; Matt et al., 2011). Further, this work found that higher hand nicotine levels are associated with younger child age, higher parental tobacco use patterns, and increased respiratory and

infectious illnesses independent of SHS exposure (Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2019).

In smokers' children, the sociodemographic patterns observed for urinary cotinine differ from those for hand nicotine levels. For example, while cotinine is higher in children who live with one or more smokers or children who are around more cigarettes (Park, 2020; Jeong et al., 2021; Mahabee-Gittens et al., 2020) and both urinary cotinine and hand nicotine levels are higher in younger children (Mahabee-Gittens et al., 2021a), only hand nicotine is higher in 2–4-year-olds (Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2019). This suggests that increased child independence, behaviors, and exploration in this age group may result in increased exposure to nicotine from THS pollution in home environments (Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2019). Further, urinary cotinine levels, but not hand nicotine levels, are higher in children of non-Hispanic Black race/ethnicity, whose parents have fewer years of education or lower income, and who live in multiunit housing (Mahabee-Gittens et al., 2021a). These unique associations observed between child age, TSE patterns, and hand nicotine levels and the different associations observed between sociodemographics and urinary cotinine levels suggest that these two TSE markers may detect separate aspects and modalities of children's TSE. Specifically, these findings are consistent with the hypothesis that hand nicotine levels are a more direct measure of exposure through children's interactions with their physical environments than urinary cotinine (Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2019), nicotine's major metabolite (Benowitz et al., 2009).

In contrast to nicotine on children's hands, cotinine and *trans*-3′-hydroxycotinine (3HC) are both metabolites of nicotine (Benowitz et al., 2009; Jacob et al., 2011) that enter the body through multiple pathways. The rate of cotinine removal is mediated by the enzyme CYP2A6 and its activity varies by sex, genotype, and race/ethnicity (Dempsey et al., 2013; Benowitz et al., 2006; Zhu et al., 2013; Benowitz et al., 2016; Benowitz et al., 2020). Children with TSE who have reduced function CYP2A6 alleles metabolize nicotine at lower rates than individuals who have normal function *CYP2A6* alleles (i.e., normal metabolizers); thus, reduced metabolizers may have higher cotinine levels compared to normal metabolizers even if both groups of children are exposed to the same levels of tobacco smoke (Dempsey et al., 2013; Benowitz et al., 2006). This would not be the case for hand nicotine, because it directly reflects THS and SHS pollutants to which the child was exposed. Finally, children's TSE biomarker levels are also affected by the half-life of the metabolite and the time interval between the exposure event and sample collection (Benowitz et al., 2009; Benowitz et al., 2020). Thus, in order to obtain a more comprehensive assessment of exposure sources, behaviors, and pathways, it is necessary to assess multiple biological measures of children's TSE. Three additional TSE biomarkers are 3HC, nicotelline N-oxides, and 4-(methylnitrosamino)-1-(3)pyridyl-1-butanol (NNAL). Cotinine is further metabolized by CYP2A6 to 3HC; on average, 3HC is the most abundant urinary nicotine metabolite (Benowitz et al., 2009; Jacob et al., 2011). N-oxides are nicotelline metabolites that measure exposure to particulate matter in tobacco smoke (Jacob et al., 2020). In adults, N-oxides have a short half-life of 2 h; thus N-oxide levels reflect very recent TSE (Jacob et al., 2020). NNAL is the metabolite of the lung carcinogen 4-(methylnitrosamino)-1-(3)pyridyl-1-butanone (i.e., NNK) (Benowitz et al., 2020). NNAL

has a long half-life of 10–40 days; thus, NNAL levels measure average TSE occurring intermittently or chronically over longer periods of time. Few studies have examined Nicotelline N-oxides in humans. One study reported levels of mean (SD) N-oxide levels of 32.8 (55.0) pg/ml in adult electronic cigarette users and adult dual users of electronic cigarettes and combustible cigarettes (Jacob et al., 2020), and another study in children with TSE reported geometric mean levels of N-oxides of 22.9 pg/ml (Mahabee-Gittens et al., 2021c). NNAL has been examined extensively in children and adolescents with TSE and in adolescent and adult smokers (Goniewicz et al., 2011; Xia et al., 2021; Benowitz et al., 2018; Benowitz et al., 2010). In a study of adolescents, a cut-point of 14.4 pg/ml was used to distinguish active adolescent smokers from adolescent nonsmokers with TSE (Benowitz et al., 2018).

While it is known that hand nicotine levels are associated with urinary cotinine levels (Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2021b; Mahabee-Gittens et al., 2018), it is unknown if hand nicotine is merely a reflection of tobacco smoke pollutants in the environment. Moreover, it is unknown if hand nicotine is also a source of nicotine uptake through dermal or oral pathways and thus affects the associations between tobacco smoke pollutants in the environment and cotinine levels measured in body fluids. In addition, it is unknown if hand nicotine levels are associated with N-oxides or NNAL biomarkers of TSE exposure. Thus, the primary study objective was to examine the contribution of hand nicotine to characterizing TSE profiles based on urinary cotinine, 3HC, nicotelline N-oxides, and NNAL and associated sociodemographics, parental smoking patterns, and child TSE patterns among 0–11-year-old nonsmoking children who live with smokers. A secondary objective was to examine if hand nicotine can serve as a plausible pathway for children's exposure to parents' active smoking when examining urinary cotinine.

2. Methods

2.1. Study design

Child participants were 0 to 11-year-old patients who were brought to the Urgent Care (UC) or Pediatric Emergency Department (PED) of a large U.S. children's hospital by a parent who smoked tobacco products. Child and parent dyads were part of a randomized controlled trial of a parental tobacco cessation intervention ("Healthy Families;" www.clinicaltrials.gov: NCT02531594) in which children 0–17-years-old were enrolled; details are published elsewhere (Mahabee-Gittens et al., 2017). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational studies were followed (von Elm et al., 2007). The hospital institutional review board approved this study. Parents signed written informed consent, and children ≥11 years old signed written assent prior to participating in any study procedures. The eligibility criteria for children in the "Healthy Families" trial were: age 0–17 years old, presented with a chief complaint that could potentially be TSE-related (e.g., wheezing), self-reported nonusers of any tobacco or cannabis products, accompanied by a parent who currently smoked cigarettes.

A sub-sample of "Healthy Families" children participated in another study titled "Healthy Families Phase II" that collected additional markers of SHS and THS exposure among 0–11-

year-old children. This age range was selected for "Healthy Families II" to avoid enrolling 12–17-year-old smokers who may have answered the eligibility questions about their tobacco product use in a socially desirable manner. In total, 175 "Healthy Families Phase II" participants were included in the current study's analytic sample and had biological (e.g., urinary biomarkers) and environmental (e.g., hand wipe nicotine) data available for analysis. Data and samples from the baseline UC/PED visit (i.e., prior to parental interventions) were analyzed.

2.2. Parental assessments

Parents completed electronic assessments during their child's UC/PED visit which included the following sociodemographic and housing items: 1) parent: highest education level, annual household income level, housing type (single-family home, apartment building, multiunit home such as townhome); and 2) child: age, sex, and race/ethnicity. In order to assess parents' smoking behavior and their child's TSE patterns, parents reported: 1) cumulative child TSE - total number of cigarettes smoked around the child by all smokers in any location in the previous week; 2) number of household smokers - total number of cigarette smokers around the child in any location in the previous week; and 3) home smoking bans - parents who reported that smoking was never allowed in the home were considered as having a home smoking ban.

2.3. Hand wipe and urine collection and processing

Clinical research coordinators obtained hand wipe and urine samples from child participants. Briefly, hand wipes were collected by wiping the palmar and volar surfaces of all fingers of the child's dominant hand with prescreened cotton rounds wetted with 1.5 mL of 0.1 % ascorbic acid; field blanks were collected and analyzed to adjust for any potential contamination (Mdn (IQR) = 1.82 (0.87; 1.82 ng/wipe). Children's hands were measured using calipers from the base of the palm to the tip of the middle finger (length) and from the right to the left-most expanse of the palm without including the thumb (width) (Mahabee-Gittens et al., 2021d); the surface area was approximated by multiplying the length and the width. Hand wipe samples ($n = 163$) were frozen at −80 °C and analyzed at San Diego State University by isotope dilution liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Mahabee-Gittens et al., 2021a; Kelley et al., 2021). The LOD was approximately 0.19 ng nicotine/wipe. Urine samples were collected from the children, frozen at −80 °C and analyzed at the University of California at San Francisco and analyzed for cotinine ($n = 175$), 3HC ($n = 175$), N-oxides ($n = 156$), and NNAL ($n = 155$) with LC-MS/MS using previously published methods (Jacob et al., 2011; Jacob et al., 2013; Jacob et al., 2008); limit of quantitation (LOQ) was: 0.02 ng/mL for cotinine, 0.10 ng/mL for 3HC, 1.37 pg/mL for nicotelline N-oxides, and 0.25 pg/mL for NNAL (Jacob et al., 2011; Jacob et al., 2013; Jacob et al., 2008).

2.4. Statistical analysis

To take advantage of the largest possible sample sizes available for each TSE marker, we examined the association between TSE markers and sociodemographic, smoking, and TSE patterns in four interrelated steps. In steps 1–2, we used multivariate linear

regression models to investigate the associations of all five log-transformed markers with sociodemographic characteristics (step 1, $N = 146$) followed by their associations with parent-reported smoking and TSE variables (step 2, $N = 83$). In step 3, we combined variables that were significantly associated with TSE markers in step 1 and 2 in a single multivariate model ($n = 83$). Finally, we replicated findings from step 3 in separate multiple regression models to take advantage of the larger sample size available for some of the TSE markers ($n = 85$ to $n = 255$). Sensitivity analyses exploring how biomarker outliers affect model estimates showed that the main findings remained unaffected. All statistical analyses were conducted using Stata Inc. V. 17 (Stata Statistical Software: Release, 2021) with a Type I error of 0.05.

3. Results

3.1. Sociodemographics, parental smoking, and child TSE patterns

The average (SD) child age in the overall sample ($N = 175$) was 5.4 (3.4) years. Over half of the children were male (58.3 %), non-Hispanic Black race/ethnicity (64.6 %), had a household income of ≤$15,000 (70.9 %), and utilized public insurance or were self-pay (96.6 %). In total, 36.7 % of children had a home smoking ban. See Table 1 for descriptive statistics on child TSE patterns and TSE marker levels.

3.2. Association of TSE markers with sociodemographic characteristics

The multivariate regression model examining the associations between the five log-transformed markers and child sex, race, age (linear and quadratic terms), income level, and parent education level showed overall statistically significant associations for urinary cotinine only ($R^2 = 0.1703$; $F(13,123) = 2.27$, $p = 0.012$). Further investigation revealed significant associations of cotinine with age and race. Older children had lower cotinine levels ($\hat{\beta} = -0.04$, $p < 0.05$), and Black children ($\hat{\beta} = 0.202$, $p < 0.05$) and those of Other racial backgrounds ($\hat{\beta} = 0.347$, $p < 0.05$) had significantly higher cotinine levels than White children. None of the other four log-transformed markers showed significant associations with child race; only NNAL showed a negative association with child age. Supplemental Table S1 shows the overall model fit statistics and parameter estimates.

3.3. Association of TSE markers with parent-reported smoking and TSE behavior patterns

The multivariate regression model examining the associations between the five log-transformed TSE markers and the cumulative child TSE, and housing type showed overall statistically significant associations for NNAL ($R^2 = 0.1056$; $F(4,79) = 3.11$, $p = 0.031$), N-oxides ($R^2 = 0.1096$; $F(4,79) = 3.24$, $p = 0.026$), and hand nicotine ($R^2 = 0.2206$; $F(13,123) = 7.45$, $p < 0.001$). There were no significant associations found between cotinine or 3HC and the parent-reported smoking and TSE variables ($p > 0.10$). Further investigations revealed that increases in the cumulative child TSE was associated with higher levels of NNAL ($\hat{\beta} = 0.12$, $p < 0.05$) and hand nicotine ($\hat{\beta} = 0.09$, $p < 0.05$). Moreover, the presence of a home smoking ban was associated with lower levels of N-oxides ($\hat{\beta} = -0.264$, $p < 0.05$) and hand nicotine ($\hat{\beta} = -0.315$, $p < 0.05$). The cumulative child TSE and housing type were

not associated with any of the TSE markers. Supplemental Table S2 shows overall model fit statistics and parameter estimates.

3.4. Joint association of markers with sociodemographic characteristics and parent-reported smoking and TSE patterns

Table 2 shows overall model fit statistics of the multivariate regression model that examines the associations of log-transformed markers and sociodemographic characteristics and parent-reported smoking and TSE variables in the sample for which all of these data were available. Cotinine and hand nicotine showed overall significant associations, accounting for 22 % ($R^2 = 0.2213$; $F(7,66) = 3.60$, $p = 0.003$) and 25 % of variance ($R^2 = 0.2468$; $F(7,66) = 4.15$, $p = 0.001$), respectively. Further investigation showed that children who were Black ($\hat{\beta} = 0.307$, $p < 0.05$), younger ($\hat{\beta} = -0.054$, $p < 0.05$), and who had higher cumulative child TSE ($\hat{\beta} = 0.010$, $p < 0.05$) had higher cotinine levels. The absence of a home smoking ban and higher cumulative TSE was associated with higher hand nicotine ($\hat{\beta} = -0.3359$, $p < 0.05$; $\hat{\beta} = 0.011$, $p < 0.05$) and higher urinary NNAL levels ($\hat{\beta} = -0.2847$, $p < 0.05$; $\hat{\beta} = 0.012$, $p < 0.05$). Moreover, the absence of a home smoking ban was associated with higher N-oxide levels ($\hat{\beta} = -0.331$, $p < 0.05$). None of the sociodemographic variables or parent-reported smoking and TSE variables were associated with 3HC biomarker levels.

3.5. Replication of joint multivariate regression findings in separate multiple regression models

Supplemental Tables S3 to S8 show model fit statistics and parameter estimates for the multiple regression models conducted separately for each of the five log-transformed markers. The findings for the separate models were based on larger sample sizes parallel to those conducted on the smaller sample sizes for the joint multivariate analyses of cotinine, NNAL, and N-oxides. Semi-partial correlations showed that child age, race, and the cumulative child TSE accounted for 6.6 %, 7.5 %, and 6.6 % of the variance in urinary cotinine, respectively ($R^2 = 0.2328$; $F(8,130) = 4.93$, $p < 0.001$). For NNAL, the cumulative child TSE and home smoking bans accounted for 5.1 % and 3.5 % of the variance, respectively ($\left(R^2 = 0.1007\right.$; $F(2,85) = 4.76$, $p < 0.011$). For N-oxides, the cumulative child TSE and home smoking bans accounted for 4.7 %, and 5.1 % of the variance, respectively ($R^2 = 0.1151$; $F(2,85) = 5.53$, $p < 0.006$).

For hand nicotine, the cumulative child TSE and home smoking bans accounted for 7.8 %, and 8.1 % of the variance. Younger children had higher levels of hand nicotine $\left(sr^2 = 0.065\right)$ while controlling for other variables. In addition, children with larger hand surfaces showed higher levels of hand nicotine $\left.sr^2 = 0.057\right)$, independent of child age, home smoking ban, and the cumulative child TSE ($R^2 = 0.12120$; $F(4,73) = 7.94$, $p = 0.0015$).

3.6. Exploring the mediating role of hand nicotine

Nicotine on children's hands is a direct marker of tobacco smoke pollutants in the child's environment and can also be a source of nicotine uptake that can be metabolized to cotinine. To examine the potential mediating role of hand nicotine in the metabolism of

nicotine, we examined the associations of hand nicotine with urinary cotinine controlling for sociodemographic characteristics and parent-reported smoking and TSE variables. Fig. 1 shows a path model of the analyses detailed in Supplemental Tables S8 and S9. Child age, hand surface area, home smoking ban, and the number of cigarettes to which a child was exposed independently accounted for 21 % of variance in hand nicotine levels ($R^2 = 0.212$, $F(4,73) = 7.94$, $p = 0.002$). Hand nicotine independently accounted for 30 % of the variance in urinary cotinine, controlling for race and child age ($R^2 = 0.389$, $F(5,155) = 18.96$, $p < 0.001$). There continued to be significant independent associations with child race (5 %) and age (4 %), but there were no longer any significant independent associations with home smoking bans and the number of cigarettes children were exposed to by all smokers in any location in the past week.

4. Discussion

This study adds to the growing evidence base supporting the need to assess hand nicotine levels and other TSE markers in addition to urinary cotinine to achieve a more comprehensive understanding of children's overall TSE patterns (Matt et al., 2022; Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2021b; Mahabee-Gittens et al., 2019; Mahabee-Gittens et al., 2018). These findings may lead to better strategies to protect children from TSE. Our results indicate that hand nicotine has several properties that make it a particularly beneficial marker of children's exposure to THS pollution in their environments. First, hand nicotine levels were associated with the most prominent source of tobacco smoke pollution, the number of cigarettes smoked in a child's environment to which a child was reportedly exposed. Second and distinctly different than urinary cotinine, hand nicotine was associated with the presence of home smoking bans, the single most important strategy to lower exposure in homes of smokers. Third and also distinctly different than urinary cotinine, hand nicotine was not associated with children's race/ethnicity. In contrast, we found that children's urinary cotinine levels varied by their race/ethnicity as children who were non-Hispanic Black had higher cotinine levels when controlling for age and the number of cigarettes to which they were exposed. These racial differences support prior research indicating that higher urinary cotinine levels in children of non-Hispanic Black race/ethnicity may be due to differences in nicotine metabolism due to variant alleles of CYP2A6 or other factors (Dempsey et al., 2013; Benowitz et al., 2006; Zhu et al., 2013; Benowitz et al., 2016; Benowitz et al., 2020). Thus, these observed differences may not necessarily be due to higher exposure to tobacco smoke. This is evident in our path model which indicates that urinary cotinine levels were not associated with home smoking bans or the number of cigarettes to which children were exposed, independent of hand nicotine since there was no direct association between these two measures and urinary cotinine levels. The path model shows, however, that hand nicotine levels were strongly associated with child age, number of cigarettes to which children were exposed, home smoking bans, and hand surface area, indicating that children's hands play a role in their exposure to SHS and THS. Hand nicotine levels accounted for 30 % of the variance in urinary cotinine independent of other variables. Thus, hand nicotine is not just an important marker of TSE sources, but hands may also play a role in the transmission of SHS and THS pollutants in children.

Notably, both hand nicotine and NNAL were associated with the number of cigarettes children were exposed to and home smoking bans - two causal factors that contribute to TSE - as they accounted for 25 % and 14 % of the variance, respectively. These findings are consistent with prior work in this cohort (Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2019; Mahabee-Gittens et al., 2021c; Merianos et al., 2022). Prior research has also found that NNAL levels are higher in children who live with more smokers and who are around more cigarettes and that NNAL levels are lower in children who live with parental smokers who do not allow smoking in their homes (Park, 2020; Jeong et al., 2021). In contrast, urinary cotinine was significantly associated with the number of cigarettes children were exposed to, but not home smoking bans. These findings underscore that cotinine alone may not be an optimal marker of behaviors relevant to TSE compared to hand nicotine or NNAL, possibly due to differences in nicotine metabolism associated with cotinine levels. When cotinine is used as the sole marker of children's TSE, the impact of home smoking bans may not be detected, and racial/ethnic differences in cotinine may be identified that are due to metabolic differences but not due to differences in exposure to tobacco smoke, home smoking bans, or exposure-relevant behaviors (e.g., contact with THS polluted dust and materials). Since the presence of home smoking bans was associated with lower urinary N-oxide and NNAL levels, this result reinforces the short-term and long-term benefits of home smoking bans in lowering children's TSE. These findings emphasize the importance of recommending strict smoking bans in smokers' homes who have not yet quit smoking or who are unwilling to quit smoking, as doing so will reduce (but not eliminate) their children's THS exposure.

Results of our regression models parallel prior studies which found that younger children and children of non-Hispanic Black and non-Hispanic Other race have higher cotinine levels compared to older children and non-Hispanic White children (Mahabee-Gittens et al., 2021a; Merianos et al., 2019; Shastri et al., 2021). It is notable that younger children also had higher NNAL levels, a finding that was observed in prior examinations of subsamples of this study cohort (Mahabee-Gittens et al., 2021c; Merianos et al., 2022). Further, younger children had higher hand nicotine levels, which parallels previous studies on a subsample of this cohort which found that hand nicotine levels are higher in 2–4-year-old children (Mahabee-Gittens et al., 2021a; Mahabee-Gittens et al., 2019). This finding may potentially be due to children's newly acquired independent exploratory behaviors compared to infants and older children and other behavioral patterns associated with this age group. Our findings that 3HC, NNAL, N-oxides, and hand nicotine levels were not associated with child sex, race, household income, and parent education level add to the existing literature that has not traditionally examined these markers. These findings are consistent with the hypothesis that the same levels of toxic tobacco smoke pollutants in a child's environment provide an equivalent exposure risk regardless of sex, race, or income. Finally, although housing type was not associated with TSE marker levels, prior work indicates that there are persistent reservoirs of THS pollution in multiunit housing, hotels, casinos, and single-family or detached homes that are smoke-free but allowed smoking in the past (Matt et al., 2016; Matt et al., 2020; Matt et al., 2014; Matt et al., 2018). Thus, future work should include detailed assessments of specific housing types (e.g., townhome, connected private home),

home smoking policies, as well as the age of homes, as these factors are likely all associated with higher levels of SHS and THS exposure.

The current study's strengths include the assessment of five separate TSE markers in addition to parent-report data in this sample of children which had high levels of TSE. Urinary nicotelline N-oxides and 3HC, and hand nicotine levels are infrequently reported in the literature. However, there are limitations that should be acknowledged. There were relatively low sample sizes for some of the TSE marker analyses (e.g., $n = 78–88$). Children were recruited from one children's hospital which limits the generalizability of the findings; however, they were recruited from four different PED/UC sites served by the hospital. Given the busy nature of the PED/UC visit, we were unable to ensure that children did not wash or sanitize their hands prior to hand wipe collection, nor was information about when the children last washed their hands uniformly collected; thus, the variability observed in children's hand wipe levels may have been affected, in part by prior washing (Li et al., 2021; Stapleton et al., 2014). However, despite this limitation, we observed high hand wipe levels and strong associations between hand wipe levels and several of our measured TSE biomarkers and other variables. Additionally, we did not correct children's urinary TSE biomarkers for creatinine, since we did not have a reference range from a similar cohort of children who were highly exposed to tobacco smoke who also had creatinine-adjusted concentrations of these biomarkers (Barr et al., 2005). Finally, data were not available on the timing of when the children's urine samples were obtained relative to when children's last TSE episode occurred. This information is important to obtain in future studies given the varying half-lives of the urinary biomarkers. For example, we may have observed fewer associations between N-oxides and our measures due to the short half-life of just 2 h in adults (Jacob et al., 2013).

In conclusion, this study supports the measurement of hand nicotine in combination with other TSE markers to better understand their association of children's sociodemographics and TSE patterns. Hand nicotine levels were associated with modifiable behaviors such as household tobacco use patterns and home smoking bans that accounted for a fairly large proportion of the variance not captured by cotinine. Unlike urinary cotinine levels, hand nicotine levels reflect parents' and household smokers' behaviors that are associated with children's TSE. Further, since hand nicotine samples are non-invasively collected and easy and feasible to obtain in the clinical and other settings, hand wipes are a practical research collection tool. Thus, hand nicotine levels may be a useful aid to include in parental tobacco cessation and child TSE reduction interventions as children's hand nicotine levels may provide feedback that will encourage parents to alter their tobacco use and home tobacco rules in order to decrease their children's TSE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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HIGHLIGHTS

- Hand nicotine may be a marker of THS pollution not captured by cotinine.
- Hand nicotine levels complement other TSE biomarkers.
- Hand nicotine levels are associated with modifiable tobacco-related behaviors such as home smoking bans.

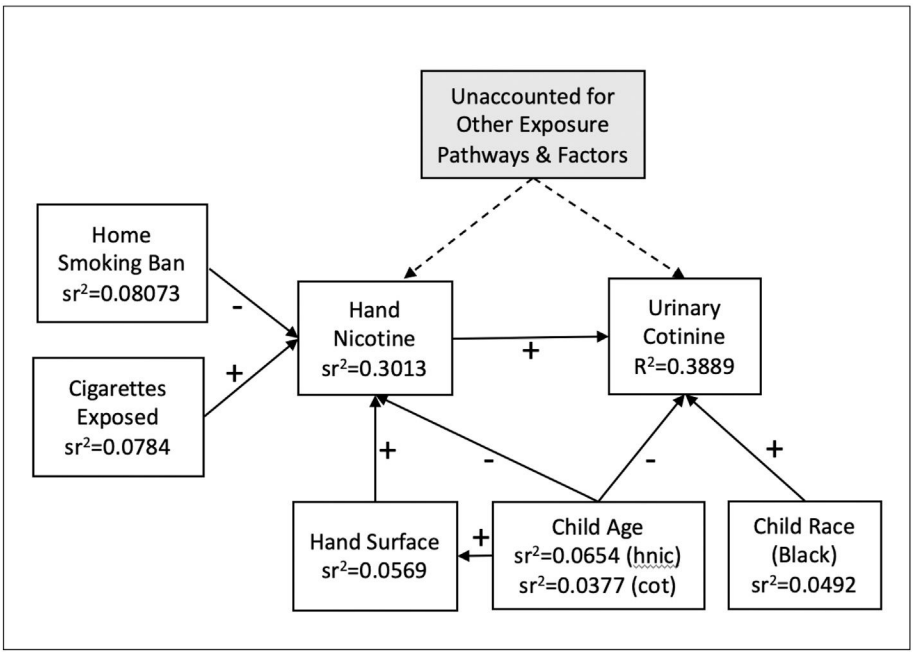

Fig. 1.

Path model illustrating the hypothesized role of hand nicotine in the exposure to tobacco smoke pollutants.

Table 1

Child/Parent sociodemographics, TSE patterns, and TSE marker characteristics.

Characteristics and TSE Marker Results	N = 175
Child Age, M (SD)	5.4 (3.4)
Child Sex - Male	58.3 %
Child Race	
White	25.7 %
Black	64.6 %
Other	8.0 %
Unknown	1.7 %
Child Insurance Type	
Commercial	3.4 %
Public/self-pay	96.6 %
Parent Education Level	
<High school graduate/equivalent	53.1 %
Income Level	
≤ $15,000	70.9 %
Housing Type	
Single-Family	35.4 %
Multifamily or Apartment	64.6 %
Cumulative Child TSE[a]: Mean (SD), Median (IQR)	9.4.1 (22.8), 4 (0; 9)
Number of Home Smokers[b]: Mean (SD), Median (IQR)	2.2 (1.3); 2 (1; 3)
Home Smoking Ban[c] - yes	36.7 %
Hand Nicotine ng/wipe (*n* = 163)	
Range	6.1–845.3
GeoMean [95 % Confidence Interval]	84.1 [72.0; 99.1]
Median (IQR)	91.6 (41.4; 156.7)
Urinary Cotinine ng/ml (n = 175)	
Range:	0.3–169.0
GeoMean [95 % Confidence Interval]	11.3 [9.5; 13.5]
Median (IQR)	11.5 (4.4; 26.5)
Urinary 3HC ng/ml (n = 175)	
Range:	0.8–780.3
GeoMean [95 % Confidence Interval]	36.3 [30.3; 44.8]
Median (IQR)	44.7 (12.7; 105.9)
Urinary N-Oxides pg/ml (*n* = 156)	
Range:	1.0–371.7
GeoMean [95 % Confidence Interval]	24.4 (19.8; 30.0)
Median (IQR)	26.5 (9.6; 68.0)
Urinary NNAL pg/ml (n = 155)	
Range:	0.2–1399.0

Characteristics and TSE Marker Results	N = 175
GeoMean [95 % Confidence Interval]	31.7 [25.6; 39.3]
Median (IQR)	35.0 (12.7; 72.7)

Abbreviations: TSE, tobacco smoke exposure; GeoM, geometric mean; CI, confidence interval; Mdn, median; IQR, interquartile range.

[a]Cumulative Child TSE: total number of cigarettes smoked around the child by all smokers in any location in the previous week.

[b]Number of Household Smokers: total number of cigarette smokers around the child in any location in the previous week.

[c]Home Smoking Ban: smoking is never allowed in the home.

Table 2

Model fit statistics and parameter estimates of a multivariate regression model of five log-transformed TSE markers as a function of child sociodemographic characteristics, TSE, and home smoking bans ($N = 83$).

	Urinary Cotinine	Urinary 3HC	Urinary NNAL	Urinary N-oxides	Hand Nicotine[a]
Model Fit	$R^2 = 0.221$	$R^2 = 0.126$	$R^2 = 0.140$	$R^2 = 0.142$	$R^2 = 0.247$
	$p = 0.003$	$p = 0.106$	$p = 0.067$	$p = 0.063$	$p = 0.001$
	$\widehat{\beta}$	$\widehat{\beta}$	$\widehat{\beta}$	$\widehat{\beta}$	$\widehat{\beta}$
Child Race					
White	Ref	Ref	Ref	Ref	Ref
Black	0.307*	0.194	− 0.063	− 0.116	−0.015
Other	0.357	0.272	− 0.111	0.032	0.232
Unknown	0.540	0.520	0.212	0.111	0.256
Child Age	−0.054*	− 0.045	− 0.003	− 0.023	−0.013
Cumulative Child TSE[b]	0.010*	0.010	0.012*	0.010	0.011*
Home Smoking Ban[c]					
No	Ref	Ref	Ref	Ref	Ref
Yes	−0.181	−0.251	−0.285*	−0.331*	−0.336*

Notes. Ref, reference.

*$p < 0.05$.

[a]Hand nicotine levels were corrected for field blank nicotine levels.

[b]Cumulative Child TSE: total number of cigarettes smoked around the child by all smokers in any location in the previous week.

[c]Home Smoking Ban: smoking is never allowed in the home.