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Original Investigation

Thirdhand Smoke Contamination and Infant Nicotine Exposure in a Neonatal Intensive Care Unit: An Observational Study

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Abstract

Introduction: Thirdhand smoke (THS) is ultrafine particulate matter and residue resulting from tobacco combustion, with implications for health-related harm (eg, impaired wound healing), particularly among hospitalized infants. Project aims were to characterize nicotine (THS proxy) transported on neonatal intensive care unit (NICU) visitors and deposited on bedside furniture, as well as infant exposure.

Methods: Cross-sectional data were collected from participants in a metropolitan NICU. Participants completed a survey and carbon monoxide breath sample, and 41.9% (n = 88) of participants (n = 210) were randomly selected for finger-nicotine wipes during a study phase when all bedside visitors were screened for nicotine use and finger-nicotine levels. During an overlapping study phase, 80 mother–infant dyads consented to bedside furniture-nicotine wipes and an infant urine sample (for cotinine analyses).

Results: Most nonstaff visitors' fingers had nicotine above the limit of quantification (>LOQ; 61.9%). Almost all bedside furniture surfaces (93.8%) and infant cotinine measures (93.6%) had values >LOQ, regardless of household nicotine use. Participants who reported using (or lived with others who used) nicotine had greater furniture-nicotine contamination (Mdn = 0.6 [interquartile range, IQR = 0.2–1.6] μg/m^2) and higher infant cotinine (Mdn = 0.09 [IQR = 0.04–0.25] ng/mL) compared to participants who reported no household-member nicotine use (Mdn = 0.5 [IQR = 0.2–0.7] μg/m^2; Mdn = 0.04 [IQR = 0.03–0.07] ng/mL, respectively). Bayesian univariate regressions supported hypotheses that increased nicotine use/exposure correlated with greater nicotine contamination (on fingers/furniture) and infant THS exposure.

Conclusions: Potential furniture-contamination pathways and infant-exposure routes (eg, dermal) during NICU hospitalization were identified, despite hospital prohibitions on tobacco/nicotine use. This work highlights the surreptitious spread of nicotine and potential THS-related health risks to vulnerable infants during critical stages of development.

Implications: THS contamination is underexplored in medical settings. Infants who were cared for in the NICU are vulnerable to health risks from THS exposure. This study demonstrated that 62% of nonstaff NICU visitors transport nicotine on their fingers to the NICU. Over 90% of NICU (bedside) furniture was contaminated with nicotine, regardless of visitors' reported household-member nicotine use or nonuse. Over 90% of infants had detectable levels of urinary cotinine during NICU hospitalizations. Results justify further research to better protect infants from unintended THS exposure while hospitalized.

Introduction

Thirdhand smoke (THS) is the ultrafine particulate matter and residue left behind in indoor environments after tobacco combustion.[1] Toxicants formed from vaping electronic nicotine delivery systems (ENDS) are similar to toxicants in combusted tobacco.[2] Accruing data from in vitro studies, animal models, and human research[3,4] has indicated that THS exposure can induce adverse cellular and health effects,[5] including DNA damage,[6] impaired wound healing,[7,8] neurobehavioral effects,[5] and increased respiratory symptoms in THS-exposed children.[9]

Infants hospitalized in neonatal intensive care units (NICUs) are highly vulnerable to respiratory-related injuries. Exploration of THS contamination in NICU and other health care settings has increased[10,11] with calls to protect pediatric patients from THS exposure in all locations.[1,12–15] NICUs present unique opportunities to explore THS exposure in vivo due to prohibitions on smoking/vaping and hospitalizations spanning weeks-to-months.[16,17] Following pilot work,[10] our objective was to more fully characterize nicotine contamination (a THS proxy) in the NICU and infant exposure.

Routes of infant THS exposure include ingestion, inhalation, and dermal absorption of tobacco constituents transported into the NICU,[18] which may travel on skin, clothing, hair, and breath. THS toxicants will transfer to NICU surfaces (eg, by contacting contaminated clothing),[15,19] such as incubators and furniture.[10] Nicotine reacts with indoor pollutants (eg, nitrous acid [HONO]) and forms new toxicants,[18] such as carcinogenic, tobacco-specific nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N'-nitrosonornicotine.[20,21] Furthermore, many THS contaminants slowly reemit in gaseous form ("offgassing").[22] Experimental evidence has shown that nicotine is absorbed dermally from airborne nicotine and nicotine residue from clothing[23] and is consistent with previous findings documenting NICU infant exposure as measured by cotinine (ie, nicotine's primary metabolite[24]) found in infants' urine.[10] Tobacco-smoke exposure in childhood is linked to later development of atrial fibrillation[25] and tobacco-specific nitrosamine exposure is linked to pancreatic disease.[26] Furthermore, 5%–60% of harm attributed to freshly emitted tobacco smoke may be attributable to cumulative THS exposure.[27]

Our aim was to determine the extent that visitors transport THS to the NICU, extending our previous work that demonstrated that 78% of medical staff transport nicotine to the NICU on their fingers.[11] Another primary aim was to quantify THS deposited on NICU-based furniture and quantify infants' nicotine exposure. A priori hypotheses were: (1) over 26% of nonstaff NICU visitors would have detectable levels of nicotine on their hands and, regardless of household members' nicotine use, (2) all infants' rooms would have detectable surface nicotine and (3) detectable levels of cotinine in infants' urine. To increase study rigor, original hypotheses related to, "smoking households" were adapted to include all individuals from homes where the participants (or other household members) use any form of nicotine ("nicotine-using homes"; ie, cigarette, cigar/cigarillos, hookah, ENDS, smokeless tobacco, or other tobacco use) compared to individuals from homes where no household members use nicotine ("nicotine-free homes"). All forms of tobacco/nicotine use (including ENDS and smokeless tobacco) contribute to nicotine contamination and potential infant exposure.[2] We hypothesized that nicotine-using homes would deposit more nicotine on bedside furniture in the NICU and that infants from nicotine-using homes would have greater levels of urine cotinine. Vapor-phase (airborne) nicotine was also explored.

Methods

Our institution (HSC-MS-15–0614) and the hospital NICU's institutional review board approved this study. All measures and data analytic details are reported herein. Two study phases recruited concurrently. A "visitor phase" screened/recruited all bedside nonstaff visitors (family/friends) from March 2017 to December 2017 to characterize nicotine transported to the NICU (n = 210). A "dyad phase" enrolled mother–infant dyads (n = 80) from March 2017 to October 2018 to assess NICU furniture nicotine contamination and infant nicotine exposure; 30 mothers participated in both study phases.

Participants and Procedure

Participants were recruited from a large, metropolitan children's hospital NICU (1400 admissions per year). Visitor-phase participants could be any bedside visitor (eg, parents and other family members) present during screening. Dyad-phase participants were primary caregivers (usually mothers). Nicotine-using households where ≥1 individual reportedly used nicotine (indoors or outside the home; including cigarettes, cigar/cigarillos, hookah, ENDS [eg, e-cigarettes], smokeless tobacco, or other tobacco) were overrecruited compared to nicotine-free homes (where no household members reportedly used nicotine) in the dyad phase (3:1 ratio; per study design). Research assistants screened household nicotine/tobacco use with a well-validated approach.[10,17,28] Participant smoking was verified by exhaled carbon monoxide (CO) values of ≥7 parts per million (ppm).[29,30] Individuals unable to complete assessments in English were excluded.

Research assistants screened bedside visitors several times a week and counterbalanced starting times and locations daily. All participants gave consent and received $10/phase ($20 maximum).

Procedures for both phases included an interview, assessing household, visitation, infant feeding, and tobacco-related information. In addition, participants gave an exhaled CO breath sample to validate smoking status; no participants' reported smoking status was recoded based on CO samples.[29,30] During the visitor phase, 41.9% (n = 88) of participants were randomly selected to complete a (dominant-hand) finger-nicotine wipe (ie, thumb, index, or middle finger). Sixty-seven randomly selected wipes were analyzed (31.9% of total visitor-phase participants) to control study costs. Prior to consent, participants and research assistants were blinded to random selection for finger wiping.[11]

Measures

The dyad phase included a furniture-nicotine wipe (ie, bedside couch/chair) and infant urine collection. Finger- and furniture-wipe procedures[19,31–33] and quantification of surface nicotine are well established.[34] Briefly, surface nicotine is collected by wetting a screened cotton wipe with a solution (of distilled water and 1% ascorbic acid) and wiping the entire finger surface or a standardized section (10- × 10-cm template) of furniture. Finger levels are reported in nanograms and furniture nicotine is reported in micrograms per meter squared. Finger area was measured to allow comparisons between finger and furniture nicotine contamination in micrograms per meter squared.[11]

Field blanks (ie, wipes handled in the same manner as sample wipes but not wiped on a surface) were collected during nicotine sampling, consistent with Quintana et al.[33] Specifically, field blanks were wetted with the water/ascorbic acid solution and exposed to the air but not used to wipe fingers/furniture, and nicotine on field blanks was subtracted from analyzed participant samples prior to reporting values. Of the field blanks, 20% were analyzed. For those matching samples, the matched field blank was subtracted. For all other wipes, the geometric mean of analyzed field blanks was subtracted from the wipe. Field blanks for participants from nicotine-free homes had a geometric mean of 1.56 ng nicotine per wipe and field blanks for participants from nicotine-using homes had a geometric mean of 2.23 ng nicotine per wipe.

To measure cotinine, cotton pads were placed in infants' diapers and expressed via syringe when saturated. Published methods were employed to quantify cotinine (LOQ = 0.05 ng/mL).[24] Vapor-phase (airborne) nicotine levels in the NICU were measured for 1 week (April 2018), with five Teflon-coated air monitors impregnated with sodium bisulfate.[35] Interviews assessed participant/household characteristics, including visitation (eg, number of days [out of past seven] visited, visitation length, and total number of visitors), infant feeding (eg, any breastmilk received), infant holding (time), and handwashing/sanitization practices and glove/gown use (see Table 1 and Supplementary Material 1).

Nicotine use was assessed for participants and household members. We measured current and lifetime cigarette smoking and ENDS use, as well as cigarettes per day,[10,17] and current use of cigars/cigarillos/hookah and smokeless tobacco products. Mothers were asked about cigarette/ENDS use during pregnancy. Establishment of home and car smoking/ENDS bans was measured separately for smoking and ENDS.[10,11,13,17] Furthermore, we measured the frequency participants reported being near smoking or ENDS in friends'/family members' homes and other locations.[11]

Data Analyses

Only one wipe per infant was analyzed, retaining infants' primary caregiver's wipe (n = 63 analyzed; see Figure 1). Three dyad-phase participants' households were reclassified to nicotine-using homes (due to initial research associate misclassification [n = 1] and reported smokeless tobacco use [n = 2]).[36] Final sample sizes for furniture-wipe and urine cotinine analyses were 63 for nicotine-using homes and 17 for nicotine-free homes.

Nicotine wipes and urine cotinine values were adjusted by natural-log transformation. For nicotine wipes, half the LOQ (0.025 ng/wipe) was imputed for values below the LOQ (<LOQ). Data analyses were conducted with R, version 3.5.1.,[37] via *rstan*[38] and *brms*.[39] Across all phases, generalized linear modeling evaluated relationships between three univariate outcomes (ie, finger nicotine, furniture nicotine, and urine cotinine) and several prespecified predictors, including household nicotine use (ie, nicotine-using vs. nicotine-free homes), participant smoking status, number of individuals in the home who smoke or use nicotine, and number of cigarettes per day smoked by the participant and all (other) household members. Furthermore, we examined other potential variable associations (ie, participant/household characteristics [eg, education], tobacco/ENDS use exposure [eg, frequency being near smoking], glove/gown use, handwashing/sanitization practices, visitation and care-by-parent practices, and infant variables [eg, birth weight; for cotinine analyses]; see Supplementary Material 2 and 3) with the outcomes. Finger nicotine was modeled as a hurdle-lognormal process, a two-part model that separately accounts for values <LOQ (via binomial distribution, predicting zero values [ie, <LOQ] vs. positive values [ie, >LOQ]) and values >LOQ (via lognormal distribution). Specifically, the binomial-portion estimates used all 63 finger-nicotine observations and the lognormal-portion estimates only used nicotine values ≥LOQ (n = 39). Furniture nicotine and urine cotinine had fewer samples <LOQ and were modeled via the lognormal distribution alone. Bayesian statistical inference[40,41] directly provided model-specific probabilities that predictor effects on the outcome existed. Models used vague, neutral priors (b = ~normal [$\mu = 0$, $\sigma^2 = 10^5$], sigma = ~Student-t [$\mu = 0$, $\sigma^2 = 10^5$]) to maximize the influence of the data on posterior probabilities (PP).[42]

Results

Table 1 (and Supplementary Material 1) provides comprehensive participant/household characteristics and other information collected during both phases (note: n = 30 participants took part in both study phases). Across both phases, a majority of participants were mothers (eg, 96.3% of dyad phase) and from ethnic/racial minorities. Participants in the visitor phase tended to be older and spanned a greater age range (Mdn = 30.5 [interquartile range, IQR: 26.5–37.3] years) compared to the dyad-phase sample (Mdn = 28.9 [IQR: 24.9–33.1] years). Fewer than 10% of mothers reported current cigarette smoking (ie, 8.1% of mothers in the visitor phase) and mothers who reported smoking (in both phases) tended to report smoking ≤10 cigarettes per day (Mdn = 5 [range: 0–10] cigarettes/day). The range of cigarettes per day reported for other household members from nicotine-using homes was comparable across visitor- (Mdn = 15 [range: 2–20] cigarettes/day) and dyad-phase samples (Mdn = 9 [range: 2–20] cigarettes/day). Figure 1 depicts study flow (and final sample sizes for study procedures) for both study phases.

Table 1. Participant, Household, and Infant Characteristics by Study Phase and Household Nicotine Use

Characteristic	Visitor phase (n = 210)		Visitor phase, finger analyzed (n = 63)		Dyad phase (n = 80)	
	Nicotine-free homes	Nicotine-using homes	Nicotine-free homes	Nicotine-using homes	Nicotine-free homes	Nicotine-using homes
			Household and participant characteristics			
Household type, *n* (%)						
Completely nicotine free	165 (100%)	0 (0.0%)	48 (100%)	0 (0.0%)	17 (100%)	0 (0.0%)
Participant lives with smoker/ENDS user	0 (0.0%)	21 (46.7%)	0 (0.0%)	6 (40.0%)	0 (0.0%)	46 (73.0%)
Participant smokes/uses ENDS, others do not	0 (0.0%)	9 (20%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	7 (11.1%)
Participant and others smoke/use ENDS	0 (0.0%)	9 (20%)	0 (0.0%)	5 (33.3%)	0 (0.0%)	8 (12.7%)
Participant uses smokeless tobacco, others do not	0 (0.0%)	3 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant lives with smokeless tobacco user(s)	0 (0.0%)	3 (6.7%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	2 (3.2%)
Race/ethnicity, *n* (%)						
American Indian–Alaskan native	1 (0.6%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	3 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Black/African American	48 (29.6%)	15 (34.1%)	15 (31.3%)	5 (33.3%)	2 (11.8%)	31 (49.2%)
Hispanic	64 (39.5%)	10 (22.7%)	16 (33.3%)	2 (13.3%)	8 (47.1%)	16 (25.4%)
White, non-Hispanic	44 (27.2%)	19 (43.2%)	16 (33.3%)	8 (53.3%)	7 (41.2%)	14 (22.2%)
Other	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Participant age (years), *M* (SD)	33.9 (11.5)	33.3 (12.3)	32.5 (10.4)	36.9 (15.0)	29.1 (5.6)	29.1 (6.8)
Highest education (years), *M* (SD)	14.3 (2.4)	12.8 (2.1)	14.2 (2.2)	13.1 (2.3)	14.4 (2.5)	13.3 (2.1)
Female (participant), *n* (%)	131 (79.4%)	33 (73.3%)	42 (87.5%)	13 (86.7%)	16 (94.1%)	61 (96.8%)
Relationship status, *n* (%)						
Married	88 (57.1%)	16 (41.0%)	27 (56.3%)	7 (53.8%)	11 (64.7%)	20 (31.7%)
Living together but not married	19 (12.3%)	11 (28.2%)	10 (20.8%)	3 (23.1%)	5 (29.4%)	22 (34.9%)
Single	39 (25.3%)	11 (28.2%)	9 (18.8%)	2 (15.4%)	1 (5.9%)	18 (28.6%)
Divorced/separated/widowed	8 (5.1%)	1 (2.6%)	2 (4.2%)	1 (7.7%)	0 (0.%)	3 (4.8%)
Relationship to infant, *n* (%)						
Mother	110 (67.9%)	26 (59.1%)	37 (77.1%)	8 (53.3%)	17 (100.0%)	60 (95.2%)
Father	26 (16.0%)	11 (25.0%)	4 (8.3%)	2 (13.3%)	0 (0.0%)	2 (3.2%)
Other relative	26 (16.0%)	7 (15.9%)	7 (14.6%)	5 (33.3%)	0 (0.0%)	1 (1.6%)[a]
Participant lives with the mother of the infant[b], *n* (%)	29 (56.9%)	12 (66.7%)	4 (36.4%)	4 (57.1%)	—	1 (33.3%)[A]
Number of adults >18 years in home, *M* (SD)	2.1 (0.8)	2.7 (1.1)	2.1 (0.7)	3.2 (1.3)	2.2 (0.4)	2.6 (0.9)
			Infant variables			
Female (infant), *n* (%)	73 (47.4%)	15 (37.5%)	25 (52.1%)	5 (38.5%)	7 (41.2%)	29 (46.0%)
Birth weight (kilograms), *M* (SD)	2.072 (0.992)	2.086 (0.885)	2.068 (0.938)	2.228 (0.759)	2.103 (0.983)	2.068 (0.956)
Gestational age (weeks), *M* (SD)	—	—	—	—	33.1 (4.4)	32.9 (4.4)
Received any breastmilk, *n* (%)	90 (68.2%)	26 (74.3%)	30 (75%)	5 (55.6%)	15 (88.2%)	46 (74.2%)
Postnatal age at assessment (weeks), *M* (SD)	2.6 (2.6)	2.3 (2.1)	2.6 (2.7)	2.0 (1.7)	2.6 (1.7)	4.1 (7.7)
Length of infant hospitalization (weeks), *M* (SD)	6.7 (7.0)	7.6 (7.8)	6.0 (6.2)	5.4 (4.9)	4.6 (2.8)	7.0 (8.7)

Data were collected between March 2017 and October 2018. Where categories do not add up to the total sample size, the remainder represent missing data. Participants in the visitor phase were nested within individual infants, and 151 unique infants had family members participate. The modal number of participants for each infant was one (*n* = 101; 66.9%), followed by two participants (*n* = 43; 28.5%), three participants (*n* = 5; 3.3%), and four participants (*n* = 2; 1.3%) for each unique infant.

ENDS = electronic nicotine delivery systems.

[a]The infant's aunt was the legal guardian and completed the interview.

[b]This question was added after the visitor phase had been recruiting for several months and it was only asked of participants who were not the mother. During the dyad phase, this question was only asked if the participant was not the infant's mother.

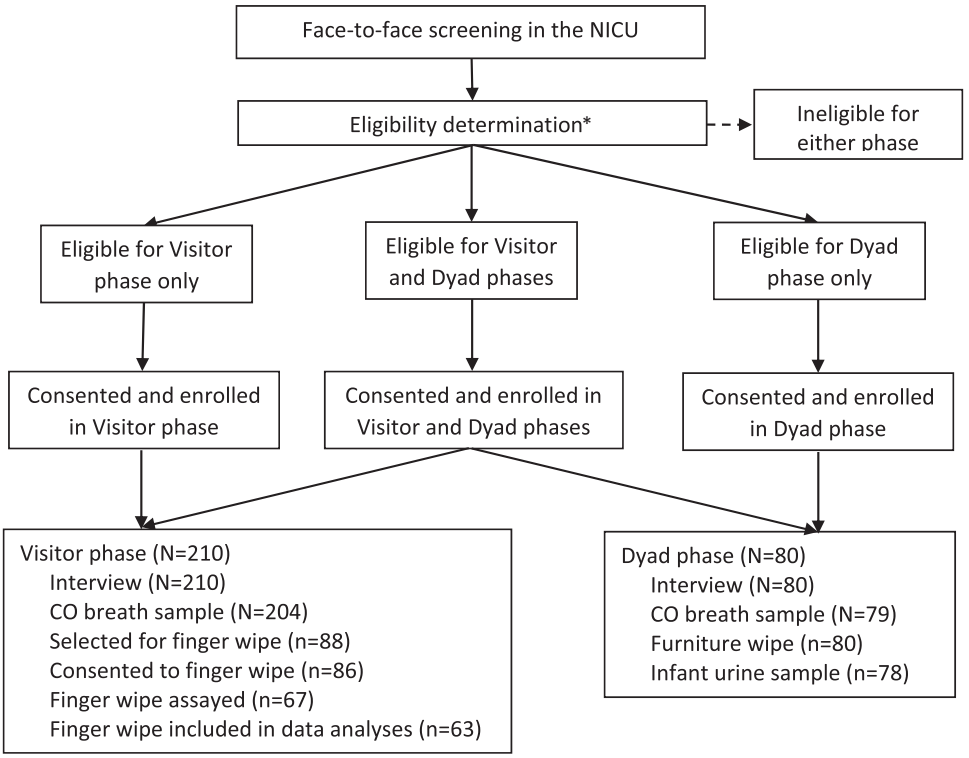

Figure 1. Study flow for the visitor and dyad phases. "NICU" = neonatal intensive care unit; "CO"=carbon monoxide. Participants for the visitor phase (n = 210) were recruited from March 2017 until December 2017. Participants for the Dyad phase (n = 80) were recruited from March 2017 until October 2018. Participants who enrolled in both phases only completed the interview once and gave a single breath sample.
*Full details on screening and recruitment for each phase, including the number of NICU visitors not approached, ineligible (including reasons for ineligibility), or who refused (including refusal reasons) are presented in Supplementary Material 4.

Visitor Phase

We screened 261 consecutive visitors face-to-face in the NICU during the visitor phase; 9.6% (n = 25) refused and 10.0% (n = 26) asked to participate at a later day/time (see Supplementary Material 4 for comprehensive screening and enrollment details), resulting in 210 enrolled visitor-phase participants. Participants tended to be from nicotine-free homes (n = 165; 78.6%; see Table 1). Eighty-six participants consented to finger wiping (n = 2; 2.3% refusal) and 67 wipes were assayed, of which 63 were included in analyses (n = 48 nicotine-free homes; n = 15 nicotine-using homes; see Table 1 (and Supplementary Material 1) for participant/household characteristics of participants whose finger wipes were analyzed).

Twenty-four participants' finger wipes were <LOQ, all of which were from nicotine-free homes, resulting in 61.9% (n = 39 of 63) of participants with quantifiable finger nicotine (see Table 2 for raw and standardized finger-nicotine data). To aid hurdle-lognormal model results' interpretation (see Supplementary Material 2), we provide a detailed example of both parts of these models. To maximize available data and simplify inferences, we focused on interpreting hurdle portions (which retained all 63 observations). See Supplementary Material 5 for more detailed descriptions, including interpretations of the lognormal-model portions (for observations ≥LOQ; n = 39). A majority of finger-nicotine predictors demonstrated PP ≥75.0% for the binomial (hurdle) portion, with most ≥90.0%, demonstrating that most predictors had ≥75% probability of a *nonzero* relationship with finger nicotine (Supplementary Material 2). The strongest predictor of having a finger-nicotine value <LOQ (binomial-model portion) was residing in a nicotine-free home relative to nicotine-using homes (PP > 99.9%; odds ratio [OR] = 3854.95). Furthermore, among the observations ≥LOQ (lognormal-model portion), participants from nicotine-free homes had significantly (PP = 98.0%) lower finger-nicotine values (ie, 97% lower).

Greater age and education, identifying as White (non-Hispanic) or Latino/Hispanic (relative to Black/African American participants), and being male were associated with greater odds of finger-nicotine values <LOQ. This suggested less exposure to nicotine for groups with greater odds of finger-nicotine values <LOQ. Most measures of nicotine use/exposure (including NICU visitation frequency by household *nicotine users* and furniture-nicotine levels [as a predictor]) correlated with finger-nicotine <LOQ such that greater use and exposure correlated with lower odds of being <LOQ on finger nicotine, with some exceptions (Supplementary Material 2). Any glove/gown use (relative to never using them) was associated with increased odds of finger-nicotine values <LOQ. Handwashing-/sanitization-practice associations with finger nicotine were more complex. Compared to participants who reported equal levels of handwashing/sanitization, participants who tended to use sanitizer had greater odds of finger nicotine <LOQ, whereas those who tended toward handwashing had lower odds of finger nicotine <LOQ.

Dyad Phase

Participants were screened for dyad-phase eligibility during the visitor phase and could participate in both phases. At the conclusion of the visitor phase (in December 2017), screening and enrollment for the dyad phase continued until 80 participants were enrolled in

Table 2. Participant Carbon Monoxide (CO), Finger Area, and Nicotine, Furniture Nicotine, and Infant Urine Cotinine Values by Study Phase and Household Nicotine Use

Measurement	Nicotine-free homes	Nicotine-using homes
	Visitor phase (n = 210)	
CO (ppm), *M* (SD)	1.1 (0.8)	3.2 (5.6)
	Visitor phase, finger analyzed (n = 63)	
CO (ppm), *M* (SD)	1.0 (0.6)	6.3 (8.4)
Finger surface area (cm^2), *M* (SD)	42.6 (10.8)	46.8 (13.9)
Finger nicotine		
Raw nicotine (ng/finger), *M* (SD)	3.6 (12.1)	313.5 (436.0)
Raw nicotine (ng/finger), median (IQR)	0.0 (0.0–1.8)	32.9 (6.6–733.9)
Raw nicotine (ng/finger), geometric mean	1.2	53.4
Standardized nicotine (μg/m^2), *M* (SD)	0.7 (2.5)	66.3 (91.1)
Standardized nicotine (μg/m^2), median (IQR)	0.0 (0.0–0.4)	7.0 (1.7–164.3)
Standardized nicotine (μg/m^2), geometric mean	0.6	11.8
	Dyad phase (n = 80)	
CO (ppm), *M* (SD)	0.8 (0.7)	3.1 (5.9)
Furniture nicotine (μg/m^2)		
M (SD)	0.6 (0.6)	2.0 (8.3)
Median (IQR)	0.5 (0.2–0.7)	0.6 (0.2–1.6)
Geometric mean	0.4	0.6
Urine cotinine (ng/mL)		
M (SD)	0.05 (0.04)	1.25 (5.84)
Median (IQR)	0.04 (0.03–0.07)	0.09 (0.04–0.25)
Geometric mean	0.04	0.13

Data were collected between March 2017 and October 2018. Participants in the visitor phase were nested within individual infants, and 151 unique infants had family members participate. The modal number of participants for each infant was one (n = 101; 66.9%), followed by two participants (n = 43; 28.5%), three participants (n = 5; 3.3%), and four participants (n = 2; 1.3%) for each unique infant. We were unable to obtain urine samples from two infants prior to discharge (n = 78 analyzable urines). "Standardized nicotine" refers to finger-nicotine values adjusted for finger surface area. Geometric means were calculated to account for zeros based on an adaptation of the formula used in the "psych" library (Revelle, W. *psych: Procedures for Personality and Psychological Research*. Evanston, IL: Northwestern University; 2018; https://CRAN.R-project.org/package=psych Version = 1.8.12) in the R statistical computing environment (R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019; https://www.R-project.org/). The adaptation took the natural log of each (nonzero) value, summed the logged values, and divided the sum by the number of all observations, after which the antilog was taken. For example, for finger-nicotine geometric mean calculations, values <limit of quantification (ie, zeros) were excluded from the numerator calculations and included in the total observations for the denominator for geometric mean calculations.
IQR = interquartile range.

October 2018 (see Figure 1 and see Supplementary Material 4 for comprehensive screening enrollment details).

Furniture Nicotine

A high proportion of the sample (93.8%) had detectable (ie, >LOQ) furniture (surface) nicotine, regardless of household nicotine use (see Table 2). Participants from nicotine-using homes (Mdn = 0.6 [IQR = 0.2–1.6] μg/m^2) had greater levels of furniture-nicotine contamination compared to participants from nicotine-free homes (Mdn = 0.5 [IQR = 0.2–0.7] μg/m^2).

We explored associations among prespecified characteristics and NICU-furniture nicotine and other characteristics' associations with furniture nicotine (Supplementary Material 3). Relative to African American/Black participants, furniture-nicotine levels were lower for Latino/Hispanic (–40.1%, PP = 88.2%), non-Hispanic White (–55.0%, PP = 96.0%), and other races/ethnicities (–81.1%, PP = 92.1%). Other household/participant characteristics demonstrated lower PP relative to race/ethnicity. Age related negatively (–1.3%/year), and education (1.4%/year) and participant (adult) female sex (6.8%) related positively, with furniture-nicotine levels. Furthermore, for each week of postnatal age, a 2.4% reduction in furniture nicotine was demonstrated (PP = 81.9%).

Among nicotine use/exposure variables, current smoking (146.3% increase, PP = 97.4%) and exposure to smoking in friends'/family members' homes (65.6% increase, PP = 89.4%) associated strongly and positively with greater NICU-furniture nicotine. Associations of other nicotine use/exposure variables with furniture-nicotine levels were mixed and generally had lower PPs (see Supplementary Material 3). For example, greater numbers of household nicotine users were associated with higher furniture-nicotine levels (13.3% increase/user, PP = 67.0%). Counterintuitively, reports of *not* having a smoking or ENDS home-and-car ban were associated with lower levels of furniture nicotine.

In general, more visitation was associated with greater furniture-nicotine levels. Daily visitation and longer visitation were associated with greater levels of nicotine. Indeed, "daily or nearly every day" visitation by a household nicotine user (ie, a household nicotine user physically came to the NICU) was associated with significantly greater furniture-nicotine levels (120.7% nicotine increase, PP = 96.6%), compared to infants, "never" visited by household nicotine users.

Urine Cotinine

Measurable cotinine levels (ie, >LOQ) were found in an overwhelming majority of infant urine samples (n = 73; 93.6%)

regardless of household nicotine use. Infants from nicotine-using homes (Mdn = 0.09 [IQR = 0.04–0.25] ng/mL) had greater urinary cotinine levels compared to infants from nicotine-free homes (Mdn = 0.04 [IQR = 0.03–0.07] ng/mL; see Table 2).

We explored prespecified characteristics associated with infant urine cotinine and other characteristics' associations with cotinine (Supplementary Material 3). Latino/Hispanic, White (non-Hispanic), and other races/ethnicities had significantly lower infant cotinine levels (range: −57.5% to −82.2% cotinine, PP ≥ 96.9%) compared to African American/Black participants. Older (−1.3% cotinine/year, PP = 67.9%) and more educated parents (−7.1% cotinine/year, PP = 80.2%) tended to have infants with lower cotinine. Female infants (−53.9%), greater birth weight (−15.7%/kg), greater gestational age at delivery (−4.2%/week), receiving breastmilk (−42.3%), and older postnatal age (−3.0%/week) were associated with lower infant urine cotinine (all variables' PP ≥ 80.5%).

Greater infant cotinine levels correlated strongly and positively with current participant smoking (423.4%, PP > 99.9%) and smoking during pregnancy and lifetime smoking (see Supplementary Material 3). Other measures of participant nicotine use (ie, cigarettes per day [both typical and on day of assessment] and ENDS use) had positive associations with cotinine and lower PPs (range: 51.9%–74.7%) compared to other nicotine use/exposure variables. Greater infant cotinine levels were strongly and positively associated with greater numbers of household nicotine users (73.7% increase/user, PP = 97.6%) and typical cigarettes per day (by others in the home; 3.5% increase/cigarette, PP = 98.1%). Reports of being near smoking in friends'/family members' homes and not having a total household ban on smoking and ENDS were each associated with greater infant cotinine levels, whereas reports of being near smoking (in other locations) and ENDS (in friends'/family homes and other locations) were negatively associated with cotinine values.

Participants who reported any glove use had infants with lower cotinine levels (60.3% decrease, PP = 96.1%); the same relationship was demonstrated for gown use (33.3%–51.1% decrease, PP ≥ 71.6%). Participants who reported equal (both) handwashing/sanitization (compared to those who leaned toward sanitizing or handwashing) had infants with the lowest cotinine values; "lean handwashing" had the highest infant cotinine levels (279.7% increase, PP = 96.0%).

Greater visitation by household members who use nicotine was strongly associated with greater infant urine cotinine, with infants being visited, "daily or nearly every day" by a household nicotine user having the highest cotinine (95.0% increase, PP = 93.4%), relative to infants, "never" visited by household tobacco users. In general, greater infant visitation (ie, total [of all] visitors, days participant visited [out of past 7]) and any care-by-parent behaviors (eg, changing diapers) were negatively associated with infant urine cotinine. Infant holding was negatively associated with cotinine, whereas greater visitation length and performing skin-to-skin holding were associated with greater cotinine; however, all three of these associations demonstrated relatively low PPs.

Furniture nicotine (as a predictor) demonstrated a strong linear relationship with urine cotinine levels (75.5% increase per 1 μg/m^2 increase, PP > 99.9%). A strong quadratic trend also emerged such that the linear trend began to flatten out as furniture nicotine levels increased.

Vapor-Phase (Airborne) Nicotine

No airborne nicotine (<LOQ; approximately 0.04 μg/m^3) was detected.

Discussion

We replicated our foundational investigation of NICU-based THS contamination,[10] demonstrating that an overwhelming majority of bedside-NICU furniture surfaces were contaminated with nicotine and an overwhelming majority of NICU infants were exposed to nicotine during their hospitalizations. As hypothesized, greater finger and furniture nicotine and infant urine cotinine were associated with higher levels of participant-reported exposure to nicotine and/or personal nicotine use. Finger-nicotine contamination and infant exposure may be reduced, but not eliminated, by barrier methods (eg, gowning) and data on hand-cleaning practices yielded mixed findings. Clearly, more research is warranted to fully protect infants from THS exposure, particularly infants being visited by household members from nicotine-using homes.

Several infant variables (ie, infant age, birth weight, and length of stay) related to nicotine and cotinine outcomes in ways that are worth noting. Specifically, younger infants, infants earlier in their NICU stay, and smaller infants each tended to have greater levels of urine cotinine—potentially placing the most vulnerable infants at the greatest risk for exposure. It is possible that parents spend less time at infants' bedside (or visiting the NICU) as infant-hospitalization durations increase, thus reducing the nicotine contamination in the infants' rooms and reducing infants' nicotine exposure later in hospitalizations. Also, infants born at younger ages often have underdeveloped skin that may facilitate more dermal nicotine absorption.[43] NICU-based practitioners may wish to familiarize themselves with these data for understanding higher THS-exposure risks.

Passive air-nicotine monitors did not detect airborne nicotine in the NICU. It is possible that hanging air-nicotine monitors for longer periods, or using active nicotine monitors with a lower limit of detection (as in Matt et al.)[44], would detect nicotine. It is also possible that the ventilation in the NICU was sufficient to remove nicotine reemitted into the air from THS reservoirs and that the placement of monitors in different NICU locations (eg, individual patient rooms) may result in airborne-nicotine detection. It is noteworthy that field blanks obtained while sampling individuals from nicotine-using homes tended to have higher nicotine than nicotine-free participant blanks. This demonstrates how nicotine from clothing, skin, and other items may transport nicotine to a room, which then can contaminate a room as a gas or attach to surfaces and particles.

Although NICU infants from nicotine-using homes will ultimately be discharged from hospitals and reenter/enter homes contaminated with higher THS levels,[13] we believe that protecting medically fragile infants during extended hospitalizations must be a priority,[11,12] given the risks of nicotine/THS exposure,[1,3,4,10] during critical developmental stages (eg, respiratory development). Furthermore, while some infants may not exhibit immediate health consequences from acute THS exposure, few infants/children will remain unaffected by chronic THS exposure as repeated exposures may negatively impact the human microbiome[45] and contribute to cytotoxicity and genotoxicity,[6] in addition to other well-documented harms from environmental tobacco exposure.[46] Increasing THS/nicotine protective practices in the NICU may reduce these risks. Due to NICU infants' increased risks to be rehospitalized[47–49] and acquire respiratory infections,[50–52] especially in the first year of life, THS-related protections should extend beyond NICU hospitalizations to infants' homes.

A major conclusion of the 2020 Surgeon General's Report on Smoking Cessation was that only a third of individuals who quit each year have been offered US Food and Drug Administration-approved medications or behavioral counseling to quit. [53,54] NICU

hospitalizations offer a unique opportunity to connect young adults who smoke or use tobacco with tobacco-cessation resources during a time when parents are concerned about infant well-being.[55] This is a critical step to mitigate THS contamination in the hospital and home by potentially increasing parental tobacco cessation and reducing infant THS exposure. In other work, we demonstrated the potential efficacy for NICU families (with household members who smoke) to initiate nicotine replacement therapy (NRT) after receiving free nicotine patches and motivational advice, regardless of motivation to quit.[56] The latter study and similar "opt out" approaches (to address tobacco use with *all* infant caregivers) could have a significant impact to increase access to NRT and other evidence-based cessation medications and behavioral counseling, ultimately reducing THS-related harm to vulnerable infants. Innovative payer solutions may be needed since the infant is the patient but infant health is clearly affected by caregivers' harmful tobacco use.

The nicotine and cotinine levels we report should be given context to other environments and study samples. Finger-nicotine levels we reported for participants who live in nicotine-using homes were similar to values reported for smokers' fingers in past studies.[19] Finger-nicotine values for nicotine-free participants were comparable to nonsmokers in previous studies who stayed a night in a nonsmoking room in a hotel that completely bans smoking[31] and finger values of nonsmokers who moved into homes previously occupied by individuals who smoked.[19] Furniture-nicotine levels in the NICU were similar to surface-nicotine samples from inside rental cars,[44] to hotel rooms in hotels that ban smoking, and to the hallways outside nonsmoking rooms in hotels that permit smoking[31] but not as high as values observed in private homes[19] (eg, 1.67 μg/m^2 was the mean surface nicotine in homes of nonsmokers [who ban indoor smoking and live in multiunit housing][57]). Hospital settings would ideally have furniture-nicotine levels below those of hotels, even those with strictly enforced smoking bans. Effective cleaning methods to remove surface nicotine are not currently well characterized. A study attempting to clean THS-polluted, low-income homes found reductions in surface nicotine immediately following cleaning but levels rebounded within 3 months.[58] Further investigation is needed into safe and cost-effective methods for hospital cleaning to ensure THS-free surfaces.

Urine cotinine results for infants varied significantly by household type and infant sex. Infants from nicotine-free homes had levels similar to nonsmoking adults who stayed a night in nonsmoking hotel rooms. Infants from nicotine-using homes had levels similar to nonsmoking adults who stayed in nonsmoking rooms of hotels permitting smoking and also overlapped with values for nonsmoking adults who stayed in smoking rooms.[31] Infant cotinine fell below levels reported for infants who were sampled in nicotine-using homes after hospital discharge.[32,55] The cotinine similarity between NICU infants and adults from hotel rooms that *permit* smoking is concerning but not surprising. Adults and infants are likely to absorb THS compounds through dermal contact as demonstrated in animal models[59] and human-lab studies.[60] Preterm infants have underdeveloped skin[43] and infants/children (after adjusting for size) breathe a greater volume of air than adults, increasing infants' dermal absorption and inhalation of THS-related compounds.[18,61] Thus, preterm infants may more readily absorb and inhale THS compounds and absorb greater relative amounts than adults or larger children, potentially leading to greater metabolic stress, despite similarities between adults and newborns to metabolize cotinine in similar ways.[62] Some research with adults has demonstrated that women tend to have higher nicotine metabolism compared to men,[63–65] but others have reported no sex-based differences.[66,67] It is noteworthy that female infants tended to have significantly lower urine cotinine levels (relative to males), potentially demonstrating sex-based metabolic differences from an early age. We are cautious to draw firm conclusions given our small-to-moderate sample size as little has been published on preterm infant nicotine metabolism.

NICU administrators attempting to reduce the risk for harm may consider programs[55] and policies to limit exposure (eg, mandatory gowning/gloving by tobacco users) and increased attention to rigorous handwashing. Individuals (in the visitor phase) who reported greater tendencies to wash their hands had lower levels of finger nicotine. Furthermore, more frequent bedding laundering/changes may be warranted as nicotine has been shown to adsorb to pillows in the homes of former smokers.[68] Attempts to protect infants from THS exposure must not deter family visitation or interfere with infant bonding—common challenges faced by NICU families[16]—and ideally messages would be positively framed to parents/visitors as opportunities to learn about protective environmental tobacco-exposure practices and engage with tobacco cessation.[17,28,55,69]

This study contributed novel understanding to THS characterization in hospitals, and follow-on studies will improve on our methods. All observations were cross-sectional and repeated hospital measures (extending into homes after discharge) would show larger cumulative doses. Cumulative exposure is more likely to be the stimulus for harm. A frequent criticism of THS research is the difficulty in linking exposure to health-related harm but recent reviews demonstrate the mounting evidence for significant risk for harm.[3] Large-scale epidemiological studies are needed to add precision to the detection of disease from biological exposures. The influence of THS on the microbiota is a promising area of investigation with neonates as changes in the microbiome are linked to health problems: recent work has linked tobacco use with changes in the oral and gut microbiota in adults who smoke.[45] A strength of this research was the use of several objective measures of smoking and nicotine exposure; however, ENDS use was not bioverified with cotinine testing and many of the predictors (eg, reports of being near smoking/ENDS) used in our models were self-reported and subject to recall error/bias and may have contributed to some counterintuitive findings.

THS contamination in the NICU and infant THS exposure are not fully captured by small numbers of sampling periods. NICU infants should be viewed in the context of extended hospitalizations during which cumulative exposure may increase health risks. As hypothesized, contamination and exposure correlated with greater reports of nicotine use/exposure but all NICU infants face risks for THS exposure. This work clearly demonstrated a potential contamination pathway and exposure route (eg, dermal) from nicotine carried on hands and deposited on NICU furniture. Furthermore, infants are clearly being exposed to nicotine throughout their time in the NICU, despite smoke-free environments and prohibitions on tobacco/nicotine use. Our work highlights the potential risks from THS exposure to vulnerable infants during a critical stage of human development. Future challenges for this line of work will be to identify infants most at risk from exposure and implement protocols to best protect all infants.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

The authors have no competing interests to declare.

Author Contributions

TFN conceptualized and oversaw the study, interpreted data analytic results, and wrote the initial draft of the manuscript in consultation with ALS. RS and CG provided statistical expertise and wrote relevant data analytic and results sections of the manuscript. EH oversaw nicotine wipe and urine cotinine analyses and interpreted these results in consultation with PJEQ, MFH, and GEM. ALS, RS, AMK, CG, PJEQ, EH, MFH, and GEM were coinvestigators of the study and all authors provided edits and revisions on several drafts of the manuscript.

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References

1. Drehmer JE, Walters BH, Nabi-Burza E, Winickoff JP. Guidance for the clinical management of thirdhand smoke exposure in the child health care setting. *J Clin Outcomes Manag*. 2017;24(12):551–559.
2. Goniewicz ML, Lee L. Electronic cigarettes are a source of thirdhand exposure to nicotine. *Nicotine Tob Res*. 2015;17(2):256–258.
3. Hang B, Wang P, Zhao Y, et al. Adverse health effects of thirdhand smoke: from cell to animal models. *Int J Mol Sci*. 2017;18(5):932–939.
4. Díez-Izquierdo A, Cassanello-Peñarroya P, Lidón-Moyano C, Matilla-Santander N, Balaguer A, Martínez-Sánchez JM. Update on thirdhand smoke: a comprehensive systematic review. *Environ Res*. 2018;167:341–371.
5. Martins-Green M, Adhami N, Frankos M, et al. Cigarette smoke toxins deposited on surfaces: implications for human health. *PLoS One*. 2014;9(1):e86391.
6. Bahl V, Shim HJ, Jacob P III, Dias K, Schick SF, Talbot P. Thirdhand smoke: chemical dynamics, cytotoxicity, and genotoxicity in outdoor and indoor environments. *Toxicol In Vitro*. 2016;32:220–231.
7. Prins JM, Wang Y. Quantitative proteomic analysis revealed N'-nitrosonornicotine-induced down-regulation of nonmuscle myosin II and reduced cell migration in cultured human skin fibroblast cells. *J Proteome Res*. 2013;12(3):1282–1288.
8. Dhall S, Alamat R, Castro A, et al. Tobacco toxins deposited on surfaces (third hand smoke) impair wound healing. *Clin Sci (Lond)*. 2016;130(14):1269–1284.
9. Jung JW, Ju YS, Kang HR. Association between parental smoking behavior and children's respiratory morbidity: 5-year study in an urban city of South Korea. *Pediatr Pulmonol*. 2012;47(4):338–345.
10. Northrup TF, Khan AM, Jacob P III, et al. Thirdhand smoke contamination in hospital settings: assessing exposure risk for vulnerable paediatric patients. *Tob Control*. 2016;25(6):619–623.
11. Northrup TF, Stotts AL, Suchting R, et al. Medical staff contributions to thirdhand smoke contamination in a neonatal intensive care unit. *Tob Induc Dis*. 2019;17:37.
12. Northrup TF, Jacob P III, Benowitz NL, et al. Thirdhand smoke: state of the science and a call for policy expansion. *Public Health Rep*. 2016;131(2):233–238.
13. Northrup TF, Matt GE, Hovell MF, Khan AM, Stotts AL. Thirdhand smoke in the homes of medically fragile children: assessing the impact of indoor smoking levels and smoking bans. *Nicotine Tob Res*. 2016;18(5):1290–1298.
14. Ferrante G, Simoni M, Cibella F, et al. Third-hand smoke exposure and health hazards in children. *Monaldi Arch Chest Dis*. 2013;79(1):38–43.
15. Matt GE, Quintana PJ, Destaillats H, et al. Thirdhand tobacco smoke: emerging evidence and arguments for a multidisciplinary research agenda. *Environ Health Perspect*. 2011;119(9):1218–1226.
16. Northrup TF, Evans PW, Lillie ML, Tyson JE. A free parking trial to increase visitation and improve extremely low birth weight infant outcomes. *J Perinatol*. 2016;36(12):1112–1115.
17. Stotts AL, Green C, Northrup TF, et al. Feasibility and efficacy of an intervention to reduce secondhand smoke exposure among infants discharged from a neonatal intensive care unit. *J Perinatol*. 2013;33(10):811–816.
18. Jacob P III, Benowitz NL, Destaillats H, et al. Thirdhand smoke: new evidence, challenges, and future directions. *Chem Res Toxicol*. 2017;30(1):270–294.
19. Matt GE, Quintana PJ, Zakarian JM, et al. When smokers move out and non-smokers move in: residential thirdhand smoke pollution and exposure. *Tob Control*. 2011;20(1):e1.
20. Sleiman M, Gundel LA, Pankow JF, Jacob P III, Singer BC, Destaillats H. Formation of carcinogens indoors by surface-mediated reactions of nicotine with nitrous acid, leading to potential thirdhand smoke hazards. *Proc Natl Acad Sci USA*. 2010;107(15):6576–6581.
21. Xue J, Yang S, Seng S. Mechanisms of cancer induction by tobacco-specific NNK and NNN. *Cancers (Basel)*. 2014;6(2):1138–1156.
22. Singer BC, Hodgson AT, Nazaroff WW. Gas-phase organics in environmental tobacco smoke: 2. Exposure-relevant emission factors and indirect exposures from habitual smoking. *Atmos Environ.*. 2003;37(39–40):5551–5561.
23. Bekö G, Morrison G, Weschler CJ, et al. Dermal uptake of nicotine from air and clothing: experimental verification. *Indoor Air*. 2018;28(2):247–257.
24. Jacob P, Yu L, Duan M, Ramos L, Yturralde O, Benowitz NL. Determination of the nicotine metabolites cotinine and trans-3'-hydroxycotinine in biologic fluids of smokers and non-smokers using liquid chromatography–tandem mass spectrometry: biomarkers for tobacco smoke exposure and for phenotyping cytochrome P450 2A6 activity. *J Chromatogr B*. 2011;879(3):267–276.
25. Dixit S, Pletcher MJ, Vittinghoff E, et al. Secondhand smoke and atrial fibrillation: data from the Health eHeart Study. *Heart Rhythm*. 2016;13(1):3–9.
26. Edderkaoui M, Thrower E. Smoking and pancreatic disease. *J Cancer Ther*. 2013;4(10A):34–40.
27. Sleiman M, Logue JM, Luo W, Pankow JF, Gundel LA, Destaillats H. Inhalable constituents of thirdhand tobacco smoke: chemical characterization and health impact considerations. *Environ Sci Technol*. 2014;48(22):13093–13101.

28. Stotts AL, Northrup TF, Schmitz JM, et al. Baby's Breath II protocol development and design: a secondhand smoke exposure prevention program targeting infants discharged from a neonatal intensive care unit. *Contemp Clin Trials*. 2013;35(1):97–105.
29. Chatkin J, Fritscher L, de Abreu C, et al. Exhaled carbon monoxide as a marker for evaluating smoking abstinence in a Brazilian population sample. *Prim Care Respir J*. 2007;16(1):36–40.
30. Middleton ET, Morice AH. Breath carbon monoxide as an indication of smoking habit. *Chest*. 2000;117(3):758–763.
31. Matt GE, Quintana PJ, Fortmann AL, et al. Thirdhand smoke and exposure in California hotels: non-smoking rooms fail to protect non-smoking hotel guests from tobacco smoke exposure. *Tob Control*. 2014;23(3):264–272.
32. Matt GE, Quintana PJ, Hovell MF, et al. Households contaminated by environmental tobacco smoke: sources of infant exposures. *Tob Control*. 2004;13(1):29–37.
33. Quintana PJ, Matt GE, Chatfield D, Zakarian JM, Fortmann AL, Hoh E. Wipe sampling for nicotine as a marker of thirdhand tobacco smoke contamination on surfaces in homes, cars, and hotels. *Nicotine Tob Res*. 2013;15(9):1555–1563.
34. Matt GE, Quintana PJE, Hoh E, et al. A Casino goes smoke free: a longitudinal study of secondhand and thirdhand smoke pollution and exposure. *Tob Control*. 2018;27(6):643–649.
35. Leaderer BP, Hammond SK. Evaluation of a vapor-phase nicotine and respirable suspended particle mass as markers for environmental tobacco smoke. *Environ Sci Technol*. 1991;25(4):770–777.
36. Curwin BD, Hein MJ, Sanderson WT, Nishioka MG, Buhler W. Nicotine exposure and decontamination on tobacco harvesters' hands. *Ann Occup Hyg*. 2005;49(5):407–413.
37. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018. https://www.R-project.org. Accessed October 29, 2018.
38. Stan Development Team. RStan, the R interface to Stan. R package version 2.19.2; 2019. http://mc-stan.org/. Accessed December 11, 2019.
39. Bürkner P-C. Advanced Bayesian multilevel modeling with the R package brms *R J*. 2018;10(1):395–411.
40. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. *Bayesian Data Analysis*. Boca Raton, FL: Chapman and Hall/CRC; 2013.
41. McElreath R. *Statistical Rethinking: A Bayesian Course With Examples in R and Stan*. Boca Raton, FL: Chapman and Hall/CRC; 2018.
42. Suchting R, Yoon JH, Miguel GGS, et al. Preliminary examination of the orexin system on relapse-related factors in cocaine use disorder. *Brain Res*. 2020;1731:146359.
43. Shwayder T, Akland T. Neonatal skin barrier: structure, function, and disorders. *Dermatol Ther*. 2005;18(2):87–103.
44. Matt GE, Fortmann AL, Quintana PJ, et al. Towards smoke-free rental cars: an evaluation of voluntary smoking restrictions in California. *Tob Control*. 2013;22(3):201–207.
45. Stewart CJ, Auchtung TA, Ajami NJ, et al. Effects of tobacco smoke and electronic cigarette vapor exposure on the oral and gut microbiota in humans: a pilot study. *PeerJ*. 2018;6:e4693.
46. United States Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General*. Rockville, MD: Public Health Service, Office of the Surgeon General; 2014.
47. Underwood MA, Danielsen B, Gilbert WM. Cost, causes and rates of rehospitalization of preterm infants. *J Perinatol*. 2007;27(10):614–619.
48. Lamarche-Vadel A, Blondel B, Truffer P, et al.; EPIPAGE Study Group. Re-hospitalization in infants younger than 29 weeks' gestation in the EPIPAGE cohort. *Acta Paediatr*. 2004;93(10):1340–1345.
49. Morris BH, Gard CC, Kennedy K; NICHD Neonatal Research Network. Rehospitalization of extremely low birth weight (ELBW) infants: are there racial/ethnic disparities? *J Perinatol*. 2005;25(10):656–663.
50. Koumbourlis AC, Motoyama EK, Mutich RL, Mallory GB, Walczak SA, Fertal K. Longitudinal follow-up of lung function from childhood to adolescence in prematurely born patients with neonatal chronic lung disease. *Pediatr Pulmonol*. 1996;21(1):28–34.
51. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births: final data from 2003. *Natl Vital Stat Rep*. 2005;54(2):1–116.
52. Villamor-Martínez E, Pierro M, Cavallaro G, Mosca F, Villamor E. Mother's own milk and bronchopulmonary dysplasia: a systematic review and meta-analysis. *Front Pediatr*. 2019;7:224.
53. US Department of Health and Human Services. *Smoking Cessation: A Report of the Surgeon General*. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2020.
54. US Department of Health and Human Services. *Smoking Cessation: A Report of the Surgeon General—Executive Summary*. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 2020.
55. Stotts AL, Northrup TF, Green C, et al. Reducing tobacco smoke exposure in high risk infants: a randomized, controlled trial. *J Pediatr*. 2020;218:35–41.
56. Northrup TF, Suchting R, Klawans MR, et al. Proactive delivery of nicotine replacement therapy to families of hospitalized infants in a NICU: a randomized controlled pilot trial. *J Neonatal Nurs*. 2020;26(4):201–206.
57. Matt GE, Quintana PJ, Hoh E, et al. Persistent tobacco smoke residue in multiunit housing: legacy of permissive indoor smoking policies and challenges in the implementation of smoking bans. *Prev Med Rep*. 2020;18:101088.
58. Matt GE, Quintana PJ, Hoh E, Zakarian JM, Dodder NG, et al. Remediating thirdhand smoke pollution in multiunit housing: temporary reductions and the challenges of persistent reservoirs. *Nicotine Tob Res*. 2021;23(2):364–372. https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntaa151/5893285.
59. Jacob III P, Havel C, Yu L, et al. Determination of two metabolites of the tobacco-specific nitrosamine NNA (4-(methylnitrosamino)-4-(3-pyridyl) butanal) in mouse urine. Application to a dermal absorption study in mice. In: 20th Annual Meeting of the Society for Research on Nicotine and Tobacco, February 5-8, 2014; Seattle, WA.
60. Beko G, Morrison G, Weschler CJ, et al. Measurements of dermal uptake of nicotine directly from air and clothing. *Indoor Air*. 2017;27(2):427–433.
61. WHO Children's Health and the Environment. Children's health and the environment: WHO training package for the health sector; 2008. www.who.int/ceh/capacity/Children_are_not_little_adults.pdf. Accessed October 16, 2019.
62. Dempsey D, Jacob P, Benowitz NL. Nicotine metabolism and elimination kinetics in newborns. *Clin Pharmacol Ther*. 2000;67(5):458–465.
63. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob III P. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin Pharmacol Ther*. 2006;79(5):480–488.
64. Gan WQ, Cohen SB-Z, Man SP, Sin DD. Sex-related differences in serum cotinine concentrations in daily cigarette smokers. *Nicotine Tob Res*. 2008;10(8):1293–1300.
65. Chen A, Krebs NM, Zhu J, Sun D, Stennett A, Muscat JE. Sex/gender differences in cotinine levels among daily smokers in the Pennsylvania adult smoking study. *J Womens Health*. 2017;26(11):1222–1230.
66. Rubinstein ML, Shiffman S, Rait MA, Benowitz NL. Race, gender, and nicotine metabolism in adolescent smokers. *Nicotine Tob Res*. 2013;15(7):1311–1315.
67. Verplaetse TL, Peltier MR, Roberts W, Moore KE, Pittman BP, McKee SA. Associations between nicotine metabolite ratio and gender with transitions in cigarette smoking status and e-cigarette use: findings across waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) study. *Nicotine Tob Res*. 2020;22(8):1316–1321.
68. Matt GE, Hoh E, Quintana PJ, Zakarian JM, Arceo J. Cotton pillows: a novel field method for assessment of thirdhand smoke pollution. *Environ Res*. 2019;168:206–210.
69. Northrup TF, Green C, Evans PW, Stotts AL. Characteristics associated with intervention and follow-up attendance in a secondhand smoke exposure study for families of NICU infants. *J Matern Fetal Neonatal Med*. 2015;28(10):1208–1213.