Published in final edited form as:

J Pediatr. 2011 November ; 159(5): 776–782. doi:10.1016/j.jpeds.2011.04.025.

A Comparison of Biomarkers and Parent Report of Tobacco Exposure to Predict Wheeze

Adam J. Spanier, MD, PhD, MPH¹, Robert S. Kahn, MD, MPH², Yingying Xu, MS², Richard Hornung, DrPH², and Bruce P. Lanphear, MD, MPH^{2,3}

¹Department of Pediatrics, Penn State University Hershey Medical Center, Cincinnati, Ohio

²Division of General & Community Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

³Child and Family Research Institute, BC Children's Hospital and Faculty of Health Sciences, Simon Fraser University, Vancouver, Canada

Abstract

Objective—To identify the optimal measure of active and passive prenatal tobacco exposure to predict wheeze in early life.

Study design—Birth cohort of 398 mother-infant dyads enrolled during the second trimester of pregnancy and followed through age two. We measured tobacco exposure by maternal report, serum cotinine, and meconium cotinine. We assessed wheeze by parent report every six months. We used a repeated measures logistic regression model.

Results—Of 367 children with respiratory data, 26% percent had parent reported active or passive prenatal maternal tobacco exposure, but cotinine was detected in 61% of mothers during pregnancy. Compared with children of mothers in the 5th percentile of tobacco exposure, children of mothers in the 95th percentile had increased odds of wheeze when exposure was measured by maternal serum cotinine (AOR=2.6, 95% CI 1.3 – 5.2, p<0.006) versus meconium cotinine (AOR=2.0, 95% CI 1.0 – 4.0, p=0.04) and total parent reported exposure (AOR=1.7, 95% CI 1.1 – 2.7, p=0.01).

Conclusions—Serum cotinine, a biomarker of tobacco exposure, was more strongly associated with wheeze than parent reported exposure. Studies that rely on parent report of prenatal tobacco exposure may underestimate risk of wheeze.

Keywords

wheeze; cotinine; prenatal; tobacco

Prenatal tobacco exposure is a major risk factor for asthma.^{1, 2} Most studies examining the relationship of prenatal tobacco exposure with asthma or childhood wheeze have relied on parent report or focused on active maternal smoking. Only 10% of women report smoking

© 2011 Mosby, Inc. All rights reserved.

Corresponding Author: Adam Spanier, Department of Pediatrics, Mail Code HS83, Penn State University, Hershey Medical Center, 500 University Drive, P.O. Box 850, Hershey, PA 17033-0850, Phone: (717) 531-8006, Fax: (717) 531-0869, aspanier@hmc.psu.edu .

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare no conflicts of interest.

during pregnancy, but over half of US children are exposed to second hand tobacco smoke before birth.³⁻⁵ The optimal measure of any prenatal tobacco exposure is unknown.

Current smoking rates do not account for underreporting or secondhand smoke exposure.³⁻⁵ Several investigators have found that when objective biomarkers of second hand exposure, such as serum cotinine, are used, the proportion of individuals with detectable exposure is significantly higher.⁴⁻⁶ In one study, the prevalence of active smoking by pregnant mothers was estimated to be 19% based on self-report, but it increased to 31% using serum cotinine.⁵ Pirkle et al showed that 88% of women of childbearing age who reported no smoking had a detectable level of serum cotinine.⁶ This suggests that *in utero* tobacco exposures may be unrecognized or underreported when relying on self-report or parent-report.

There is considerable evidence implicating prenatal tobacco exposure as a risk factor for respiratory infections, wheeze, and decreased pulmonary function in children.⁷⁻¹⁵ Even though most studies explored prenatal exposure with self reported data or serum cotinine, Nuesslein et al found that meconium cotinine above the median was associated with a 12.5 fold odds (95% CI 1.9-82.4) of respiratory infection in the first six months of life; in contrast, reported exposure was not associated.¹⁵ Questions remain about the optimal measures for examining the relationship of prenatal tobacco exposure with child wheeze.¹⁶ The objective of this project was to characterize the relationship of prenatal active and passive tobacco exposure with wheeze in early childhood to determine the optimal measure of prenatal tobacco exposure to predict wheeze.

Methods

We used data from the Health Outcomes and Measures of the Environment (HOME) Study. The HOME Study is a prospective birth cohort study designed to investigate the effects of prenatal and postnatal exposure to environmental toxicants on the development and behaviors of children. The HOME Study enrolled 468 English-speaking women at 16 ($\pm$ 2 weeks) gestation who were 18 years of age or older and lived in a home built before 1979. Women were followed through pregnancy, and their children are still being followed. Women had to reside within five Ohio counties surrounding Cincinnati, receive prenatal care from a participating obstetrical clinic (8), and deliver at a participating hospital (3). Women were ineligible if they were HIV positive, taking anti-epileptic medication, on chemotherapy, diabetic (not gestational), had bipolar disorder, or had schizophrenia. Infants born to participating mothers were eligible for the longitudinal study which included an embedded randomized control trial of a lead hazard reduction intervention and injury hazard reduction control. HOME Study participants delivered 398 live-born infants (randomly excluding one child for twin births), and respiratory data was available for 367 children (92%), who were included in this analysis. The institutional review boards of Cincinnati Children's Hospital Medical Center and the involved hospitals approved the HOME Study and this project.

Exposure Assessment

We quantified exposure by surveys and biomarkers. We collected maternal serum at enrollment (~16 weeks gestation: 15.9 ± 1.9 weeks), 26 weeks gestation and birth. We also obtained newborn meconium. Meconium was collected from infants using cellulose fiber inserts placed in infant diapers. Once soiled, the diaper and insert were stored in a plastic bag in a designated hospital refrigerator until collected by study staff, usually within 24 hours.¹⁷ Cotinine, a metabolite of nicotine, was measured in serum and meconium. Analyses of serum cotinine and meconium cotinine were performed in the Division of Laboratory Science at the Centers for Disease Control and Prevention using high-performance liquid chromatography (HPLC) / atmospheric-pressure ionization tandem mass spectrometry (MS)

and HPLC-MS/MS.^{15, 17-19} Serum and meconium cotinine limits of detection were 0.015 ng/mL and 0.07 ng/g respectively. Child serum was collected annually starting at age one. The tobacco exposure surveys were based on a previously validated survey to estimate second hand smoke exposure accounting for exposure in terms of number of cigarettes smoked per day.²⁰ We collected other environmental exposure information by survey.

Outcome Measure

The primary outcome, wheeze, was collected every six months through age two years using parent-reported surveys. The primary question was based on National Health and Nutrition Examination Survey (NHANES) questions.²¹ We asked, “Has (child) had wheezing or whistling in his/her chest in the last 6 months?” We also asked about the number of wheeze attacks. We dichotomized the reported wheeze variable at each time point (no wheeze vs. any wheeze) to minimize effects of extreme values and recall bias.

Covariates

Extensive surveys were conducted by trained research assistants to collect data on potential covariates including demographic characteristics, socioeconomic status, health status, and others. Surveys were conducted at baseline and every 6 months after the child was born. Demographic and socioeconomic characteristics such as maternal education, race, occupation, income, housing volume, and health insurance status were considered as possible covariates in all models. We accounted for factors associated with wheeze by considering them as possible covariates (e.g. season, daycare attendance, history and duration of breastfeeding, family history of asthma, family history of allergy, participant eczema, participant allergy, neonatal characteristics, pet ownership, and cockroach exposure).^{1, 22-27} We also collected postnatal tobacco exposure data (child serum cotinine) for consideration as a covariate.

Statistical Analysis

We first calculated descriptive statistics and made comparisons between the participants with and without respiratory data using t-tests and Chi square tests. We produced arithmetic and geometric means, arithmetic and geometric standard deviations, and ranges for variables measured. Because cotinine data are approximately log-normal, we log-transformed all cotinine data, and we used the geometric mean and geometric standard deviation as the primary descriptors of central tendency and dispersion. When cotinine values were below the limit of detection, we imputed values by sampling randomly from the left tail of a lognormal distribution. For ease of comparing effect sizes, we calculated the difference in odds of wheeze by comparing children in the 95th percentile of prenatal tobacco exposure with children in the 5th percentile of exposure.

Our primary predictor variables were mean prenatal maternal serum cotinine (16 weeks, 26 weeks, and birth), meconium cotinine, and reported prenatal tobacco exposure. For parent reported prenatal tobacco exposure, we performed three separate analyses: (1) reported number of cigarettes smoked per day by mom alone (active), (2) the sum of reported number of cigarettes smoked per day by mom (active) and by other household members (passive), and (3) reported active and passive exposure as two separate, equally weighted variables in the same model. We analyzed the dichotomous outcome variable (wheeze) with a repeated measures logistic regression. We first conducted univariable repeated measures analysis to evaluate the association of the different prenatal tobacco smoke exposure measures and potential covariates with wheeze. After univariable analysis, we conducted a multivariable repeated measures analysis considering potential covariates. In the initial multivariable model, we included covariates that had a p value ≤ 0.2 in univariable analysis. We used backward elimination techniques for variable reductions. Covariates were retained in the

analysis if they were significant or if removal caused a greater than 10% change in the estimate for prenatal tobacco exposure. In all analyses, we included a variable for survey point (6, 12, 18, or 24 months) and for intervention arm to account for any potential design effects of the embedded trial. We employed the standard two sided 5% level to determine statistical significance. SAS Version 9.2 (SAS Institute, Inc., Cary, NC) was used for all data analyses.

Results

Participants for whom data was available were more likely to be White, have a mother with more than a high school education, have private insurance, live in non-urban environment, have married parents, have an older mother, have a higher income, have reportedly less prenatal tobacco exposure, and have lower maternal mean prenatal cotinine (Table I).

Twelve percent of mothers reported active exposure, and 26% reported active or passive exposure (Table I). Cotinine was detectible in 68.6% of 16 week maternal serum samples and in over half of the samples at other prenatal time points (Table II). Cotinine was detectible in an even higher percentage of child serum samples; the mean serum cotinine concentrations were higher in child than maternal serum cotinine (Table II). Cotinine concentrations in serum and meconium were significantly correlated, (Pearson's $r=0.49$ to 0.94 , Table III). Prenatal maternal serum cotinine at each time point was more closely correlated with the other prenatal serum cotinine and meconium biomarkers than with reported exposure.

By age two, 44.9% of children had wheezed at least once. In the first six month period 18.5% of the children had at least one reported wheeze episode, in the second six month period (age six to twelve months) 22.3% had at least one wheeze episode, in the third six month period (age twelve to eighteen months) 19.3% had at least one wheeze episode, and in the fourth six month period (age eighteen to twenty-four months) 15.3% had at least one wheeze episode. The mean number of wheeze episodes was 0.5 from birth to six months, 0.7 from six months to 12 months, 0.5 from 12 months to 18 months, and 0.6 from 18 months to 24 months of age.

In bivariate analysis of tobacco exposure, there was an association of 16 week maternal serum cotinine, 26 week maternal serum cotinine, birth maternal serum cotinine, mean maternal serum cotinine, reported active prenatal smoke exposure, and reported total (active plus passive) tobacco exposure with wheeze (Table IV). There was no association of cord serum cotinine, meconium cotinine, or child serum cotinine with wheeze (Table IV). When the two variables, reported active exposure and reported passive exposure, were included in the same analysis there was no association of either with wheeze.

In bivariate analysis of potential covariates, there was an association of maternal allergy, maternal asthma, home density (house volume/ child), and season with wheeze. There was no association of sex, maternal race, gestational age, breastfeeding duration, reported cat exposure, reported dog exposure, reported cockroach exposure, reported paternal allergy, reported paternal asthma, reported child allergy, or daycare exposure with wheeze.

In multivariable analysis, we found a 2.6 fold increase in odds of wheeze for children born to mothers in the 95th percentile of mean prenatal maternal serum cotinine compared with children born to mothers in the 5th percentile (AOR=2.61, 95% CI 1.31 – 5.19, $p<0.006$, Table IV) and a 2.0 fold increase in odds of wheeze for children born to mothers in the 95th percentile of meconium cotinine compared with children born to mothers in the 5th percentile (AOR 2.04, 95% CI 1.03 – 4.06, $p=0.04$). We analyzed reported prenatal tobacco exposure in three separate ways. First, we found a 2.0 fold increase in odds of wheeze for

children born to mothers in the 95th percentile of reported active exposure compared with children born to mothers in the 5th percentile (AOR=2.0, 95% CI 1.18 – 3.4, p=0.01). Second, for the sum of reported active maternal tobacco smoking and reported passive (other household members) tobacco smoking we found a 1.7 fold increase in odds of wheeze for children born to mothers in the 95th percentile of reported total exposure compared with children born to mothers in the 5th percentile (AOR=1.73, 95% CI 1.13 – 2.66, p=0.01). Third, we evaluated reported active and passive exposure as separate variables with equal weight in the same analysis and found that the associations were attenuated (reported active smoking p=0.07 and reported passive tobacco smoking p=0.34). We did not find any significant interactions for cotinine with maternal race or season.

In secondary analysis, we examined timing of exposure by using the maternal serum cotinine level measured at different times during pregnancy. In the adjusted analysis of 16 week maternal serum cotinine, we found a 2.8 fold increase in odds of wheeze for children born to mothers in the 95th percentile of reported total exposure compared with children born to mothers in the 5th percentile (AOR=2.83, 95% CI 1.31 – 6.14, p=0.009). The findings were similar for the analysis of 26 week maternal serum cotinine (AOR=2.65, 95% CI 1.30 – 5.39, p=0.008) and birth maternal serum cotinine (AOR=2.52, 95% CI 1.15 – 5.52, p=0.02).

In other secondary analyses we examined the association of childhood exposure with wheeze. In a multivariable analysis without prenatal tobacco exposure, we found that postnatal child serum cotinine was not associated with wheeze. We found a 1.6 fold increase in odds of wheeze for children in the 95th percentile of serum cotinine compared with children in the 5th percentile (AOR=1.58, 95% CI 0.77 – 3.24, p=0.21).

Discussion

Only 26% of mothers in this cohort reported active or passive tobacco exposure, but over 60% had measurable levels of exposure using serum cotinine. Thus, many pregnant women may not recognize or may underreport tobacco exposure. This exposure can have important health effects for the mother as well as the fetus. We found that higher levels of prenatal tobacco exposure were associated with increased odds of wheeze in children during the first two years after birth; however, the magnitude of this relationship would have been underestimated if we had not incorporated biologic measures of exposure.

Consistent with other research, we found that biomarkers of prenatal tobacco exposure measures at each time point were more highly correlated with each other than with parent reported exposure.²⁸ Child serum cotinine levels were also correlated with prenatal measures, but the correlation was not as high as the correlation of prenatal biomarkers was with the other prenatal biomarkers. This may reflect that there is more variation of exposure in early childhood.

Our data indicates that prenatal tobacco exposure is underestimated by using maternal report. Social desirability might have affected the report of exposure, but the levels of reported active smoking are similar to levels reported in other representative studies at the time of study enrollment.^{29, 30} This suggests that a large part of the difference between reported and measurable exposure is due to under-recognized smoke exposure. Thus, reliance on maternal report of exposure will result in greater exposure misclassification than biomarkers of exposure.^{5, 31, 32} Although measureable exposure does not necessarily equate to clinical effect, we found that exposure measured using serum cotinine was more strongly associated with wheeze than parent reported exposure. In epidemiologic studies it is

important to account for all exposure, and this is especially important given the mounting evidence of the association of lower levels of smoke exposure with adverse health effects.

All three measures of prenatal maternal serum cotinine were associated with increased odds of wheeze in early childhood. Cotinine from the earlier trimesters of pregnancy demonstrated higher odds of wheeze, but all time points were comparable, suggesting that there may not be a singular window of prenatal vulnerability. In contrast, we didn't find an association of postnatal exposure with wheeze. Most studies which have explored the role of prenatal vs. postnatal tobacco have noted stronger effects of prenatal exposure. Investigators from the Tucson Children's Respiratory Study reported findings similar to ours.³³ Tager et al, noted that prenatal tobacco exposure had a greater effect than postnatal exposure on lung function in children.¹³ In larger cohort studies, Pattenden et al and Haberg et al both reported that both pre and postnatal parental smoking was associated with poorer child respiratory health outcomes, but the effect of prenatal exposure was stronger.^{34, 35} It remains challenging to separate out the roles of prenatal and postnatal tobacco exposure because most women who smoke during pregnancy continue to smoke in the postnatal period, and household member smoking patterns do not usually vary over a similar timeframe.

We found that maternal serum cotinine, a biomarker of prenatal tobacco exposure was more strongly associated with wheeze than parent-reported exposure. The association of parent reported exposure with wheeze varied depending on which exposure measure we evaluated. Maternal reported number of cigarettes smoked per day alone (without passive exposure) was the best of our three approaches for evaluating the association of reported prenatal tobacco exposure with wheeze. The problem with this approach, however, is that it assumes that active maternal smoking and passive maternal exposure convey equal hazard to the fetus.

There are several limitations to this study. First, wheeze was based on parent report and could have been under or over-reported by parents. Second, there is no validated method to combine reported active and passive exposure to account for potential effects of each exposure. For this reason, we evaluated the sum of reported active and passive exposure, as well as, the variables independently. Although the combined variable was associated with wheeze, it was weaker than serum cotinine. A third limitation is the HOME Study was not a random sample. Finally, our sample was limited by differential attrition; minority, low-income families were less likely to continue participation. Still, the levels of exposure in this sample are comparable with national levels suggesting that the results from this study are relevant for many children.

Using serum cotinine, a biomarker of tobacco exposure, we found that many pregnant women underestimate tobacco exposure that was associated with increased odds of wheeze in early childhood. We also found that serum cotinine was more strongly associated with wheeze in children than meconium cotinine or parent reported exposure. We found that a single measure of cotinine may be sufficient for studies evaluating wheeze, but studies of the respiratory effects of prenatal tobacco exposure that do not use biologic measures may underestimate the impact of prenatal tobacco exposure on wheeze in childhood.

Acknowledgments

Supported by Flight Attendant Medical Research Foundation Young Clinical Scientist Award, NIEHS 1K23ES016304, and NIEHS PO1ES11261.

Abbreviations

AOR	Adjusted Odds Ratio
CI	Confidence Interval
HOME	Health Outcomes and Measures of the Environment
NHANES	National Health and Nutrition Examination Survey

References

1. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr*. 2003; 143:S118–26. [PubMed: 14615710]
2. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis*. 2002; 2:25–32. [PubMed: 11892493]
3. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Kirmeyer S, et al. Births: Final data for 2007. *National vital statistics reports*. 2010; 58
4. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; Atlanta, GA: 2006.
5. Ford RP, Tappin DM, Schluter PJ, Wild CJ. Smoking during pregnancy: how reliable are maternal self reports in New Zealand? *J Epidemiol Community Health*. 1997; 51:246–51. [PubMed: 9229052]
6. Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR. Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. *Jama*. 1996; 275:1233–40. [PubMed: 8601954]
7. Mannino DM, Moorman JE, Kingsley B, Rose D, Repace J. Health effects related to environmental tobacco smoke exposure in children in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Med*. 2001; 155:36–41. [PubMed: 11177060]
8. Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD. The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics*. 1998; 101:E8. [PubMed: 9445518]
9. Sekhon HS, Keller JA, Benowitz NL, Spindel ER. Prenatal nicotine exposure alters pulmonary function in newborn rhesus monkeys. *Am J Respir Crit Care Med*. 2001; 164:989–94. [PubMed: 11587984]
10. Sekhon HS, Keller JA, Proskocil BJ, Martin EL, Spindel ER. Maternal nicotine exposure upregulates collagen gene expression in fetal monkey lung. Association with alpha7 nicotinic acetylcholine receptors. *Am J Respir Cell Mol Biol*. 2002; 26:31–41. [PubMed: 11751201]
11. Wang NS, Chen MF, Schraufnagel DE, Yao YT. The cumulative scanning electron microscopic changes in baby mouse lungs following prenatal and postnatal exposures to nicotine. *J Pathol*. 1984; 144:89–100. [PubMed: 6491836]
12. Chen MF, Kimizuka G, Wang NS. Human fetal lung changes associated with maternal smoking during pregnancy. *Pediatr Pulmonol*. 1987; 3:51–8. [PubMed: 3588051]
13. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy. Effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med*. 1995; 152:977–83. [PubMed: 7663813]
14. Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax*. 2000; 55:271–6. [PubMed: 10722765]
15. Nuesslein TG, Beckers D, Rieger CH. Cotinine in meconium indicates risk for early respiratory tract infections. *Hum Exp Toxicol*. 1999; 18:283–90. [PubMed: 10333316]

16. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics*. 2004; 113:1007–15. [PubMed: 15060193]
17. Braun JM, Daniels JL, Poole C, Olshan AF, Hornung R, Bernert JT, et al. A prospective cohort study of biomarkers of prenatal tobacco smoke exposure: the correlation between serum and meconium and their association with infant birth weight. *Environ Health*. 2010; 9:53. [PubMed: 20799929]
18. Bernert JT Jr. Turner WE, Pirkle JL, Sosnoff CS, Akins JR, Waldrep MK, et al. Development and validation of sensitive method for determination of serum cotinine in smokers and nonsmokers by liquid chromatography/atmospheric pressure ionization tandem mass spectrometry. *Clin Chem*. 1997; 43:2281–91. [PubMed: 9439445]
19. Bernert JT Jr. McGuffey JE, Morrison MA, Pirkle JL. Comparison of serum and salivary cotinine measurements by a sensitive high-performance liquid chromatography-tandem mass spectrometry method as an indicator of exposure to tobacco smoke among smokers and nonsmokers. *J Anal Toxicol*. 2000; 24:333–9. [PubMed: 10926356]
20. Coghlin J, Hammond SK, Gann PH. Development of epidemiologic tools for measuring environmental tobacco smoke exposure. *Am J Epidemiol*. 1989; 130:696–704. [PubMed: 2773917]
21. U.S. Department of Health and Human Services. Public Health Service, Centers for Disease Control and Prevention, National Center for Health Statistics. Vital and Health Statistics: Plan and Operation of the Third National Health and Nutrition Examination Survey 1988-94. http://www.cdc.gov/nchs/data/series/sr_01/sr01_032.pdf
22. Oddy WH, Peat JK, de Klerk NH. Maternal asthma, infant feeding, and the risk of asthma in childhood. *J Allergy Clin Immunol*. 2002; 110:65–7. [PubMed: 12110822]
23. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med*. 2000; 343:538–43. [PubMed: 10954761]
24. Young S, Sherrill DL, Arnott J, Diepeveen D, LeSouef PN, Landau LI. Parental factors affecting respiratory function during the first year of life. *Pediatr Pulmonol*. 2000; 29:331–40. [PubMed: 10790244]
25. Fleming DW, Cochi SL, Hightower AW, Broome CV. Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance? *Pediatrics*. 1987; 79:55–60. [PubMed: 3797171]
26. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med*. 1999; 160:227–36. [PubMed: 10390405]
27. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol*. 2003; 111:661–75. quiz 76. [PubMed: 12704342]
28. Wu FY, Chiu HT, Wu HD, Lin CJ, Lai JS, Kuo HW. Comparison of urinary and plasma cotinine levels during the three trimesters of pregnancy. *Paediatr Perinat Epidemiol*. 2008; 22:296–301. [PubMed: 18426525]
29. Martin JA, Kochanek KD, Strobino DM, Guyer B, MacDorman MF. Annual summary of vital statistics--2003. *Pediatrics*. 2005; 115:619–34. [PubMed: 15741364]
30. Centers for Disease Control and Prevention. Smoking during pregnancy--United States, 1990-2002. *MMWR Morb Mortal Wkly Rep*. 2004; 53:911–5. [PubMed: 15470322]
31. Jedrychowski W, Whyatt RM, Cooper TB, Flak E, Perera FP. Exposure misclassification error in studies on prenatal effects of tobacco smoking in pregnancy and the birth weight of children. *J Expo Anal Environ Epidemiol*. 1998; 8:347–57. [PubMed: 9679216]
32. England LJ, Grauman A, Qian C, Wilkins DG, Schisterman EF, Yu KF, et al. Misclassification of maternal smoking status and its effects on an epidemiologic study of pregnancy outcomes. *Nicotine Tob Res*. 2007; 9:1005–13. [PubMed: 17852766]

33. Stein RT, Holberg CJ, Sherrill D, Wright AL, Morgan WJ, Taussig L, et al. Influence of parental smoking on respiratory symptoms during the first decade of life: the Tucson Children's Respiratory Study. *Am J Epidemiol.* 1999; 149:1030–7. [PubMed: 10355379]
34. Pattenden S, Antova T, Neuberger M, Nikiforov B, De Sario M, Grize L, et al. Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure. *Tob Control.* 2006; 15:294–301. [PubMed: 16885578]
35. Haberg SE, Stigum H, Nystad W, Nafstad P. Effects of pre- and postnatal exposure to parental smoking on early childhood respiratory health. *Am J Epidemiol.* 2007; 166:679–86. [PubMed: 17625224]

Table I**Characteristics and Exposures of Study Participants**

	Included N (%)	Excluded N (%)	P Value
Number of participants	367 (92)	31 (8)	-
Male	164 (44.7)	17 (54.8)	<0.01
Race			
White	240 (65.4)	4 (12.9)	<0.01
Black	104 (28.3)	17 (54.8)	
Other	23 (6.3)	4 (12.9)	
Not identified	--	6 (19.4)	
Maternal Education (high school or less)	78 (21.3)	17 (54.8)	<0.01
Marital Status			
Married	250 (68.1)	6 (19.4)	<0.01
Not married, living with partner	46 (12.5)	10 (32.2)	
Not married, living alone	71 (19.3)	9 (29.0)	
Not known		6 (19.4)	
Household income			
<\$25,000	88 (24.0)	14 (45.2)	
\$25,000 - \$50,000	78 (21.3)	6 (19.4)	<0.01
\$50,000 - \$80,000	92 (25.1)	0 (0)	
>\$80,000	102 (27.8)	3 (9.6)	
Unsure	7 (1.9)	8 (25.8)	
Residence			
Rural	12 (3.3)	1 (3.2)	<0.01
Suburban	135 (36.8)	4 (12.9)	
Urban	220 (59.9)	26 (83.9)	
Maternal Age at Delivery, years (mean $\pm$ standard deviation)	29.7 $\pm$ 5.7	24.6 $\pm$ 5.2	<0.01
Gestational Age, weeks (mean $\pm$ standard deviation)	39 $\pm$ 1.7	37.9 $\pm$ 2.9	0.06
Reported Prenatal Tobacco Exposure			
No exposure	272 (74.1)	17 (54.8)	0.03
Any exposure	95 (25.9)	14 (45.2)	
Maternal Smoking (active)	44 (12.0)	5 (16.1)	
Household Member Smoking (passive)	81 (22.1)	11 (35.5)	
Active and Passive	30 (8.2)	2 (6.5)	
Mean Maternal Serum Cotinine (mean of prenatal levels, ng/mL) (geometric mean, 95% confidence interval)	0.096 (0.0005, 17.7)	1.68 (0.006, 510.9)	<0.01

Table II

Tobacco Exposure levels of the Study Participants

	N	Geometric Mean	Range	Difference between the 95 th and 5 th Exposure Percentile $\diamond$	N >LOD	% >LOD
16 week maternal serum cotinine	355	0.05	LOD* – 388	62.1	240	67.6
26 week maternal serum cotinine	350	0.03	LOD* – 252	55.4	207	59.1
Birth maternal serum cotinine	326	0.03	LOD* – 323	29.1	185	56.7
Birth cord serum cotinine	273	0.02	LOD* – 261	19.0	139	50.9
Mean maternal serum cotinine (16 wk, 26 wk, birth)	367	0.06	LOD* – 356	41.6	225	61.3
Meconium cotinine	328	0.20	LOD [†] – 314	31.7	223	68.0
Reported Maternal Smoking (Active) [‡]	367	0.02	0 – 20	4	44**	12.0**
Reported Total Exposure (Active + Passive) [‡]	367	0.05	0 – 66	25	95**	25.9**
Reported Exposure [‡]						
Active (Mother)	367	0.02	0 – 20	4	44**	12.0**
Passive (Other)	367	0.04	0 – 66	20	81**	22.1**
Child 12 month serum cotinine	275	0.09	LOD* – 35.3	3.89	239	86.9
Child 24 month serum cotinine	206	0.07	LOD* – 10.5	3.04	176	85.4

$\diamond$ The difference between the value for children in 95th percentile of exposure for the given measure and children in the 95th percentile of exposure using imputed values for cotinine below the LOD

* Limit of detection (LOD) for serum cotinine 0.015 ng/mL

[†] LOD for meconium cotinine 0.07 ng/g

[‡] Number of cigarettes per day

*** Number or percent with greater than zero cigarettes per day reported

Table III

Correlation of Tobacco Exposure Measures: Cotinine and Reported Exposure

	26-week Maternal Serum Cotinine	Birth Maternal Serum Cotinine*	Mean Maternal Serum Cotinine (16wk, 26wk, birth)	Meconium Cotinine*	12-month Child Serum Cotinine*	24-month Child Serum Cotinine*	Reported Maternal Cigarettes Smoked/day [†]	Reported Other Cigarettes Smoked/day [†]	Total Reported Cigarettes Smoked/day [†]
16-week maternal serum cotinine*	0.82	0.82	0.94	0.66	0.70	0.69	0.45	0.46	0.55
26-week maternal serum cotinine*		0.80	0.92	0.60	0.67	0.67	0.41	0.42	0.50
Birth maternal serum cotinine*			0.91	0.67	0.70	0.69	0.45	0.43	0.53
Mean maternal serum cotinine (16wk, 26wk, birth)*				0.70	0.73	0.73	0.46	0.45	0.54
Meconium cotinine*					0.49	0.52	0.37	0.30	0.40
12-month child serum cotinine*						0.80	0.33	0.40	0.47
24-month child serum cotinine*							0.39	0.37	0.46
Reported maternal cigarettes smoked/day (active) [†]								0.43	0.63
Reported other cigarettes smoked/day (passive) [†]									0.92

* Pearson Correlation Coefficients

[†] Spearman Correlation Coefficients

Unadjusted and Adjusted Associations of Tobacco Exposure with Wheeze

 t_i = Number of cigarettes per day