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Prenatal exposure to pesticide ingredient piperonyl butoxide and childhood cough in an urban cohort

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Abstract

Rationale—Previously we reported that airborne concentrations of *cis*-permethrin, but not *trans*-permethrin, measured during pregnancy in an inner city pediatric cohort was associated with cough by age 5. However, the effect of subsequent exposures to both permethrins during early childhood, and to piperonyl butoxide (PBO, a synergist for residential pyrethroid insecticides) remains to be elucidated. We hypothesized that prenatal and age 5-6 year measures of PBO and permethrins would be associated with cough at age 5-6 years in this cohort. Further, we explored the associations between these pesticides measures and wheeze, asthma, seroatopy, and fractional exhaled nitric oxide (FeNO).

Methods—PBO and permethrins were measured in personal air during the third trimester of pregnancy and indoor residential air at age 5-6 years (n=224). Health outcome questionnaires were

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administered to the mothers of 5-6 years old children. Indoor allergen specific and total immunoglobulin (Ig) E production was measured from sera collected at age 5, and FeNO was measured at 5-6 years. The hypotheses were tested using regression models adjusting for common confounders.

Results—Noninfectious cough was reported among 14% of children at age 5-6 years. Measures of prenatal PBO, but not age 5-6 year PBO or permethrins, increased the odds of cough [OR (95% CI): 1.27 (1.09-1.48), $p < 0.01$; $n = 217$]. No significant associations were found for other measured health outcomes.

Conclusions—Prenatal PBO exposure was associated with childhood cough. It is unclear whether the observed effect is due mainly to PBO itself or residential pyrethroids of which PBO is an indicator.

Keywords

prenatal pesticide exposure; cough; piperonyl butoxide; permethrin

1. Introduction

Cough continues to be one of the most common complaints for which patients seek medical attention and spend health care money (Irwin et al., 1998; US CDC 2012). For children under 5 years, conditions related to cold, cough, and runny nose accounted for 10% of the ambulatory care visits during 1993-1995 in data collected from the National Health Survey (Freid et al., 1998). Prenatal and early childhood exposure to both ambient and indoor air pollutants has been linked to pediatric respiratory disease including cough (Miller et al., 2004; Patel et al., 2009), wheeze (Patel et al., 2009), and asthma (Fedulov et al., 2008; Gergen et al., 1998; Rosa et al., 2011). The contributions of other common environmental exposure such as residential pesticides to the development of these disorders are not as well described.

With the phase-out of organophosphates in US homes (Horton et al., 2011a; US EPA 2000, 2001), pyrethroids have been used increasingly more commonly in residential settings, particularly for pest control. In the Columbia Center for Children's Environmental Health (CCCEH) birth cohort, following the phase-out, pyrethroids were the most common active insecticide ingredients used in both professional and non-professional pest controls, and permethrin was the most common pyrethroid type used (Horton et al., 2011a). Permethrin is also the most frequently detected pesticide in residential floor wipe samples measured nationwide (Stout et al., 2009). Given the pervasiveness of this exposure, it is important to understand the potential health impact on children resulting from long-term low-level residential pyrethroid use.

Despite these concerns, the effects of pyrethroid exposure on pediatric respiratory health have not been well-studied. In one of the few studies, exposure to permethrin in occupational/agricultural settings was associated with asthma (Hoppin et al., 2008) and wheeze in farmers (Hoppin et al., 2002). In addition, few cohort studies have measured airborne pyrethroid levels as indicators of respiratory exposure, and instead relied on surrogate measures detected from questionnaires (Salam et al., 2004) or considered urine metabolites that may detect exposures from other routes (Heudorf and Angerer 2001; Lu et al., 2006).

Our previous research demonstrated that prenatal exposure to *cis*-permethrin, but not *trans*-permethrin, measured in prenatal personal air samples was associated positively with cough for children by age 5 (i.e. at 2, 3, and 5 years) (Reardon et al., 2009). Because no postnatal

exposure measurement was available, and piperonyl butoxide (PBO), a common synergist used in pyrethroid formulations for residential use (Horton et al., 2011a, 2011b), was not considered, it was unclear whether subsequent exposure to permethrins or PBO exposure specifically during early childhood also may be associated with respiratory complaints in urban children.

In the current study, we address these gaps by examining prenatal and concurrent pyrethroid exposure and respiratory complaints in children at age 5-6 years. We hypothesized that prenatal and age 5-6 year exposure to PBO and permethrin would be associated with cough in 5-6 years old children. In addition, we explored the associations between pesticide exposure and other respiratory outcomes, including asthma, wheeze, immunoglobulin (Ig) E production, and fractional exhaled nitric oxide (FeNO). Our approach was to assess both prenatal and 5-6 year airborne PBO and permethrin concentrations, and determine their associations with age 5-6 year cough and other respiratory symptoms.

2. Methods

2.1. Cohort

Seven hundred twenty seven children from the CCCEH birth cohort were fully enrolled as described (Miller et al., 2004; Whyatt et al., 2002). Briefly, African American or Dominican mothers were enrolled between 1998 and 2006 when they were aged 18 to 35 years. Eligible non-smoking mothers were free of diabetes, hypertension, known HIV infection, and documented/reported drug use, and had resided in upper Manhattan and the south Bronx for at least one year. The primary data set included in this paper consisted of 224 CCCEH children who had health outcome measures at age 5-6 years and possessed measures of PBO, *cis*- and *trans*-permethrin during the 3rd trimester of pregnancy and at age 5-6 years. The exclusions were due to (1) missing air measures of PBO, *cis*- and *trans*-permethrin during the prenatal period (333, 118, and 142, respectively) and at age 5-6 years (362, 355, and 341, respectively); (2) invalid air measures (14 and 4 during the prenatal and at age 5-6 years, respectively); (3) missing at least one of the pesticide measures at either time point (for PBO, *cis*- and *trans*-permethrin at prenatal and age 5-6 years: 154, 369, and 345, respectively; and 135, 142, and 156, respectively); and (4) lack of questionnaire data on cough outcome (n=2 children). The study was approved by the Institutional Review Board of Columbia University, and informed consent was provided by all participating mothers.

2.2. Pesticide measures

Maternal personal air samples were collected during the 3rd trimester of pregnancy (March 1998-April 2006) for two consecutive days, as described (Whyatt et al., 2002). Briefly, mothers wore a small backpack containing the personal air monitor during daytime hours, and placed the monitor near the bed at night. Pesticides bound to fine ($2.5 \mu\text{m}$) particulate matter or present in gaseous phases were collected on a precleaned quartz microfiber filter and a polyurethane foam cartridge as previously described (Whyatt et al., 2003).

Residential air pesticides were collected over 2 consecutive weeks in participants' home when the child was 5 or 6 years old (October 2005-May 2011). The indoor sampler, same as those used in the prenatal monitoring, was placed in the room where the child spent majority of his/her time, mostly child's bedroom (50.8%) and living room (40%), as described (Jung et al., 2010, 2012; Whyatt et al., 2007). Seventy two percent of residential air measures were measured at age 5 while 28% were completed at age 6.

The filter and foam were Soxhlet-extracted, and concentrations of PBO, *cis*- and *trans*-permethrin from all prenatal and 5-6 year samples were measured by gas chromatography-

mass spectrometry at Southwest Research Institute (San Antonio, Texas) (Whyatt et al., 2002, 2007; Williams et al., 2008)

2.3. Respiratory outcomes and seroatopy

Questionnaires that addressed an array of respiratory symptoms in the child were administered to the mothers of 5 and 6 years old children. The primary outcome, noninfectious cough, was defined by a positive response to “Has your child had cough without cold in the past 3 months?” Two additional cough-related outcomes were defined as: (1) noninfectious cough of at least two days duration; (2) a positive answer to “Has your child had cough in the past 3 months?” and used in secondary analyses. Wheeze was defined by a positive response to “Has your child ever had wheezing or whistling in the chest in the past 12 months?” from the International Study of Asthma and Allergy in Childhood questionnaire (Jenkins et al., 1996). Asthma was defined by a positive answer to “Has your child had doctor diagnosed asthma” in the Brief Respiratory Questionnaire that has been validated in a population similar to the study population (Bonner et al., 2006).

Serum IgE levels for five indoor allergens (cockroach, mouse, *Dermatophagoides farinae*, cat, and dog; n=205) and total IgE (n=192) were measured at age 5 by Immuno-CAP (Donohue et al., 2008). A child was considered to be sensitized to indoor allergens if he/she had high (> 0.35 IU/ml) IgE levels in any of the five allergens. In addition, seroatopy was assessed based on continuous total IgE levels in further analyses. FeNO, an indicator of airway inflammation, was measured by the offline method at age 5-6 years as described (Perzanowski et al., 2010).

2.4. Covariates

Known relevant covariates were selected from detailed questionnaires and included: child's sex; maternal race/ethnicity, maternal education (below or above high school level), socioeconomic status (currently receiving Medicaid); maternal asthma history (self-reported asthma); environmental tobacco smoke exposure (whether there are smokers at home); and cold/Influenza season (September 1 - March 31). Because they are commonly found in the house dust of the CCCEH subjects (Chew et al., 2003; Olmedo et al., 2010) and could potentially confound the associations between pesticide exposure and allergic sensitization, cockroach (Bla g 2) and mouse urine protein (MUP) allergens were measured in settled dust collected from child's bedroom and kitchen, respectively, as described (Chew et al., 2003). In addition, early childhood cough, indicated by a binary variable for noninfectious cough at age 2-3 years, was used as a covariate as it was related to both prenatal pesticide exposure (Reardon et al., 2009) and potentially cough at age 5-6 years.

2.5. Statistical analysis

All the continuous variables with skewed distributions were natural log-transformed for parametric model assumptions. Below limit of detection (LOD) pesticide data points were replaced by $0.5 \times \text{LOD}$ values. The above LOD frequencies for *cis*-permethrin, *trans*-permethrin, and PBO were 38%, 31%, and 88% for age 5-6 year residential air, respectively, similar to the prenatal personal air samples (Horton et al., 2011a, 2011b).

To compare children included and excluded in the current study, chi-square was used for categorical variables. Wilcoxon rank sum test was used to compare pesticide concentrations measured at the two time points. Spearman correlation coefficient was used to indicate bivariate association between pesticides. Linear models were used for continuous outcome variables of total IgE and FeNO, and logistic model was used for seroatopy defined by increased indoor specific IgE and compared to pesticide levels. Logistic regression models with repeated measures were used to examine the associations between prenatal and

postnatal exposures of PBO and permethrin and binary respiratory health outcomes of reported cough, asthma, and wheeze at age 5 and 6 years. The generalized estimating equation approach using all available observations was used to estimate model parameters in order to have statistical inference robust to misspecification of within subject correlation.

PBO were treated mainly as continuous variables while binary permethrin variables were used. Notably, *cis*- and *trans*-permethrin were treated as separate continuous variables in the previous study (Reardon et al., 2009). With the current data set, we were able to reproduce the previous results (i.e. prenatal exposure to *cis*-permethrin was associated positively with cough for children by age 5-6 years) (Reardon et al., 2009). However, to reduce correlation between the two isomers (Horton et al., 2011a, 2011b), and to maximize the use of observations above LOD (i.e. an additional 16%), a binary permethrin variable combining *cis*- and *trans*-permethrin (i.e. *cis*- or *trans*-permethrin > LODs vs. otherwise) was created and used in this study.

Additional analysis was conducted to test the associations between PBO and cough at age 5 and 6 years. By dichotomizing exposure at upper tertile (67th percentile), a categorical PBO exposure variable was created combining prenatal and 5-6 year PBO exposures, i.e. High High (HH) for PBO above upper tertile at both time points, High Low (HL) for exposure higher in prenatal while lower at 5-6 year; Low High (LH) for exposure lower in prenatal but higher at 5-6 year; and Low Low (LL) for PBO below cut point at both time points used as a reference category). The variable was then used as a main predictor in logistic regression models for cough at age 5 and 6 years.

Previously described covariates were included in the models (i.e. full models with and without insecticide concentrations) initially and those statistically significant ($p < 0.1$) in the initial full models remained in the final models reported here. As a sensitivity analysis, the final model of noninfectious cough-PBO association also was run on a data set that excluded PBO concentrations 1.5X interquartile range (i.e. excluded outliers and extreme values).

Statistical analyses were performed using SPSS software (v.15). Odds Ratio (OR) and 95% confidence interval (CI) reported were derived from logistic models.

3. Results

3.1. Cohort characteristics

Statistically significant differences in demographic variables between those children included and excluded in the current analyses were not detected (Table 1). Overall, a majority of the mothers were Dominicans (69%), had low socioeconomic status (91% receiving Medicaid) and at least high school level education (63%). Approximately 23% of the mothers reported asthma. The prevalence of cough, asthma, wheeze, or seroatopy ranged from 14% to 30% at age 5-6 years, similar to those found in the unselected cohort. Children with cough outcome in the selected subset were more likely to have asthmatic mother [OR (CI): 1.74 (1.06-2.86)] in comparison to analyses conducted among the unselected cohort.

3.2. Pesticide measures

Values of LODs, blanks, and duplicates in the 5-6 year residential air samples were similar to those found in the prenatal personal air samples (Whyatt et al., 2002; Williams et al., 2008). For 5-6 year *cis*-permethrin, *trans*-permethrin, and PBO, LODs were 0.1, 0.2, and 0.06 ng/m³, respectively; and the average relative standard deviations of field duplicates (n=18 pairs) were 6%, 2%, and 19%, respectively. Pesticide concentrations of field blanks were generally below LODs (n=23), with only two PBO blanks that were 35% and 51% higher than the LODs, respectively.

The distribution of the concentrations of all three pesticide species (n=224) were shown in Fig. 1. Statistically significant differences between prenatal and age 5-6 years concentrations were found for *cis*-permethrin and *trans*-permethrin (Wilcoxon signed rank test, $p<0.001$), but not for PBO ($p=0.95$). Similar results were found when observations that ranged below LOD were excluded (data not shown). *Cis*- and *trans*-permethrin was highly correlated (Spearman's correlation, Table 2) in both prenatal personal ($r=0.73$, $p<0.01$) and 5-6 year residential measures ($r=0.75$, $p<0.01$). Weaker, but statistically significant, correlations between samples collected at prenatal and age 5-6 years were found for *cis*-($r=0.17$, $p<0.01$) and *trans*-($r=0.14$, $p<0.01$) permethrin. PBO had similar correlations with *cis*- and *trans*-permethrin in both prenatal ($r=0.24$ and 0.20 , respectively, $p<0.01$) and in 5-6 year samples ($r=0.34$, and 0.30 , respectively, $p<0.01$), though prenatal PBO did not correlate significantly with age 5-6 year PBO. Similar correlations among the three species were found when below LOD data points were excluded (data not shown).

3.3. Pesticide exposure and cough

Two hundred twenty four children had PBO measured at age 5 and 195 at age 6, respectively. Excluding those with PBO measured at age later than the respiratory outcome assessment, 337 observations from 217 children were used in the repeated measure analysis. A positive association between prenatal PBO and noninfectious cough in children aged 5 and 6 years was found with an OR of 1.27 for unit change in log PBO [(CI): 1.09-1.48], $p<0.01$; Fig. 2]. The final model included continuous concentrations of both prenatal and age 5-6 year PBO, and control variable of early childhood cough (i.e. noninfectious cough at age 2-3 years). Controlling for other relevant confounders (i.e. maternal asthma history, child's sex, race/ethnicity, ETS, mother's education level, Medicaid recipient status, allergen levels, cold/influenza season, and seroatopy status), that were not significant in the initial full models, had little impact on the observed association (changes in OR $<2\%$). Prenatal PBO remained to be the significant predictor for noninfectious cough in a data set that excluded PBO concentrations 1.5X interquartile range ([OR (CI): 1.64 (1.03-2.61)], $p<0.05$, $n=119$), and for noninfectious cough of at least 2-day duration ([OR (CI): 1.27 (1.09-1.48)], $p<0.01$, $n=217$). There were no significant associations with *cis*- and *trans*-permethrin and cough measured prenatally or at age 5-6 years (Fig. 2). In analyses with secondary outcome of any cough (i.e. regardless of having a cold), statistically significant associations with PBO and permethrin levels were not detected, even after controlling for cold/influenza season (data not shown). In additional logistic analysis, compared to children with low PBO at both time points, odds of cough tended to be higher in children with high PBO prenatally but not at age 5-6 years [OR (CI): 2.27 (1.11-4.67), $p=0.03$; $n=217$], indicating the importance of prenatal exposure relative to age 5-6 year exposure.

3.4. Pesticide levels and asthma, wheeze, seroatopy, and FeNO

Concentrations of permethrin and PBO were not associated with asthma or wheeze in any of the models (Fig. 2). Permethrin and PBO levels were not associated with elevated indoor allergen-specific IgE levels (data not shown). However, age 5-6 year, but not prenatal, *cis*- and *trans*-permethrin levels were correlated positively with total IgE levels ($p=0.04$, $r=0.15$, $n=191$). FeNO was not correlated with permethrin or PBO exposure (data not shown).

4. Discussion

These novel results suggest that exposure to prenatal PBO is associated with noninfectious childhood cough in an urban pediatric cohort. This paper advances our previous report (Reardon et al., 2009) by showing that prenatal and not age 5-6 year PBO levels are associated with age 5-6 year cough. Also new is the finding that age 5-6 residential measures of *cis*- and *trans*-permethrins are not associated with cough, wheeze or asthma at

age 5-6 years. The finding that prenatal PBO but not age 5-6 year PBO is associated with cough suggests the independent role of prenatal exposure on later symptoms regardless of more concurrent exposures. Our finding lends further scientific support to the emerging premise that the developing immune and respiratory systems are especially vulnerable to toxic insults that occur *in utero*; these toxic insults may lead to adverse respiratory health outcomes during childhood (Duramad et al., 2007; Miller and Marty, 2010; Peden 2000).

The finding that PBO but not permethrin is associated with 5-6 year cough suggests that PBO, which is used as a synergist to and is more volatile than most pyrethroid insecticides including permethrin (Horton et al., 2011b; Whyatt et al., 2007), may indicate better childhood residential exposure to permethrin, and possibly other types of pyrethroid that are not measured in this study. Indeed the common exposure of PBO and permethrin was supported by the significant correlations between permethrin (*cis*- and *trans*-) and PBO in both personal and residential air samples. Alternatively, PBO, while inherently low in intrinsic toxicity, itself induces cough in these children. Mechanisms may relate to PBO's ability to both inhibit and induce cytochrome P450 (CYP) activity (Franklin 1976). For example, the CYP-inhibitory effect of PBO enhanced the potency of pyrethroids by slowing their breakdown (Franklin 1976). On the other hand, CYP was upregulated following dietary exposure to PBO, resulting in increased production of reactive oxygen species (ROS) in rats (Muguruma et al., 2007, 2009). In other epidemiological and experimental studies, the production of ROS has been associated with cough (Chung and Pavord 2008; Niimi et al., 2005), airway inflammation (Barnes 1990), and asthma (Fitzpatrick et al., 2009). Further, PBO has been shown to interfere with the metabolism of medications such as acetaminophen (Brady et al., 1988), whose usage also is implicated in asthma and/or airway inflammation (Perzanowski et al., 2008).

The underlying reason why prenatal measures of PBO may be associated with cough but not wheeze and asthma remains to be elucidated. Exposure to permethrin estimated from questionnaires has been associated with increased risk of asthma and wheeze in farmers (Hoppin et al., 2002, 2008) and in children (Salameh et al., 2003). In this study, the associations between prenatal PBO and asthma and wheeze trended in the positive direction, though without statistical significance. Thus the effects of prenatal pyrethroid exposure on asthma and wheeze may be small and we are insufficiently powered to detect them. Alternately, the explanation may relate to the fact that cough may represent a different disorder than asthma, or even reactive airway disease, including postnasal drip, sinusitis, recent upper and lower respiratory tract infections (Irwin et al., 1998). Accordingly the mechanisms underlying PBO-induced cough may differ from the airway inflammation associated with asthma and wheeze. For example, permethrins have been shown to act on voltage-sensitive Ca^{2+} channels (Brecknridge et al., 2009), some of which are expressed in airway chemosensory nerves (Zurberg et al., 2007), and known to enhance the cough reflex (Grace and Belvisi 2011).

The significant associations between permethrin and total IgE are consistent with a few reported experimental findings. In one, pyrethroids and PBO have been shown to inhibit human T-lymphocyte production of the counter-regulatory cytokine interferon- γ (IFN- γ) (Diel et al., 1999). However, in this study, borderline significant association between age 5-6 year permethrin was found only with seroatopy defined by total IgE, and not indoor allergen-specific IgE. This suggests that an effect of permethrin exposure was driven by sensitization to outdoor pollen or food allergens, or simply not a robust finding.

The present study has several strengths. The measurement of airborne pesticide concentrations provides a more direct and quantitative assessment of childhood exposure to specific pesticides when compared to history or home survey. Another strength was this

study's ability to compare two time periods of exposures, prenatal and age 5-6 years. Further, the cough outcome assessed on questionnaire was able to differentiate cough with versus without a cold, and analyses controlled for cold and influenza season. However, due to the lack of an existing standardized questionnaire to assess cough, it is unclear how well these measures of cough compare to those used in other studies. Indicators of severity or quality of cough, such as sputum production, were not tested. Other limitations include the inability to assess dietary and dermal pyrethroid exposure. Finally, these models, as in all models, were subject to the influence of unmeasured confounders.

5. Conclusion

Despite the prevalent use of pyrethroids in US residential environment, few studies have measured directly children's pesticide exposure at home, especially over the long-term. We found that PBO air levels measured during pregnancy, but not at age 5-6 years, were associated with increased odds of cough at 5-6 years. Age 5-6 year permethrin measures were not associated with any other respiratory health outcomes examined, except total IgE in some models. Cough, an extremely common symptom, may be indicative of a variety of disorders and imposes an enormous health burden on children. In addition, pyrethroid pesticides are used widely in the urban environment, in large part to counteract common cockroach and mouse allergens in the homes (Chew et al., 2003; Olmedo et al., 2010). Further research is needed to assess the role of pyrethroid pesticides during critical windows of development in pediatric respiratory health.

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Abbreviations

CCCEH	Columbia Center for Children's Environmental Health
CI	95% confidence interval
ETS	environmental tobacco smoke
FeNO	fractional exhaled nitric oxide
IgE	immunoglobulin E
LOD	limit of detection
OR	odds ratio
PBO	piperonyl butoxide

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Highlights

- The health impact of residential pyrethroid exposure has not been evaluated fully.
- We examined permethrin and a common pyrethroid synergist piperonyl butoxide (PBO).
- Permethrin and PBO were measured in air samples prenatally and at age 5-6 years.
- Exposure to prenatal PBO only was associated with increased odds of cough.
- *In utero* exposure to PBO or pyrethroids may lead to cough in early childhood.

Fig. 1.

Boxplots of pesticide concentrations (natural log transformed) of prenatal personal and age 5-6 years residential air samples. The line inside the box=Medians; the box length=interquartile range (IQR); Whiskers= the highest and lowest values that are not outliers (o , $1.5 \times IQR - 3 \times IQR$) or extreme values ($*$, $> 3 \times IQR$).

Abbreviations: PBO=piperonyl butoxide; Pre= prenatal personal air; yr= year.

Fig. 2.

Prenatal PBO, not age 5-6 year PBO or *cis*- and *trans*-permethrin, is associated with cough.

*, $p < 0.05$.

Abbreviations: PBO=piperonyl butoxide; Pre= prenatal personal air; yr= year.

Table 1

Demographic variables for subset children included and excluded in this study from the parent CCCEH parent cohort.

Characteristics		Subset analyzed ^f	Subset unselected
		Sample size (proportion, %)	Sample size (proportion %)
Child's Sex	Male	113/224 (50)	238/503 (47)
	Female	111/224 (50)	265/503 (53)
Race/Ethnicity	African American	69/224 (31)	185/503 (37)
	Dominican	155/224 (69)	318/503 (63)
Mother's Education	High School	140/224 (63)	316/489 (65)
	<High School	84/224 (37)	173/489 (35)
Medicaid recipients	Yes	203/223 (91)	454/500 (91)
	No	20/223 (9)	46/500 (9)
ETS ^a	Yes	102/224 (46)	250/499 (50)
	No	122/224 (54)	249/499 (50)
Maternal history of asthma	Yes	53/224 (24)	110/503 (22)
	No	171/224 (76)	393/503 (78)
Noninfectious	Yes	57/418 (14)	87/580 (15)
Cough ^{b,c}	No	361/418 (86)	493/580 (85)
Asthma ^b	Yes	125/411 (30)	161/544 (30)
	No	286/411 (70)	383/544 (70)
Wheeze ^b	Yes	97/411 (24)	132/542 (24)
	No	314/411 (76)	410/542 (76)
Seroatopyd	Yes	51/205 (25)	84/292 (29)
	No	154/205 (75)	208/292 (71)
Total IgE ^e		40.05 [192]	41.10 [274]
FeNO ^e		7.28 [130]	8.10 [52]

^a, Environmental tobacco smoke.

^b, Repeated outcome measures at age 5 and 6 years combined.

^c, Children with cough outcome in the subset cohort analyzed were more likely to have asthmatic mother [OR (CI): 1.74 (1.06-2.86)] in comparison to analyses conducted among the unselected CCCEH children.

^d, Any specific IgE (0.35 IU/ml) to one of the five indoor allergens tested.

^e, medians [sample size].

^f, The primary subset data (n=224) were selected after exclusion of children with missing data due to (1) lack of available pesticide air measures (for PBO, *cis*- and *trans*- permethrin at prenatal and age 5-6 years: 333, 118, and 142, respectively; and 362, 355, and 341, respectively); (2) invalid air measures (n=14 and 4 at prenatal and age 5-6 years, respectively); (3) missing any pesticide species at either time point (for PBO, *cis*- and *trans*- permethrin at prenatal and age 5-6 years: 154, 369, and 345, respectively; and 135, 142, and 156, respectively); (4) lack of questionnaire data on cough outcome (n=2 children).

Table 2

Spearman's correlations among pesticide concentrations (n=224).

	Prenatal personal air		Age 5-6 year residential air	
	<i>cis</i> - permethrin	<i>trans</i> - permethrin	<i>cis</i> - permethrin	<i>trans</i> - permethrin
Prenatal personal air				
<i>cis</i> -permethrin		0.73**		
<i>trans</i> -permethrin	0.24**	0.20**		
Age 5-6 yr residential air				
<i>cis</i> -permethrin	0.17**	0.15*	-0.03	
<i>trans</i> -permethrin	0.24**	0.14*	0.07	0.75**
PBO	0.12	0.16*	0.06	0.34**

Variables were natural log transformed.

** , p<0.01;

* , p<0.05.