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Tobacco smoke exposure and allergic sensitization in children: A propensity score analysis

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Abstract

Background and objective—There is conflicting evidence of the effect of environmental tobacco smoke (ETS) on the development of allergic diseases in children. Studies have shown that this relationship differs depending on maternal history of the disease. We sought to employ the rigor of propensity score methods to assess this relationship using data from a birth cohort.

Methods—Using n=662 children from the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) we assessed the relationship between early life ETS and subsequent allergic sensitization via a positive skin prick test (SPT+) or at least 1 specific IgE 0.35 (sIgE+) in children aged 2–3 years. Propensity score estimation followed by full and nearest neighbor matching was compared to standard multivariable regression models.

Results—Among children without a maternal history of allergic disease ETS was positively associated with allergic sensitization in children with an adjusted odds ratio (aOR) for SPT+ of 2.32 (95% confidence interval (CI): 1.28–4.22) and the aOR for sIgE+ was 2.53 (95% CI: 1.43–4.48). Contrarily, for children with a positive maternal history the aOR for SPT+ and sIgE+ was 0.56 (95% CI: 0.24–1.32) and 0.43 (95% CI: 0.20–0.91), respectively.

Conclusion—Using propensity score methods to rigorously control for confounding factors we found that early life ETS exposure reduces the risk of allergic sensitization in children aged 2–3 years, but only in children with a positive maternal history. There is a strong association between early life ETS and the development of allergic sensitization for children without maternal history.

Keywords

allergic sensitization; birth cohort; propensity score; tobacco smoke

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Role of authors

GW, EMZ, DRO and CCJ participated in the parent study conception and design. SH performed statistical analysis with input from all other authors. SH, GW, EMZ, KW, JE, DRO and CCJ had varying responsibilities in hypothesis generation, study conduct and/or data quality. All authors contributed to the interpretation of data. All authors made critical revisions of the paper and have approved the final version.

INTRODUCTION

Although not often widely discussed, there is conflicting evidence of the effect of exposure to environmental tobacco smoke (ETS) and the development of allergic sensitization in children.¹ Several large, well-known birth cohorts have published studies where ETS was shown to be protective against allergic sensitization.^{2–6} A recent study using a mouse model indicated that cigarette smoke suppressed allergic activation of mast cells, suggesting a biologic mechanism that would support a protective role for ETS in allergic sensitization.⁷ However, there have also been many studies that showed a negative (increased risk) or neutral effect of ETS on allergic sensitization or allergy-related disease.^{8–11} A major concern of all the human studies done to date is that there are differences in other variables (covariates) between children of smoking and non-smoking households which may lead to a biased estimate of the ‘true’ effect of ETS. The gold standard for evaluation of the effect of an exposure (tobacco smoke in this case) on an outcome is through a randomized controlled trial (RCT) whereby covariate balance is presumed through the process of randomization. Obviously, it is neither desirable nor ethical to randomize children to be exposed to cigarette smoke in their homes. As an alternative propensity score techniques were used to balance covariates (potential confounders) between the smoke-exposed and non-smoke exposed groups.

Comparative effectiveness research (CER) methodology has brought to prominence statistical methodologies such as propensity scoring which is an attempt to reduce any possible inherent bias. This methodology can be helpful in situations where RCTs are unethical or too expensive or prolonged to conduct.^{12–14} We hypothesized that propensity scores would help clarify the association of ETS exposure and allergic sensitization in a large population-based birth cohort. If through the use of propensity score methods balance can be achieved—meaning equal distribution of baseline characteristics in the ‘treated’ (smoke-exposed) vs. ‘control’ (no smoke) group—then this observational study design would theoretically mimic what a randomized trial accomplishes through the process of randomization.

METHODS

Using data from a birth cohort, the relationship between early life exposure to household tobacco smoke and subsequent development of allergic sensitization was examined at age 2 to 3 years. Based on published literature it was hypothesized, *a priori*, that maternal history of allergy/asthma would modify the association.^{2,8}

Study Population

The Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) from southeastern Michigan is a multiracial, population-based birth cohort that has been previously described at length.¹⁵ Briefly, pregnant women in the urban and suburban Detroit area were recruited during pregnancy, and updates on their children’s health were obtained at approximately 1-, 6-, 12- and 24-months of age. Information on demographics, prior pregnancies, pet-keeping and employment status was obtained at the enrollment interview. The 24-month update included a clinic visit with a physician trained in the study protocol (average age of child was 2.3 years (standard deviation (s.d.) = 0.4)). Blood was drawn for IgE analyses and skin prick testing was performed. All aspects of this research were approved by the Henry Ford Hospital Institutional Review Board.

Exposure

Early life household ETS was evaluated through a pre-natal and a post-partum interview (approximately 1 month after birth of child) with the mother. A child was considered to be exposed to early life ETS if the mother reported a frequent visitor (20 hours or more) or household member who smoked at least 1 tobacco product per day in the home. Pre-natal versus post-natal exposure could not be evaluated due to the small number (n=17) of households with smoke exposure solely after birth.

Outcomes

Specific allergens for both blood and skin prick testing were measured for *Alternaria* (mix), cat, cockroach (*Blattella germanica*), dog, dust mite (*Dermatophagoides farinae*), short ragweed, Timothy grass, egg, milk and peanut. A child was classified as seroatopic if at least one of their specific IgE (sIgE) values was ≥ 0.35 kU/L. A child was classified as skin prick test positive (SPT+) if at least one of the allergen-specific wheal diameters was 3 mm or greater than the control. There were n=662 children who had results from at least one of the testing methods: IgE testing (specific IgE; n=488) or skin prick testing (n=585).

Analytical Approach and Statistical Methods

Using the R language, a generalized boosted modeling (GBM), a nonparametric regression tree technique, was used to estimate the propensity score.^{16–18} This technique is similar to the more often used logistic regression model in that it models ETS as a function of measured covariates (listed in table 1) but it is importantly different in that it easily models potential non-linear relationships and includes interactions terms as needed. The resulting propensity score is the predicted probability of ETS exposure for each child. Two types of propensity score matching were performed. A full matching method which preserves the original sample size¹⁹ and a more rigorous 2 to 1 nearest neighbor match within a caliper (or distance) of 0.05.²⁰ Caliper is defined as the difference in propensity scores between selected matches. Propensity scores are simply a probability that ranges from 0 to 1. “2 to 1 nearest neighbor matching”, briefly, selects for each smoke-exposed child the two non-exposed children with the smallest absolute difference in propensity scores. By setting a caliper of 0.05 we are pre-specifying the largest allowable absolute difference in propensity scores for matched subjects, thus ensuring closer balance. Balance of the baseline characteristics listed in Table 1 was assessed post-matching using a measure of standardized bias (similar to an effect size it is defined as the mean difference divided by the common standard deviation). All standardized biases were acceptable at < 0.2 .^{21–23} To be conservative, all of the baseline variables were additionally included in the final model.²⁴ Although modeling of this type is not the most parsimonious, the goal was to instead have the most unbiased estimate possible for the association between ETS and allergic sensitization.

Table 1 lists the 11 variables included in the propensity score model. Although p-values are displayed, these variables were pre-selected based on literature review and were not, and should not be, selected based on a certain p-value level. The p-values in Table 1 are for descriptive purposes and show the baseline differences that existed in the cohort between households of children exposed and not exposed to ETS. The households with ETS-exposed children were more likely to have mothers of African American race, unmarried mothers, lower household income, less maternal education and an urban address (Table 1). Using propensity score techniques will diminish these covariate imbalances, resulting in an ETS exposed population that is overall more similar on socioeconomic and racial makeup to the unexposed. These are the differences that one would **not** expect to be present in a RCT and thus propensity score techniques are used in an attempt to eliminate the differences

RESULTS

There was strong statistical evidence that, as pre-specified, maternal history of asthma/allergy modified the association between ETS and sIgE and SPT (both interaction p-values < 0.01). Within the group of children with maternal history of asthma/allergy there were reduced odds of allergic sensitization associated with ETS for seroatopy (Odds Ratio and 95% confidence interval (OR) = 0.48 (0.25, 0.94)) and a statistically non-significant trend of a similar effect (OR=0.54 (0.25, 1.16) for skin prick test positive. In contrast, within children with no maternal history of asthma/allergy, ETS was associated with increased odds of allergic sensitization for both seroatopy ((OR=1.72 (1.05, 2.81)) and SPT+ (OR=1.84 (1.10, 3.09)).

Propensity score adjustment, similar to multivariable regression resulted in a strengthened association between ETS and allergic sensitization among children without a maternal history of allergic disease (Table 2). Among children without a positive maternal history, the odds of subsequent allergic sensitization associated with ETS increased by 47% and 26% for seroatopy and SPT+, respectively. Among children with a maternal history, the odds ratio for ETS on SPT+ increased 32%, weakening the point estimate of the association from 0.54 to 0.71. However, the propensity score analysis of the risk of ETS on seroatopy for the children with maternal history resulted in no change in the protective effect (aOR=0.43 (0.20, 0.91)).

DISCUSSION

The analyses suggest that even after the rigor of propensity score matching is applied to the data among children with a maternal history of allergy/asthma, the protective effect of ETS on sensitization remains. However, the unadjusted odds ratio estimates of ETS on allergic sensitization within children without maternal history may be underestimated. Propensity score methods were used to see if this statistical technique might shed some light on the conflicting, and controversial, evidence of a potential protective effect of smoking on allergy. While we do not believe we have obtained the definitive answer in this controversy, our results are in line with those found by others.^{2–6,25} For example in previous birth cohort studies of children in Turkey and the Netherlands a similar modifying effect based on maternal allergic history was seen between prenatal smoke exposure and allergic sensitization in older children (8–20 years of age) than our cohort.^{3,25} Another birth cohort reported that both personal and parental smoking reduced odds of development of a positive skin test response between ages 13 and 32 year, but only among those with a family history of allergy response (OR=0.2, 95% CI=0.1–0.5).² Several cross-sectional studies that reported examining maternal allergic history as a potential effect modifier showed that current smoking in young adults lowered the odds of allergic sensitization to certain allergens.^{4,6} Further, the NHANES study reported higher serum cotinine levels to be associated with increased odds of positive skin test response (OR=0.7, 95% CI=0.5–0.9).⁵ Our study extends these findings to a racially diverse population of children aged 2–3 years old. We also think the use of propensity scores has strengthened the cumulative evidence.

Considering the consistency of results across the literature in total, there may be a publication bias that has suppressed studies confirming this association due to reluctance of both authors and reviewers/editors to present evidence that smoking has a protective effect on any health issue when it so clearly has a deleterious effect on many others.

A limitation to this method is it is not known whether we measured the ‘correct’ variables and incorporated them in the propensity score model. This is a concern because unlike RCTs (theoretically via randomization) the propensity score method does not control for unknown

confounders. We would encourage other researchers with birth cohorts to use and evaluate statistical methods such as propensity score analysis in an attempt to reduce bias in results from observational studies. Propensity score methodology is fairly commonly applied in fields such as surgical research where randomization to type of surgery can be difficult or impossible, but has seldom been used in the field of asthma/allergy with a notable recent exception by Juhn et al.¹⁴ Within allergic disease research, there are important risk factors of interest that are impossible or unethical to randomize such as race, gender, delivery type and pet-keeping. Research in this field may benefit from an attention to statistical techniques such as propensity scores that can assist in providing less biased estimates of effects.

In conclusion, this study used propensity score methods to rigorously control for confounding factors and found that early life ETS exposure reduces the risk of allergic sensitization in children aged 2–3 years, but only in children with a positive maternal history. Contrarily there is a strong association between early life ETS and the development of allergic sensitization for children without maternal history.

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Abbreviations used

CER	Comparative effectiveness research
RCT	Randomized controlled trial
IgE	Immunoglobulin E
ETS	Environmental household tobacco smoke
CI	Confidence interval
kU/L	Standard International Unit
SPT+	Skin prick test positive
sIgE+	at least one specific IgE 0.35 IU/ml

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Summary at a glance

Using propensity score methods to rigorously control for confounding factors we found that early life exposure to household tobacco smoke reduces the risk of allergic sensitization in children aged 2–3 years, but only in children with a maternal history of allergy/asthma. There is a strong increased risk for children without maternal history.

Table 1

Baseline characteristics used to define propensity of early life household smoke exposure

	Household Smoke exposure		
	Yes n (%)	No n (%)	p-value
Married			<0.001
Yes	84 (19.1)	356 (80.9)	
No	95 (42.8)	127 (57.2)	
African American race			0.028
Yes	117 (30.2)	270 (69.8)	
No	62 (22.6)	213 (77.4)	
Post High school degree			<0.001
Yes	27 (12.0)	199 (88.0)	
No	152 (34.9)	284 (65.1)	
Urban address			<0.001
Yes	112 (33.0)	227 (67.8)	
No	67 (20.7)	256 (79.3)	
2 or more dog/cat(s)			<0.001
Yes	45 (40.5)	66 (59.5)	
No	134 (24.3)	417 (75.7)	
First Pregnancy			0.31
Yes	36 (23.8)	115 (76.2)	
No	143 (28.0)	368 (72.0)	
Unemployed			0.11
Yes	40 (32.8)	82 (67.2)	
No	139 (25.7)	401 (74.3)	
Household Income > \$80000			<0.001
Yes	24 (13.2)	158 (86.8)	
No	155 (32.3)	325 (67.7)	
Makes a rental or mortgage payment			<0.001
Yes	118 (22.9)	398 (77.1)	
No	61 (41.8)	85 (58.2)	
Mother seroatopic			0.93
Yes	103 (27.2)	276 (72.8)	
No	76 (26.9)	207 (73.1)	
Mother's age in years, Mean (s.d.)	28.4 (5.2)	30.7 (5.1)	<0.001

Table 2
Association of early life household smoke exposure to allergic sensitization at ages 2–3 years old

	Early Life Household smoke exposure		Unadjusted Logistic regression	Multivariable Logistic regression	Propensity score matching method	
	Yes n (%)	No n (%)	OR (95% CI)	aOR* (95% CI)	Full aOR* (95% CI)	1 to 2 matching aOR* (95% CI)
Strata: Maternal history of allergy or asthma = Yes						
Seroatopic						
Y	20 (40.8)	77 (58.8)	0.48 (0.25, 0.94)	0.44 (0.20, 0.94)	0.43 (0.20, 0.91)	0.42 (0.18, 0.98)
N	29 (52.9)	54 (41.2)				
Skin test positive						
Y	10 (16.7)	44 (27.0)	0.54 (0.25, 1.16)	0.57 (0.24, 1.34)	0.56 (0.24, 1.32)	0.71 (0.27, 1.86)
N	50 (83.3)	119 (73.0)				
Strata: Maternal history of allergy or asthma = No						
Seroatopic						
Y	54 (58.1)	96 (44.6)	1.72 (1.05, 2.81)	2.52 (1.42, 4.74)	2.53 (1.43, 4.48)	3.16 (1.72, 5.81)
N	39 (41.9)	119 (55.4)				
Skin test positive						
Y	32 (32.6)	55 (20.8)	1.84 (1.10, 3.09)	2.39 (1.32, 4.32)	2.32 (1.28, 4.22)	2.34 (1.12, 4.90)
N	66 (67.4)	209 (79.2)				

* adjusted for all variables listed in Table 1