Journal of Agromedicine
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t792303961

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To cite this Article Lawson, Joshua A. , Dosman, James A. , Rennie, Donna C. , Beach, Jeremy , Newman, Stephen C. and Senthilselvan, Ambikaipakan(2009) 'Relationship Between Indoor Environment and Asthma and Wheeze Severity Among Rural Children and Adolescents', Journal of Agromedicine, 14: 2, 277 — 285
To link to this Article: DOI: 10.1080/10599240902772910
URL: http://dx.doi.org/10.1080/10599240902772910

Journal of Agromedicine, 14:277–285, 2009

ISSN: 1059-924X print/1545-0813 online
DOI: 10.1080/10599240902772910

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ABSTRACT. Few studies have examined the associations between environmental characteristics and asthma severity among children in a rural setting. The authors studied these associations using a number of asthma severity indicators. They conducted a case-control study of 6- to 18-year-old children and adolescents in Humboldt, Saskatchewan, and the surrounding area. Only cases representing subjects reporting wheeze in the past 12 months or doctor-diagnosed asthma were used for the present analysis (n = 98). Data were collected by questionnaire, while vacuumed dust (mattress and play area floor) was used for the quantification of endotoxin exposure, and saliva was used for the measurement of cotinine to assess tobacco smoke exposure. Severity indicators included wheeze frequency, breathing medication use, sleep disruption from wheeze, and school absenteeism, all in the past 12 months. A majority of cases were male (62.3%). Wheezing 1 to 3 times was reported by 40.8% of cases, whereas 17.3% wheezed 4 or more times in the past 12 months. Short-acting beta agonist medications or inhaled corticosteroids alone were used by 24.5% of the cases, whereas 33.7% of the cases used multiple or additional breathing medications. Sleep disruption was reported by 28.6% of the cases, whereas 12.2% reported at least one school absence. High tobacco smoke exposure was associated with increased wheeze frequency. There was an inverse association between play area endotoxin concentration and school absenteeism, with some indication of interaction with tobacco smoke exposure. House-cleaning behaviors and changes in health behaviors resulting from the child's respiratory condition were different between those with and without report of sleep disruption due to wheeze. Several environmental variables were associated with severity indicators. However, the associations

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Support for this study was received from the Canadian Institutes of Health Research (grant no.: MOP-57907).

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were not consistent between indicators, suggesting that other factors or changes in behavior resulting from the disease should be considered when assessing these associations.

KEYWORDS. Asthma, breathing medication, children and adolescents, cotinine, endotoxin, rural, school absenteeism, tobacco smoke exposure, wheeze

INTRODUCTION

Asthma is a chronic respiratory disease that is common among children and can lead to poorer quality of life and increased health care utilization and costs. Examination of risk factors for asthma severity could identify exposures that aggravate disease and aid attempts to reduce morbidity. The Canadian Asthma Consensus Guidelines suggest that the severity of asthma should be judged by the frequency and duration of respiratory symptoms, the presence of persistent airflow limitation, the medication required to maintain disease control, nocturnal symptoms, school absenteeism, and health care visits such as hospitalizations or emergency room visits when not being treated.[1] While treated, these markers would indicate suboptimal control of asthma.

Two indoor exposures suspected to play a role in the severity of asthma and wheeze include environmental tobacco smoke and endotoxin. Environmental tobacco smoke has been studied frequently among school aged children and has been associated with increased frequency of symptoms,[2,3] intensity of symptoms,[2] asthma medication use,[2] school absenteeism,[3] and nighttime symptoms.[4]

Ambient endotoxin levels are elevated in farming environments,[5] an environment that has been associated with a lower asthma prevalence.[6] Despite this, endotoxin exposure in agricultural environments has been associated with increased markers of disease severity among adults,[7] as has domestic endotoxin exposure with asthma severity among urban dwelling adults.[8] Endotoxin's association with asthma or wheeze has been inconsistent, with few studies investigating the impact of endotoxin on asthma severity among children. Two population-based studies using different measures of asthma severity have been completed among school-aged children, with conflicting results. Previous studies examining asthma severity and endotoxin have not focused on rural populations.

The purpose of the present analysis was to investigate the associations between endotoxin and tobacco smoke exposure with indicators of asthma severity, both independently and jointly, among a population of rural school-aged children.

METHODS

Study Population and Study Design

We completed this study in Humboldt, Saskatchewan, a largely agriculturally based community (population approximately 5100). We conducted a case-control study between October and April 2005–2007, but only included cases (children with asthma or wheeze as defined by a parental-report of physician diagnosis of asthma or a report of wheeze in the past 12 months) in the current analysis. A previous cross-sectional study, conducted in 2004, was used as the sampling frame for subject recruitment. Data used for the current analysis were from questionnaire reports, while dust was collected for endotoxin and saliva for cotinine. Ethical approval was obtained from the University of Alberta and the University of Saskatchewan. The local school boards approved the project. Prior to data collection, consent and assent forms were completed by parents and children, respectively.

Data Collection

Interviewer-administered questionnaires were completed by the subject's parent and were based on standardized questionnaires.[9–11] Information was collected on respiratory symptoms and personal and environmental

characteristics. Outcomes of interest included frequency of wheeze (0, 1–3, 4 or more episodes), breathing medication use (none, short-acting beta agonists or inhaled corticosteroids alone, and combination or multiple medication use), sleep disruption due to wheeze (present/absent), and school absenteeism of at least 3 days due to a chest illness (occurred versus did not occur), all in the past 12 months. These outcomes represent indicators of poor disease control, which when not treated could be an indicator of asthma severity. We did not have enough information on medication use to establish severity based on the amount of medication required to maintain control. Information was also collected on changes made to the home because the child had asthma, allergic, or respiratory problems.

Household dust was collected (Solaris vacuums; Miele S514) from the floor where the child spent most of his/her free time and from the child's mattress. Dust collection followed the International Study of Asthma and Allergies in Childhood protocol,[12] with the exception that a sock filter to collect dust was made of Connaught satin instead of ALK filters. After collection, dust was stored at 4°C.

Saliva was collected without pharmacologics to stimulate the flow of saliva. Subjects spit into a sterile container and the samples were stored in a –80°C freezer until laboratory analysis.

Laboratory Analyses

Laboratory technicians were blinded to case-control status and exposure information. Assays to determine the concentration of endotoxin in dust samples were conducted following the protocol used by Gerada and colleagues.[13] Endotoxin levels were measured by the kinetic chromogenic *Limulus* assay (Cambrex Bio Science, Kinetic QCL, Walkersville, MD) and expressed as concentration (endotoxin units [EU]/mg) and load (EU/m^2). Cotinine levels (ng/ml) were determined using saliva cotinine microplate enzyme immunoassay kits (Cozart, UK).

Statistical Analyses

Analysis was completed using STATA statistical software (College Station, TX). Endotoxin levels were log-transformed prior to analysis. Tobacco smoke exposure was categorized as high or low based on the median cotinine level (1.24 ng/ml). Statistical analyses were completed using proportional odds ordinal logistic regression (wheeze frequency), multinomial logistic regression (breathing medication use), and standard logistic regression (sleep disruption due to wheeze and school absenteeism). Generalized estimating equations were used to account for clustering within families. For each outcome, a separate model was fitted for each measure of endotoxin (play area concentration, play area load, mattress concentration, mattress load) and included variables for tobacco smoke exposure and potential confounders. Relevant interaction terms were assessed.

RESULTS

In total, 322 children (43.4% of the children selected and determined to be eligible), including cases and controls, took part in this study. Of these, 98 were cases with complete data and were included in the present analysis. All the cases were between the ages of 6 and 18 years. Among the cases 34% were female. Wheezing 1 to 3 times was reported by 40.9% of cases, whereas 17.3% reported wheezing 4 or more times. No breathing medication use was reported by 41.8% of cases, whereas 24.5% used either short-acting beta agonist or inhaled corticosteroids alone and 33.7% used multiple or additional breathing medications. Finally, 28.6% of cases reported sleep disruption due to wheeze in the past year and 12.2% reported school absenteeism in the past year. Children reporting at least one school absence had significantly ($p < .05$) lower mean play area endotoxin concentrations compared to those who did not report an absence (Table 1). High tobacco smoke exposure was reported more frequently as the frequency of wheeze increased (Table 1).

In the multivariate analysis, high tobacco smoke exposure was significantly associated with more frequent wheeze (Table 2). With regard to the other severity indicators, there was statistically significant interaction between tobacco smoke exposure and both play area

TABLE 1. Distribution of Play Area and Mattress Endotoxin Levels and Proportion of Children with High Tobacco Smoke Exposure for Different Severity Indicators Based on the Past Year

	n	Play area endotoxin concentration (EU/mg) GM (95%CI)	Play area endotoxin load (EU/m^2) GM (95%CI)	Mattress endotoxin concentration (EU/mg) GM (95%CI)	Mattress endotoxin load (EU/m^2) GM (95%CI)	% with high tobacco smoke exposure
Frequency of wheeze in the past year						
None	41	59.9 (42.8–83.9)	919.2 (635.5–1329.5)	21.8 (15.6–30.4)	263.1 (172.2–402.2)	36.6
1–3 times	40	43.1 (30.9–60.2)	886.1 (602.7–1303.2)	18.7 (13.4–26.0)	308.8 (198.0–481.6)	57.5
4 or more times	17	55.1 (29.9–101.7)	763.5 (290.3–2007.1)	14.7 (6.1–35.2)	258.8 (108.7–616.6)	70.6†
Breathing medication use in the past year						
None	41	60.8 (44.9–82.2)	1032.0 (696.3–1529.7)	20.8 (14.5–29.7)	304.7 (189.4–490.1)	56.1
SABA or ICS alone	24	43.8 (26.7–71.9)	912.9 (557.6–1494.9)	19.7 (13.4–29.1)	302.7 (204.6–447.6)	54.2
Multiple and/or additional	33	47.5 (31.6–71.7)	695.5 (408.7–1183.6)	16.8 (10.2–27.6)	238.5 (135.2–420.7)	42.4
Sleep disruption from wheeze in the past year						
None	70	51.5 (39.9–66.6)	988.7 (729.0–1252.9)	19.5 (14.6–26.0)	274.5 (196.3–383.9)	48.6
At least once	28	51.8 (33.6–79.9)	707.1 (366.4–1364.9)	18.2 (11.9–27.8)	294.6 (167.5–518.2)	57.1
School absenteeism for a chest illness of 3 days or more in the past year						
None	86	56.9 (45.8–70.6)	920.7 (692.0–1224.6)	19.8 (15.2–25.7)	279.3 (203.8–382.6)	52.3
At least once	12	25.9 (11.1–60.3)*	618.9 (287.4–1332.3)	14.8 (8.6–25.3)	286.1 (154.5–530.0)	41.7

*$p < .05$ compared to the reference group using standard logistic regression with generalized estimating equations to account for clustering within families. Measures of endotoxin were log transformed prior to analysis.
†$p < .05$ when using proportional odds ordinal logistic regression with generalized estimating equations to account for clustering within families. Measures of endotoxin were log transformed prior to analysis.
EU, endotoxin units; GM, geometric mean; ICS, inhaled corticosteroid; SABA, short-acting beta agonist.

endotoxin concentration and play area endotoxin load in relation to sleep disruption due to wheeze. When there was low tobacco smoke exposure, there was an increased risk of sleep disruption due to wheeze associated with play area endotoxin, whereas when there was a high tobacco smoke exposure, there was a lower risk of sleep disruption due to wheeze, although none of the joint associations were statistically significant (Table 2). There was also interaction between tobacco smoke exposure and play area endotoxin load in relation to school absenteeism (Table 2). There was lower risk of school absenteeism associated with play area endotoxin load when there was low tobacco smoke exposure (Table 2). Play area endotoxin concentration was associated with school absenteeism independently (Table 2). Finally, there was a statistically significant interaction between age and mattress endotoxin load among children older than 12 years, and there was a statistically significant inverse association between mattress endotoxin load and school absenteeism (Table 2).

To examine whether changes in behaviors due to having asthma biased the associations between severity indicators and factors considered, comparisons of cleaning habits (vacuuming, mopping, and dusting per month) and changes made because of asthma, allergic, or respiratory disease (changes in pet keeping, smoking amount, smoking location, pillows or bedding, or flooring, or moving homes) were conducted between levels of severity indicators. When there was a report of sleep disruption due to wheeze in the past 12 months, there were higher mean levels of dusting and a higher proportion of subjects in homes where there was reduced smoking or smoking was removed altogether because of the child's respiratory or allergic condition (Table 3).

TABLE 2. Odds Ratios (95% Confidence Intervals) from Multiple Logistic Analyses* for the Association Between Endotoxin and Tobacco Smoke Exposure with Indicators of Asthma Severity Based on the Past Year

	Wheeze frequency OR (95% CI)	Breathing medication use (none vs. SABA/ICS alone) OR (95% CI)	Breathing medication use (none vs. additional and/or combination) OR (95% CI)	Sleep disruption due to wheeze OR (95% CI)	School absenteeism of at least 3 days due to a chest illness OR (95% CI)
Model 1					
Tobacco smoke exposure	2.73 (1.25–5.98)†	0.30 (0.07–1.37)	0.48 (0.16–1.44)	§	0.60 (0.16–2.19)
Play area endotoxin concentration	0.78 (0.34–1.79)	0.46 (0.13–1.70)	0.64 (0.21–1.76)	§	0.17 (0.05–0.54)†
Low tobacco smoke	—	—	—	2.62 (0.68–10.09)	—
High tobacco smoke	—	—	—	0.44 (0.13–1.55)	—
Model 2					
Tobacco smoke exposure	2.76 (1.26–6.02)†	0.72 (0.21–2.54)	0.46 (0.19–1.11)‡	§	§
Play area endotoxin load	0.91 (0.44–1.90)	0.51 (0.14–1.87)	0.57 (0.19–1.74)	§	§
Low tobacco smoke	—	—	—	2.34 (0.72–7.58)	0.16 (0.03–0.81)†
High tobacco smoke	—	—	—	0.34 (0.12–1.00)‡	0.99 (0.29–3.42)
Model 3					
Tobacco smoke exposure	2.63 (1.17–5.92)†	1.18 (0.36–3.85)	0.56 (0.19–1.67)	1.52 (0.67–3.45)	0.54 (0.14–2.11)
Mattress endotoxin concentration	0.73 (0.31–1.72)	0.55 (0.15–1.99)	0.57 (0.20–1.67)	1.13 (0.47–2.70)	0.38 (0.08–1.75)
Model 4					
Tobacco smoke exposure	2.82 (1.29–6.15)†	2.14 (0.76–5.98)	0.52 (0.14–1.97)	1.55 (0.68–3.54)	0.65 (0.18–2.30)
Mattress endotoxin load	1.15 (0.61–2.15)	0.71 (0.31–1.61)	0.62 (0.21–1.77)	1.27 (0.54–2.97)	¶
≤12 years	—	—	—	—	1.50 (0.35–6.34)
>12 years	—	—	—	—	0.27 (0.09–0.81)†

*Models 1, 2, 3, and 4 are independent of each other and will include one measure of endotoxin and the variable indicating tobacco smoke exposure. Associations were also adjusted for age and sex (wheeze frequency); sex, history of allergic disease, age, parent's education level, burning sources of heat in the home, mold or dampness in the home, current farm exposure, cat as a pet in the past 12 months, and early childhood respiratory illness (breathing medication use); age, sex, parents' education level, and having a dog as a pet (sleep disruption due to wheeze); age, sex, personal history of allergic disease, home mold or dampness, current farm exposure (school absenteeism).

†$p < .05$.

‡$p < .10$.

§The independent effects are not provided as there was interaction between tobacco smoke exposure and the measure of endotoxin.

¶The independent effects are not provided as there was interaction between mattress endotoxin load and age group.

CI, confidence interval; ICS, inhaled corticosteroids; OR, odds ratio; SABA, short-acting beta agonist.

TABLE 3. Cleaning Behaviors and Changes in Behavior by Asthma Severity Indicators Based on the Past Year

	Wheeze frequency (episodes)			Breathing medication use			Sleep disruption from wheeze		School absenteeism from a chest illness	
	None (*n* = 41)	1–3 (*n* = 4)	>3 (*n* = 17)	None (*n* = 41)	SABA or ICS alone (*n* = 24)	Multiple or additional (*n* = 33)	No (*n* = 70)	Yes (*n* = 28)	No (*n* = 86)	Yes (*n* = 12)
Mean number vacuum per month (SD)	6.8 (6.4)	10.4 (9.9)	4.7 (4.7)	6.8 (6.4)	10.4 (9.9)	4.7 (4.7)	7.6 (7.6)	8.9 (9.1)	7.6 (7.7)	10.6 (10.1)
Mean number mopping per month (SD)	5.2 (6.0)	5.8 (7.5)	4.7 (3.6)	5.2 (6.0)	5.8 (7.5)	4.7 (3.6)	4.7 (5.5)	6.9 (7.7)	5.6 (6.6)	3.5 (1.4)
Mean number dry dust per month (SD)	3.4 (2.6)	4.1 (6.2)	2.6 (1.9)	3.4 (2.6)	4.1 (6.2)	2.6 (1.9)	3.0 (2.3)*	4.9 (7.3)	3.7 (4.7)	2.8 (1.7)
Mean number wet dust per month (SD)	2.9 (2.0)	4.3 (5.2)	3.1 (2.2)	2.9 (2.0)	4.3 (5.2)	3.1 (2.2)	2.9 (2.4)*	5.0 (5.7)	3.5 (3.7)	3.8 (4.0)
% removed pets[†]	17.1	7.5	0.0	7.3	8.3	15.2	12.9	3.6	9.3	16.7
% changed pillows or bedding[†]	22.0	15.0	29.4	22.0	16.7	21.2	20.0	21.4	18.6	33.3
% changed floor coverings[†]	19.5	17.5	11.8	17.1	12.5	21.2	18.6	14.3	17.4	16.7
% stopped/reduced smoking[†]	12.2	17.5	11.8	7.3	20.8	18.2	8.6*	28.6	16.3	0.0
% moved[†]	2.4	2.5	5.9	2.4	4.2	3.0	2.9	3.6	2.3	8.3
% changed place where you smoke[†]	9.8	10.0	17.6	7.3	12.5	15.2	10.0	14.3	11.6	8.3

*$p < .05$ between levels of the severity indicator; statistical comparisons were based on linear regression or logistic regression using generalized estimating equations to account for clustering within families.

[†]The value presented in each cell of this row is the proportion of participants classified within the category of the asthma severity indicator (i.e., the column percent) reporting the change in behavior due to this child's asthma, allergy or respiratory problems.

ICS, inhaled corticosteroids; SABA, short-acting beta agonists; SD, standard deviation.

DISCUSSION

In this study of cases with asthma or wheeze in a rural population, tobacco smoke exposure was associated with frequency of wheeze and was an effect modifier in the association between endotoxin and sleep disruption due to wheeze, as well as endotoxin and school absenteeism due to a chest illness. We also found that those with sleep disruption due to wheeze changed smoking habits due to the presence of respiratory problems and dusted more. These results highlight the potential for tobacco smoke exposure to increase severity of disease among children with asthma or wheeze, the potential for environmental exposures to interact with each other, and the need to consider environmental changes resulting from the disease when interpreting results from epidemiological studies.

Tobacco smoke exposure showed strong associations with the reported frequency of wheeze based on the 12 months prior to the home visit. This supports other studies investigating the association between environmental tobacco smoke and the severity of asthma or wheeze in children, which have shown increased frequency of asthma episodes[14] or increased severity of asthma. Our results extend these findings to a rural population where smoking exposures may be different than in urban populations. Other than with frequency of wheeze, there were no independent associations between tobacco smoke exposure and any indicators of asthma severity. Differences in results between the current study and previous studies with regard to breathing medication use, nocturnal symptoms and school absenteeism, may have been due to the levels of exposure experienced. Previous studies have shown that higher levels of tobacco smoke exposure may be required to observe associations with respiratory outcomes.[15] Our levels were lower compared to other studies using cotinine.[16] Exposure may have been sufficient to result in symptoms but not enough for more extreme outcomes such as school absenteeism.

Of the analyses completed between measures of endotoxin and asthma severity indicators, only one showed an independent statistically significant association. This was between school absenteeism and play area endotoxin concentration. Few published studies have investigated associations between home endotoxin and indicators of asthma severity using population-based studies and none, to our knowledge, have considered a primarily agricultural-based population. One study showed an increased risk of school absenteeism among children with asthma who were atopic,[17] whereas another showed associations with increased nighttime symptoms.[18] Our results contradict those of the previous study that investigated school absenteeism.[17]

Tobacco smoke exposure acted as an effect modifier in the association between play area endotoxin and sleep disruption due to wheeze. There was an increased risk of sleep disruption from wheeze among those with low tobacco smoke exposure, whereas among those with high tobacco smoke exposure, there was an inverse association. These findings are opposite of what was expected and difficult to explain, but could result from changes in smoking behaviors or differences in cleaning behaviors in response to symptoms or may be due to some residual confounders. Although none of the joint odds ratios were statistically significant, requiring the results to be interpreted with caution, the associations were relatively strong and the statistical interaction was highly statistically significant. One study that also considered asthma symptoms related to sleep found that higher endotoxin levels measured using personal monitors were associated with increased risk of symptoms.[18]

Differences in the associations witnessed in this study and previous studies with regard to endotoxin and severity indicators may be due to the amounts and types of endotoxin experienced. The types of endotoxin encountered in rural environments may be different than in urban environments, although this has never been studied. A study conducted to characterize lipopolysaccharide within homes found that there were qualitative differences regarding the type of lipopolysaccharide between locations in the home.[19] Endotoxin activities vary with structurally different types of lipopolysaccharide. These variations in structure have the potential to affect human health differentially. A study

that considered endotoxin measured from schools in China found that total lipopolysaccharide was associated with an increased risk of attacks of breathlessness in students.[20] However, after characterization of the types of lipopolysaccharide, the shorter length lipopolysaccharide molecules were inversely associated with attacks of breathlessness.[20]

Investigation of potential behavior change revealed that stopping or reducing smoking exposure as a result of the subject's asthma, allergic, or respiratory problems occurred in a significantly higher proportion of homes among those with sleep disruption due to wheeze compared to homes of those without sleep disruption due to wheeze. This was determined from responses to a question asking directly about changes resulting from the child's asthma, allergic, or respiratory problems.

Dusting was completed more frequently in homes where the subject had a report of sleep disruption due to wheeze compared to those where subjects did not experience sleep disruption from wheeze. Although we are unable to determine whether the dusting frequency or symptoms came first, the presence of these differences can be interpreted to mean that the effect cleaning might result in altered associations between endotoxin, tobacco smoke exposure and sleep disruption due to wheeze.

The results from this study indicate that there were differences in the association between endotoxin and respiratory outcomes depending on the source of the dust (i.e., play area versus mattress) used in the analysis. This could be explained by a number of factors. First, endotoxin levels have been shown to vary between areas in the home.[19] The current study corroborates results from other studies that have shown that mattress endotoxin levels tend to be lower than floor endotoxin levels.[19] Although the levels of endotoxin are lower in mattress dust, the physical interaction between the subject and the measured dust may be different as the mattress endotoxin is in closer proximity to the breathing area of the subject compared to dust from the play area. Second, predictors of endotoxin have been shown to vary for different locations in the home.[17]

Endotoxin from different types of bacteria may not be uniform in molecular composition and could lead to different health outcomes, as previously reported.[20]

A limitation experienced in this study was the low participation rate. A comparison of those who completed the case-control study versus those who did not complete the case-control study based on data from the original cross-sectional survey found few differences, suggesting that the study population was representative of those who took part in the cross-sectional study (data not shown). Among children who were selected as potential cases, those who completed the case-control study were less likely to have a father who currently smokes and were younger compared to those who did not complete the case-control study.

Objective exposure measures were collected at a single point in time whereas several outcomes were cumulative based on the past year. Current exposure levels measured in this study may not reflect those that were occurring at the time of the event (i.e., in the past year). For example, the current measured endotoxin levels may not reflect the level of exposure present when the reported episode of wheeze actually happened previously in the year. This could result in spurious associations.

We examined the associations between endotoxin and tobacco smoke exposure with indicators of asthma and wheeze severity among a population of school children from a primarily rural area. Farming environments have been associated with lower prevalence of asthma among children,[6] with endotoxin suggested to be the exposure of interest. However, these results have not been consistent. Also, it is important to examine how endotoxin affects children who have asthma or wheeze in a rural population, as we have done, given the differences in endotoxin exposure levels between rural and urban areas. We found that tobacco smoke exposure was a risk factor for wheeze frequency in a rural population, despite experiencing lower levels when using an objective measure of exposure. This study also highlights the potential for environmental exposures to interact. Finally, we also emphasize the need to consider changes in behavior that result from

disease in interpreting the results of an epidemiological study. Future studies of endotoxin and asthma severity among children should consider environmental interactions and the types of endotoxin in various locations, especially between rural and urban populations, to help explain inconsistencies between studies.

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