A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP2452.

House Dust Endotoxin Association with Chronic Bronchitis and Emphysema

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Background: Endotoxin has been reported to be associated with chronic bronchitis or emphysema (CBE) at high occupational exposures. However, whether levels found in domestic environments have similar effects is unknown.

Objectives: We aimed to study the association between house dust endotoxin and CBE in a sample representative of the U.S. population.

Methods: We analyzed data from 3,393 participants ≥20 y old from the National Health and Nutrition Examination Survey (NHANES) 2005–2006. House dust from bedding and from bedroom floors was analyzed for endotoxin content. NHANES participants received questionnaires and underwent examination as well as extensive laboratory testing. Logistic regression was used to examine the association of endotoxin levels with CBE diagnosis and symptoms, adjusting for covariates. The survey design and weights were applied so that estimates were nationally representative and so that statistical inferences were made appropriately.

Results: The median endotoxin concentration in house dust was 14.61 EU/mg dust, and CBE was reported by 8.2% of participants. In the adjusted analysis, one unit (EU/mg) increase in $\log_{10}$-transformed endotoxin concentrations was associated with a 27% increase in the odds of CBE diagnosis [OR = 1.27 (95% CI: 1.00, 1.61)] and a 78% increase in the odds of chronic bronchitis symptoms (defined as cough and phlegm for ≥3 mo in a year for ≥2 y) [OR = 1.78 (95% CI: 1.01, 3.12)]. Sensitization to inhalant allergens ($p = 0.001$) modified the relationship between endotoxin and CBE diagnosis, with stronger associations observed in sensitized participants [OR = 2.46 (95% CI: 1.72, 3.50) for a unit increase in $\log_{10}$-endotoxin].

Conclusions: In a population-based sample of U.S. adults, endotoxin levels in homes were associated with a self-reported history of CBE diagnosis and chronic bronchitis symptoms, with stronger associations among people sensitized to inhalant allergens. https://doi.org/10.1289/EHP2452

Introduction

Chronic bronchitis is a common condition that affects 10 million Americans (American Lung Association 2014; Kim et al. 2015). The condition is characterized by airway inflammation and airway remodeling and is typically defined as chronic cough with sputum for ≥3 mo per year for at least two consecutive years (Kim et al. 2015). Emphysema is a complex disease defined by alveolar wall destruction leading to a loss of elastic recoil (Barnes 2000; Sciurba 2004). Both chronic bronchitis and emphysema are phenotypes of chronic obstructive pulmonary disease (COPD), which affects >15 million Americans and is the third leading cause of death in the United States and worldwide (Burney et al. 2015; Diaz-Guzman and Mannino 2014; Heron 2013).

COPD is mainly caused by cigarette smoking, but other environmental exposures are increasingly recognized as playing a role in its development (Eduard et al. 2009; To et al. 2016). Among these environmental exposures, endotoxin is of particular interest because of its known proinflammatory properties and its effects on respiratory health (Thorne et al. 2005, 2015). Endotoxin is a lipopolysaccharide from the outer membrane of Gram-negative bacteria that is ubiquitous in our environment (Thorne et al. 2009). Animal models suggest that endotoxin induces lesions of the lung that are similar to those found with COPD, and according to preclinical *in vivo* models, stimulus by endotoxin can be used to reproduce COPD inflammation (Brass et al. 2008; Håkansson et al. 2012; Korsgren et al. 2012).

Despite the results obtained with animal models, only a few studies have examined the association of endotoxin with COPD in humans. These studies have all included occupational exposure to high concentrations of endotoxin, but to date, there has been no study on the levels of endotoxin found in homes (Basinas et al. 2012; Eduard et al. 2009; Mehta et al. 2010). Therefore, we examined the association of house-dust endotoxin with chronic bronchitis or emphysema (CBE) suggestive of COPD in a large sample representative of the U.S. population using the National Health and Nutrition Examination Survey (NHANES). The topic is of public health interest given the ubiquity of endotoxin in our environment and the high morbidity of chronic obstructive pulmonary conditions in the United States.

Materials and Methods

Data Source and Study Design

We used data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). NHANES is a continuous cross-sectional survey of the U.S. noninstitutionalized civilian population, selected using a complex multistage sampling design to derive a representative sample of the U.S. population. People below the poverty level, 12 to 19 y old, ≥60 y old, pregnant women, African Americans, and Mexican Americans were oversampled in the 2005–2006 cycle to ensure adequate subgroup analyses. Of the 3,403 NHANES participants ≥20 y old who had data on house dust endotoxin, 3,393 (99.7%) also had data on emphysema, chronic bronchitis, or both and were included in our study.

NHANES protocols were approved by the Institutional Review Boards of the NCHS and the CDC, and informed consent was obtained from all participants. Details of the IRB approval are available here: http://www.cdc.gov/nchs/nhanes/irba98.htm. Details on NHANES procedures and methods are available here:

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Supplemental Material is available online (https://doi.org/10.1289/EHP2452).
The authors declare they have no actual or potential competing financial interests.
Received 4 July 2017; Revised 30 January 2018; Accepted 31 January 2018; Published 23 March 2018.

https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/manuals.aspx?BeginYear=2005.

Endotoxin analysis

Combined bed and bedroom floor dust samples were collected at each participant's home using a vacuum cleaner fitted with a Mitest™ Dust Collector (Indoor Biotechnologies, Inc). A surface area of 0.84 m^2 on beds and the adjacent floors were each vacuumed for 2 min. These composite dust samples were analyzed for endotoxin at our University of Iowa laboratory using a kinetic chromogenic *Limulus* amebocyte lysate assay with expansive quality assurance measures as previously described (Thorne et al. 2015). Sieved dust was extracted with sterile pyrogen-free water plus 0.05% TWEEN® 20. Control standard endotoxin (*Escherichia coli* 055:B5) was used to develop 12-point standard curves, and samples were assayed at four dilutions increasing four-fold from 1:400 to 1:25,600. Endotoxin concentrations were reported in endotoxin units per milligram of sieved dust (EU/mg dust). The lower limit of detection was 0.000488 EU/mg dust. A detailed description of our laboratory methods for the endotoxin assay is available (Thorne 2014).

CBE assessment

CBE was assessed using a questionnaire administered to each study participant. Chronic bronchitis diagnosis was defined by a positive response to the question "Has a doctor or other health professional ever told (you/study participant) that (you/s/he) had chronic bronchitis?" Emphysema diagnosis was defined by a positive response to the question "Has a doctor or other health professional ever told (you/study participant) that (you/s/he) had emphysema?" CBE was defined as reporting emphysema or chronic bronchitis or both.

NHANES participants ≥40 y old were also asked about chronic bronchitis symptoms as part of the NHANES Household Questionnaire Interview. The questions included cough ≥3 mo during the year ["(Do you/Does study participant), cough on most days for ≥3 consecutive months during the year?"], the number of years of cough ["For how many years (have you/has study participant) had this cough?"], phlegm ≥3 mo during the year ["(Do you/Does study participant) bring up phlegm on most days for 3 consecutive months or more during the year?"], wheezing in the past year [In the past 12 mo, (have you/has study participant) had wheezing or whistling in (your/his/her) chest?"], and number of years of phlegm production ["For how many years (have you/has study participant) had trouble with phlegm?"].

Covariates

Data on age, gender, race/ethnicity, family income, current asthma, and smoking were collected using questionnaires. Poverty income ratio (PIR) was estimated using guidelines and adjustment for family size, year, and state. Participants were dichotomized by PIR into levels below and above 1.85, the cutoff for Supplemental Nutrition Assistance Program (SNAP) eligibility.

The NHANES assessed cigarette smoking using the question "Have you smoked at least 100 cigarettes in your entire life?" (Pirkle et al. 1996). Participants who answered "No" were classified as "never smokers." Those who answered "Yes" were identified as smokers, and based on their answer to the question "Do you smoke cigarettes now?" they were classified as "current smokers" ("Yes") or "former smokers" ("No"). The NHANES also asked questions about exposure to secondhand smoke at home ["Does anyone smoke in (your/the study participant's) home?"] and in the workplace ("At this job or business, how many hours per day can you smell the smoke from other people's cigarettes, cigars, and/or pipes?"). We classified participants as exposed to secondhand smoke if they reported exposure at home, in the workplace, or both, and as nonexposed if they reported not being exposed at home and in the workplace.

Sensitization status was defined as serum-specific immunoglobulin E (IgE) against any of 15 inhalant allergens ≥0.35 kU/L [*Alternaria alternata*, *Aspergillus fumigatus*, Bermuda grass, birch, cat dander, cockroach, dog dander, dust mites (Der p 1 and Der f 1), mouse urine proteins, oak, ragweed, rat urine proteins, Russian thistle, or rye grass]. IgE levels were measured using the Pharmacia Diagnostics ImmunoCAP® 1000 System, now known as Thermo Scientific ImmunoCAP™ Specific IgE.

Statistical analysis

p-Values for differences in proportions or means by CBE status were calculated using a chi-squared test for categorical variables and Student's *t* test for continuous variables. Multivariate logistic regression was used to assess the association of endotoxin with diagnosis of CBE and chronic bronchitis symptoms. The models were adjusted for age, gender, race/ethnicity, PIR, cigarette smoking, exposure to secondhand smoke, and current asthma. The analysis of the association between endotoxin and chronic bronchitis symptoms was restricted to participants who did not report having asthma to ensure that asthma and/or asthma exacerbations did not account for the symptoms. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the associations were reported for $\log_{10}$-transformed endotoxin for the highest (≥29.67 EU/mg dust) versus lowest (<7.05 EU/mg dust) endotoxin quartile and for endotoxin levels above versus below the 90th percentile (58.73 EU/mg dust). Smoking, exposure to secondhand smoke, and sensitization to inhalant allergens were tested for effect modification on the association between endotoxin and CBE by including a product term of endotoxin and the specified variable in the model. All analyses were performed in SAS (version 9.4; SAS Institute Inc.). NHANES sample weights were used in all analyses to obtain unbiased national estimates. Standard errors (SEs), CIs, and *p*-values were developed in accordance with the complex survey design by using Taylor series linearization methods. *p*-Values <0.05 were considered statistically significant. The relationship between endotoxin and CBE was evaluated graphically to show the prevalence of CBE across a range of concentrations. This smooth plot was generated using R (version 3.4.2; R Core Team), and the modeling was performed using the GAM package.

Results

The characteristics of the study participants are described in Table 1. The median endotoxin concentration was 14.61 EU/mg dust (interquartile range: 7.05–29.67; min: 0.0003 EU/mg dust; max: 4722.66 EU/mg dust). CBE prevalence was 8.2%. The mean ± SE age of participants was 46 ± 0.64 y. Compared to participants who did not report CBE, those with CBE tended to be older and to be female. They were also more likely to be non-Hispanic white, to be impoverished, to be smokers, and to have asthma (Table 1).

In adjusted logistic regression models, endotoxin concentration in house dust was associated with higher prevalence of CBE [OR = 1.27 (95% CI: 1.00, 1.61) for $\log_{10}$(endotoxin); OR = 1.49 (95% CI: 1.05, 2.11) for highest vs. lowest endotoxin quartile; OR = 1.82 (95% CI: 1.18, 2.82) for above vs. below 90th endotoxin percentile] (Table 2). The positive association between endotoxin and CBE appeared to be limited to participants who were sensitized to inhalant allergens [e.g., for log(endotoxin), OR = 2.46 (95% CI: 1.72, 3.50) compared with OR = 0.80 (95% CI: 0.53, 1.22) for nonsensitized participants; interaction *p*-value = 0.001] (Table 2). The relationship between endotoxin concentrations and the prevalence of CBE increased

Table 1. Characteristics of study participants ≥20 y old by chronic bronchitis or emphysema (CBE) status from NHANES 2005–2006 ($n = 3{,}393$).

Characteristic	All participants	CBE		p-Value
		No	Yes	
Prevalence, n (%)	3,393 (100)	3,147 (91.8)	246 (8.2)	
Age, mean ± SE, years	46 ± 0.64	46 ± 0.68	52 ± 1.11	
Gender, n (%)				0.01
Males	1,654 (48.1)	1,544 (49.0)	110 (38.3)	
Females	1,739 (51.9)	1,603 (51.0)	136 (61.7)	
Race/ethnicity, n (%)				0.0001
Non-Hispanic white	1,598 (71.5)	1,439 (70.9)	159 (78.2)	
Non-Hispanic black	823 (11.4)	773 (11.8)	50 (7.8)	
Mexican American	727 (8.0)	711 (8.5)	16 (1.8)	
Other	245 (9.0)	224 (8.8)	21 (12.1)	
PIR, n (%)				0.008
<1.85	1,381 (28.8)	1,265 (28.0)	116 (37.7)	
≥1.85	1,868 (68.1)	1,749 (68.9)	119 (59.2)	
Missing	144 (3.1)	133 (3.1)	11 (3.2)	
Smoking, n (%)				<0.0001
Never smokers	1,751 (49.2)	1,678 (50.6)	73 (32.4)	
Current smokers	796 (25.6)	702 (24.4)	94 (39.2)	
Past smokers	843 (25.2)	764 (24.9)	79 (28.4)	
Secondhand smoke, n (%)				0.060
Exposed	1,013 (31.8)	915 (31.1)	98 (40.2)	
Not exposed	2,320 (66.7)	2,176 (67.4)	144 (58.1)	
Missing	60 (1.5)	56 (1.5)	4 (1.8)	
Current asthma, n (%)	276 (8.3)	199 (6.1)	77 (32.6)	<0.0001
Sensitization to inhalant allergens, n (%)	1,396 (40.4)	1,298 (40.5)	98 (38.3)	0.58
Endotoxin, median (IQR), EU/mg	14.61 (7.05–29.67)	14.57 (6.87–29.18)	14.87 (9.50–39.50)	

Note: p-Values are reported for differences in proportions or means by CBE. Reported percentages are adjusted for study design and NHANES sampling weights. EU, endotoxin units; IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; SE, standard error.

over the range of exposure values without obvious evidence of a threshold effect (Figure 1). Crude ORs for associations between endotoxin and CBE were similar to adjusted estimates for the total population, and in subgroup analyses by sensitization status to inhalant allergens (see Table S1).

In the adjusted analysis restricted to participants >40 y old who did not report asthma, endotoxin was associated with chronic bronchitis defined as cough and phlegm for ≥3 mo in a year for ≥2 y [OR = 1.78 (95% CI: 1.01, 3.12)] (Table 3). Crude ORs for associations between endotoxin and chronic bronchitis symptoms were similar to adjusted estimates (see Table S2).

Discussion

We examined the relationship between residential endotoxin levels and CBE prevalence in the U.S. general population. Our results suggest that the prevalence of CBE is associated with higher endotoxin concentrations in the home and that sensitization status modifies the relationship. The odds of CBE associated with increased endotoxin levels were higher in participants sensitized to inhalant allergens than in nonsensitized subjects.

Our results are consistent with the findings of some occupational studies on endotoxin and CBE or COPD but are surprising given the modest levels of exposure in most homes. In Norway, a cross-sectional study including 4,735 highly exposed farmers (with a geometric mean of all-seasons airborne endotoxin of 31,000 EU/m^3) found a significant but modest association of a 10-fold increase in endotoxin with chronic bronchitis [OR = 1.30 (95% CI: 1.00, 1.60)] and COPD [OR = 1.20 (95% CI: 1.00, 1.50)] (Eduard et al. 2009). Similar to our study, those authors defined chronic bronchitis as cough and phlegm ≥3 mo/y in the past 2 y, and COPD was defined as the 5% lower limit of normal prebronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio (Eduard et al. 2009). Among Dutch and Danish veterinarians as well as in agricultural workers with a median airborne endotoxin exposure level of 219 EU/m^3, Basinas et al. (2012) concluded that exposure to endotoxin levels >1,000 EU/m^3 increased by four times the odds of chronic bronchitis compared with levels of exposure <50 EU/m^3. In China, a longitudinal study of textile workers found that cumulative endotoxin exposure >1,000 EU/m^3-years had a partially significant association with chronic bronchitis in a cohort of 447 cotton workers who were followed for 5 y (Mehta et al. 2010). Conversely, a study in 105 never-smoker farmers working in confinement buildings found no relationship between airborne endotoxin and COPD (Monsó et al. 2004). In animal models, it was also demonstrated that endotoxin could induce emphysematous changes in the lung parenchyma (Brass et al. 2008). It is possible that the effect sizes

Table 2. Odds ratios and corresponding 95% confidence intervals for association of endotoxin with CBE overall and by sensitization to any of 15 inhalant allergens: NHANES 2005–2006.

Exposure contrast	All participants ($n = 3{,}393$)		Non-sensitized ($n = 1{,}788$)		Sensitized ($n = 1{,}396$)		Interaction p-values
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	
Log_{10}(endotoxin)	1.27 (1.00, 1.61)	0.047	0.80 (0.53, 1.22)	0.30	2.46 (1.72, 3.50)	<0.0001	0.001
Q4 (≥29.67 EU/mg dust) versus Q1 (<7.05 EU/mg dust)	1.49 (1.05, 2.11)	0.026	0.73 (0.37, 1.46)	0.37	5.57 (2.06, 15.07)	0.0007	0.0064
≥90th versus <90th percentile (58.73 EU/mg dust)	1.82 (1.18, 2.82)	0.0072	0.82 (0.30, 2.26)	0.70	2.92 (1.76, 4.82)	<0.0001	0.040

Note: Models adjusted for age, gender, race/ethnicity, poverty income ratio (PIR), cigarette smoking, exposure to secondhand smoke, and current asthma. OR with corresponding 95% CI reported for log(endotoxin), for highest (Q4) vs lowest (Q1) endotoxin quartile, and for ≥90th vs. <90th endotoxin percentile. CBE, chronic bronchitis or emphysema; CI, confidence interval; EU, endotoxin units; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; Q1, quartile 1; Q4, quartile 4.

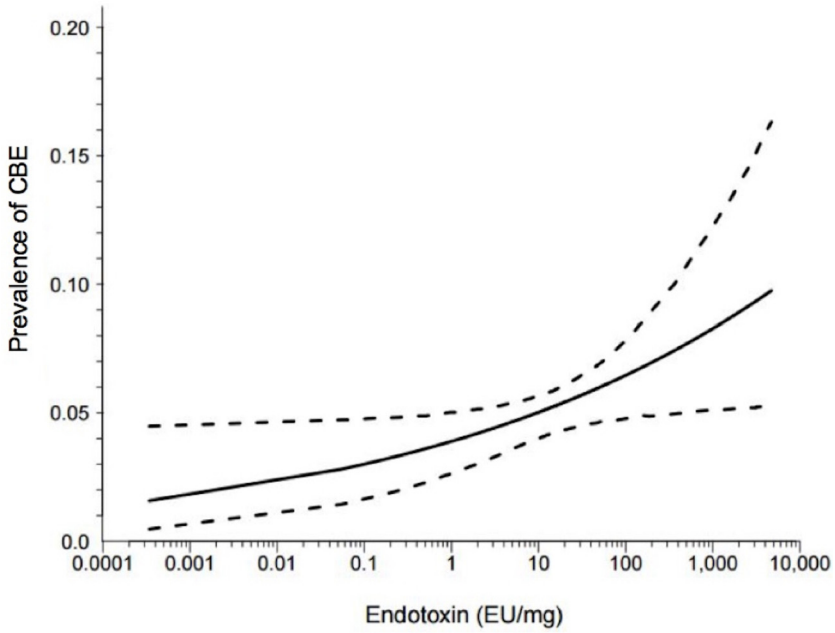

Figure 1. Smoothed plot illustrating the increase in adjusted prevalence of chronic bronchitis or emphysema (CBE) as a function of endotoxin. The model is adjusted for age, gender, race/ethnicity, poverty income ratio (PIR), cigarette smoking, exposure to secondhand smoke, and current asthma. The solid line represents the smoothed mean CBE prevalence, and the dashed lines indicate the upper and lower 95% confidence intervals.

reported in occupational studies were attenuated by a healthy worker effect or by a survival bias. For example, Mehta et al. (2010) reported that 39 out of 260 cotton workers and 31 out of 243 silk workers died by the end of their study. In one of their surveys, 30 cotton workers and 44 silk workers did not undergo spirometry testing because of poor health.

To our knowledge, our study is the first to examine the relationship between residential endotoxin exposures and CBE in the general U.S. population. A few smaller-scale studies have investigated the health status of patients with COPD. Osman et al. (2007) examined whether indoor pollutants were associated with worse health status in 148 patients with severe COPD and reported no significant results for endotoxin. Likewise, Bose et al. (2016) studied household exposure to airborne as well as settled dust endotoxin and respiratory morbidity in a cohort of 48 former smokers with moderate or severe COPD; they also did not find an association. The levels of endotoxin in these studies were high compared with those in our analysis. Osman et al. (2007) reported a surprising mean endotoxin concentration of 95.8 EU/mg of dust. In the study by Bose et al. (2016), the median endotoxin concentrations were 74.3 (interquartile: 40.7–129) EU/mg in dust from bedroom floors and 133.5 (interquartile: 86.3–236) EU/mg in living room floor dust. These concentrations far exceed the values reported in the National Survey of Endotoxin in U.S. Housing (Thorne et al. 2005) or in this NHANES endotoxin study (Thorne et al. 2015).

There are many mechanisms by which endotoxin might be associated with CBE and COPD. Endotoxin is known to cause neutrophilic airway inflammation and to prompt the transcription of inflammatory cytokines with an invasion of the lungs by neutrophils. The neutrophils activated by tumor necrosis factor–α (TNF-α) and cytokines release neutrophil elastase, which damages the lung parenchyma and induces hypersecretion of mucus, causing emphysema and chronic bronchitis (Doreswamy and Peden 2011; Hađina et al. 2008; Hunt et al. 1994; Nightingale et al. 1998; Astrakianakis and Murray 2014; Sikkeland et al. 2009). In mice, repeated exposure to aerosolized endotoxin was found to be associated with significant increases in hydroxyproline as well as expression of metalloproteinases. This increase has also been observed in the alveolar macrophages of people with emphysema (Brass et al. 2008). Endotoxin can also induce lung injury through oxidative stress with the production of free radicals involved in lipid peroxidation. Consistent with our findings of a stronger association between endotoxin and CBE in participants sensitized to inhalant allergens, endotoxin has been found to have worse effects in atopy via goblet cell hyperplasia and subsequent mucus hypersecretion causing peribronchial inflammation in atopic people (Charavaryamath et al. 2005; Takeyama et al. 2001).

Table 3. Association between $\log_{10}$(endotoxin) and chronic bronchitis symptoms in participants ≥40 y old who did not report asthma: NHANES 2005–2006.

Symptoms	*n*/*N*	OR (95% CI)	*p*-Value
Cough ≥3 mo in year	194/1,866	1.47 (1.15, 1.89)	0.0021
Cough ≥3 mo in year for ≥2 y	145/1,857	1.58 (1.09, 2.29)	0.016
Phlegm ≥3 mo in year	189/1,869	1.54 (1.20, 1.98)	0.0007
Phlegm ≥3 mo in year for ≥2 y	148/1,862	1.55 (1.19, 2.01)	0.0011
Wheezing in past year	212/1,871	1.48 (1.03, 2.12)	0.032
Cough and phlegm ≥3 mo in year	107/1,870	2.35 (1.52, 3.63)	0.0001
Cough and phlegm ≥3 mo in year for ≥2 y	77/1,864	2.08 (1.10, 3.297)	0.025
Cough and phlegm ≥3 mo in year for ≥2 y or CBE diagnosis	221/1,900	1.67 (1.26, 2.22)	0.0004

Note: Models adjusted for age as a continuous variable and gender (male and female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other), poverty income ratio (PIR; <1.85 vs. ≥1.85), cigarette smoking, diabetes, sensitization to inhalant allergens, occupation, and hypertension as categorical variables. Analysis was restricted to participants who did not report having asthma to ensure that asthma did not account for chronic bronchitis symptoms. CBE, chronic bronchitis or emphysema; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

Our study has limitations. Owing to the cross-sectional design of the study, temporality between endotoxin exposure and CBE cannot be established. Dust for endotoxin analysis was only sampled once, but endotoxin measured in mattresses and from bedroom floors has been suggested to indicate long time exposures (Heinrich et al. 2003). There was no information on the duration of potential exposure to endotoxin; thus, we do not know for how long the participants would have to be exposed to house-dust endotoxin for CBE or chronic bronchitis symptoms to occur. CBE was defined by self-report of doctor or health-care professional diagnosis and could not be confirmed. We did not perform the subgroup analyses for the association between endotoxin and self-reported doctor-diagnosed emphysema and chronic bronchitis separately because of the limited number of outcome events. We were unable to directly examine the relationship between house-dust endotoxin and COPD owing to the lack of spirometry data documenting airflow obstruction in our participants. Nonetheless, our study has major strengths. To our knowledge, it is the first study to ever examine the association of endotoxin levels in homes with the prevalence of chronic bronchitis and emphysema. It used a large sample representative of the U.S. population, which increases the generalizability of its findings. We used a precise measurement of endotoxin with rigorous quality-control measures. Our analysis adjusted for several covariates to reduce confounding. Because self-reports tend to underestimate smoking, our analysis used a strong definition of cigarette smoking, including serum cotinine levels to more accurately assess current smoking and self-reporting to account for past smoking (Connor Gorber et al. 2009). In addition to examining the association between endotoxin and reported CBE, our study also looked at chronic bronchitis symptoms to capture potential under-reported cases, and our results consistently confirmed the association found between endotoxin and CBE.

Conclusion

In conclusion, exposure to endotoxin found in house dust at doses well below occupational levels was associated with higher odds of CBE, particularly in people sensitized to inhalant allergens. Future studies should examine whether public health measures aimed at lowering endotoxin exposure in housing can help reduce the prevalence of CBE in addition to the recognized reduction in wheeze and asthma outcomes.

Acknowledgments

A.M. assisted with development of the research questions and data analysis and was the principal author of this manuscript. P.S.T. directed the endotoxin analysis of the NHANES samples, contributed to the study design, collaborated on development of the research questions and edited the manuscript. D.C.Z. and P.S. contributed to the conception, hypothesis delineation, and design of this component of the NHANES study. J.W. and R.D.C. contributed to the statistical analysis and interpretation of the data. All authors provided edits and comments on the manuscript.

The authors acknowledge N. Metwali, who directed the laboratory analysis of endotoxin samples, and thank C. Co for assistance with the GAM plot.

Sample extraction and endotoxin analysis work at the University of Iowa was funded by the Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics (NCHS) (200-2010-34238 NCE1). Data analysis was funded through a grant to the University of Iowa, Environmental Health Sciences Research Center [National Institutes of Health (NIH) P30 ES005605], the University of Iowa Center for Health Effects of Environmental Contamination (CHEEC), and through a contract to Social & Scientific Systems, Inc. (HMSN291200555553). This work was also funded in part by the Intramural Research Program of the NIH/National Institute of Environmental Health Sciences (NIEHS) (NIH Z01 ES025041).

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