Environment International 112 (2018) 218–226

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Endotoxin predictors and associated respiratory outcomes differ with climate regions in the U.S.

Angelico Mendy[a], Jesse Wilkerson[b], Päivi M. Salo[c], Richard D. Cohn[b], Darryl C. Zeldin[c], Peter S. Thorne[a,*]

[a] Department of Occupational and Environmental Health, University of Iowa, Iowa City, IA, United States
[b] Social & Scientific Systems, Inc., Durham, NC, United States
[c] Division of Intramural Research, National Institute of Environmental Health Sciences, NIH Research Triangle Park, NC, United States

ARTICLE INFO

Keywords:
Endotoxin
Asthma
Wheeze
Climate
House dust

ABSTRACT

Rationale: Although endotoxin is a recognized cause of environmental lung disease, how its relationship with respiratory outcomes varies with climate is unknown.
Objective: To examine the endotoxin predictors as well as endotoxin association with asthma, wheeze, and sensitization to inhalant allergens in various US climate regions.
Methods: We analyzed data on 6963 participants in the National Health and Nutrition Examination Survey. Endotoxin measurements of house dust from bedroom floor and bedding were performed at the University of Iowa. Linear and logistic regression analyses were used to identify endotoxin predictors and assess endotoxin association with health outcomes.
Results: The overall median house dust endotoxin was 16.2 EU/mg; it was higher in mixed-dry/hot-dry regions (19.7 EU/mg) and lower in mixed-humid/marine areas (14.8 EU/mg). Endotoxin predictors and endotoxin association with health outcomes significantly differed across climate regions. In subarctic/very cold/cold regions, $\log_{10}$-endotoxin was significantly associated with higher prevalence of wheeze outcomes (OR:1.48, 95% CI:1.19–1.85 for any wheeze, OR:1.48, 95% CI:1.22–1.80 for exercise-induced wheeze, OR:1.50, 95% CI:1.13–1.98 for prescription medication for wheeze, and OR:1.95, 95% CI:1.50–2.54 for doctor/ER visit for wheeze). In hot-humid regions, $\log_{10}$-endotoxin was positively associated with any wheeze (OR:1.66, 95% CI:1.04–2.65) and current asthma (OR:1.56, 95% CI:1.11–2.18), but negatively with sensitization to any inhalant allergens (OR:0.83, 95% CI:0.74–0.92).
Conclusion: Endotoxin predictors and endotoxin association with asthma and wheeze differ across U.S. climate regions. Endotoxin is associated positively with wheeze or asthma in cold and hot-humid regions, but negatively with sensitization to inhalant allergens in hot-humid climates.

1. Introduction

The incidence and severity of lung illnesses are greatly affected by environmental factors such as pathogen-associated molecular patterns (PAMPs) of which, endotoxin has arguably been the most studied (Sigsgaard and Heederik, 2011). Endotoxin is a lipopolysaccharide (LPS) from the outer membrane of Gram-negative bacteria cell wall and is ubiquitously found in our environment (Thorne and Heederik, 1999). It has been described to cause neutrophilic airway inflammation by binding to CD14 associated with TLR4 and MD2 (LY96), triggering the activation of nuclear factor κB and the stimulation of the Th1 arm of the immune system (Doreswamy and Peden, 2011). As a result, endotoxin inhalation causes neutrophilic asthma and wheeze not only in occupational settings, but also in households (Michel et al., 1989; Thorne et al., 2005). There are, however, postulates that early-life exposure to low doses of endotoxin and other microbial components may protect against allergy and immunoglobulin E (IgE)-mediated asthma (von Mutius, 2016). The mechanism is not fully understood, but seems to be due to a downregulation of Th2 immune response. Yet, this Th1/Th2 paradigm does not fully explain the protective effect against asthma. Hypo-responsiveness with decreased IFN-γ, tumor necrosis factor-α, IL-10, and IL-12 has been proposed to be another likely possibility (Braun-Fahrlander et al., 2002).

Endotoxin predictors and endotoxin association with respiratory outcomes have been examined previously in the US population using the National Health and Nutrition Examination Survey (NHANES), and

* Corresponding author at: University of Iowa College of Public Health, 100 CPHB, S341A, 145 N Riverside Dr., Iowa City, IA 52242-2207, United States.
E-mail address: peter-thorne@uiowa.edu (P.S. Thorne).

https://doi.org/10.1016/j.envint.2017.12.003
Received 19 September 2017; Received in revised form 1 December 2017; Accepted 1 December 2017

results suggested that endotoxin was associated with higher prevalence of wheeze irrespective of sensitization status (Thorne et al., 2015). Some studies have reported that climate affects the determinants of indoor pollutants such as benzene, toluene, formaldehyde, acetaldehyde, particulate matter, and nitrogen dioxide, as well as their relationship with respiratory conditions (Héroux et al., 2010; Pönkä, 1991). However, no study to date has examined whether endotoxin predictors or the association of endotoxin with respiratory outcomes differ by climate. Our study is the first to examine climatic variability in a large sample representative of the US population.

2. Materials and methods

2.1. Data source and study design

We used data from the 2005–2006 NHANES by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). It is a continuous cross-sectional survey of the US non-institutionalized civilian population selected using a complex multistage sampling design to derive a representative sample of the US population. Individuals with low-income, adolescents 12–19 years, people aged ≥ 60 years, African-Americans, and Mexican-Americans were oversampled to ensure suitable samples for these subgroups. To protect participant confidentiality, all data analysis using restricted, not publicly available variables (i.e., climate regions) was conducted at the NCHS Atlanta Research Data Center (RDC). For our study, all the 6963 NHANES child and adult participants who were aged 1 to 150-year-old and had data on house dust endotoxin were included. NHANES protocols were approved by the Institutional Review Boards of the NCHS and CDC and informed consent was obtained from all participants (CDC, 2006).

2.2. Climate regions

As required by NCHS, 8 US climate regions were aggregated into four categories: subarctic/very cold/cold, mixed-humid/marine, hot-humid, and mixed-dry/hot-dry to avoid data suppression due to small sample cells. The definition of each of the climate region is provided by the US Department of Energy guide to determining depending on temperature and precipitation. A detailed description of the different climate regions is available at https://www1.eere.energy.gov/buildings/publications/pdfs/building_america/ba_climateguide_7_1.pdf (Baechler et al., 2010).

A map of the US with the climate regions by county included in the study is displayed in Fig. 1.

2.3. Endotoxin measurement

Combined bed and bedroom floor dust samples were collected at each participant's home using a Sanitaire™ Model 3683 vacuum cleaner and a Mitest™ Dust Collector (Indoor Biotechnologies, Inc., Charlottesville, VA). A 1-square yard (0.84 m^2) surface on both bed and adjacent floor was independently vacuumed for two minutes. Details on the dust collection methods are available at https://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/allergen_manual_06.pdf). Dust samples were analyzed for endotoxin at the University of Iowa Pulmonary Toxicology Facility using a kinetic chromogenic *Limulus* amebocyte lysate assay previously described and with extensive quality assurance measures. The quality assurance measures included rigorous chain of custody verification, internal and external audits, bar coding of samples, use of a single lot of assay reagents, blind repeats of NHANES dust samples ($N = 665$), use of a single microplate reader, and application of Westgard rules to accept or reject a run. Endotoxin concentrations were reported in Endotoxin Units (EU) per mass of sieved dust (mg). The lower limit of detection was 0.0005 EU/mg. Our updated data on dust endotoxin concentration in NHANES was released in February 2014.

2.4. Wheeze and asthma outcomes

Wheeze and asthma were assessed using a questionnaire administered to each study participant (SP) or their parent if they were a young child (< 12-year-old). Wheeze outcomes were measured using the following questions: "*In the past 12 months, {have you/has SP} had wheezing or whistling in {your/his/her} chest?*" (Any wheeze), "*In the past 12 months, {has your/has SP's} chest sounded wheezy during or after exercise or physical activity?*" (Exercise-induced wheeze), "*In the past 12 months, {have you/has SP} taken medication prescribed by a doctor for wheezing or whistling?*" (Prescription medication for wheeze), *"In the past 12 months, how many times {have you/has SP} gone to the doctor's office or the hospital emergency room for one or more of these attacks of wheezing or whistling?"* (Doctor/ER visit for wheeze). The link to the NHANES wheeze questionnaire can be found at https://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/RDQ_D.htm#RDQ070.

Asthma outcomes were defined using the questions: "*Has a doctor or other health professional ever told {you/SP} that {you have/s/he/SP has} asthma?*" (Diagnosed asthma), "{*Do you/Does SP} still have asthma?*" (Current asthma), "*During the past 12 months, {have you/has SP} had an episode of asthma or asthma attack?"* (Asthma attack in past 12 Months). Asthma medication in past 30 days was determined through self-report of prescription medications use by the participant within the one-month period prior to the survey. The link to the NHANES asthma questionnaires can be found at https://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/MCQ_D.htm#MCQ010.

2.5. Sensitization to inhalant allergens

Serum IgE specific to fifteen inhalant allergens (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat, dog, cockroach, *Alternaria alternata*, ragweed, rye grass, bermuda grass, oak, birch, *Aspergillus fumigatus*, thistle, mouse, rat) was measured using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan), now known as Thermo Scientific™ ImmunoCAP Specific IgE. Sensitization status was defined as IgE specific to any of the inhalant allergens ≥ 0.35 kU/L.

2.6. Covariates

Data on socio-demographics and home characteristics were collected using questionnaires. The socio-demographic characteristics considered were age, gender, race/ethnicity, and family income. The home characteristics included questions on whether the was rented or owned, the type of home (single family detached, multifamily, or trailer), when was home built, the number of years lived in the home, the presence of mildew or musty smell, carpeted surface, pets, cockroach, of a smoker, and of children in the home. Data on the room temperature was also collected during the home visits. The surveys collecting data on the outcomes and the covariates were administered approximately two weeks before the house dust samples.

2.7. Statistical analysis

In the descriptive analysis, the participants' characteristics were compared across the climate regions using the chi-square test. For each climate region, we assessed endotoxin predictors and the endotoxin relationship with respiratory outcomes as well as sensitization to inhalant allergens. Endotoxin predictors were first determined in the overall study population using forward stepwise linear regression. The threshold for entry was set as $P < 0.10$ and the threshold for removal was set as $P > 0.20$. A multiple linear regression analysis was subsequently performed in each climate regions to find endotoxin predictors specific to each of them. The multiple linear regression models included