Sleep Health xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Sleep Health

Journal of the National Sleep Foundation

journal homepage: sleephealthjournal.org

Sleep apnea and pesticide exposure in a study of US farmers☆

Brittney O. Baumert, MPH [a], Megan Ulmer Carnes, PhD [a], Jane A. Hoppin, ScD [b], Chandra L. Jackson, PhD [a], Dale P. Sandler, PhD [a], Laura Beane Freeman, PhD [c], Paul K. Henneberger, ScD [d], David M. Umbach, PhD [e], Srishti Shrestha, PhD [a], Stuart Long, BS [f], Stephanie J. London, MD, DrPH [a,*]

[a] Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA
[b] Department of Biological Sciences, Center for Human Health and the Environment, North Carolina State University, NC, USA
[c] Occupational and Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD, USA
[d] Respiratory Health Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, USA
[e] Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA
[f] Westat, Durham, NC, USA

ARTICLE INFO

Article history:
Received 17 May 2017
Received in revised form 17 August 2017
Accepted 18 August 2017
Available online xxxx

Keywords:
Pesticides
Sleep apnea
Carbofuran
Carbamates
Sleep disorder breathing
Agriculture

ABSTRACT

Introduction: Carbamate and organophosphate pesticides inhibit acetylcholinesterase, and poisoning leads to respiratory depression. Thus, involvement in sleep apnea is plausible, but no data exist at lower levels of exposure. Other pesticides could impact sleep apnea by different mechanisms but have not been studied. Our study examines the associations between pesticide exposure and sleep apnea among pesticide applicators from a US farming population.

Participants and methods: We analyzed data from 1569 male pesticide applicators, mostly farmers, from an asthma case-control study nested within the prospective Agricultural Health Study. On questionnaires, participants reported use of specific pesticides and physician diagnosis plus prescribed treatments for sleep apnea. We used multivariable logistic regression to estimate associations between ever use of 63 pesticides and sleep apnea (234 cases, 1335 noncases).

Results: The most notable association was for carbofuran, a carbamate (100 exposed cases, odds ratio 1.83, 95% confidence interval 1.34-2.51, $P = .0002$). Carbofuran use began before reported onset of sleep apnea in all cases.

Discussion: This study adds to the known adverse health outcomes of exposure to carbofuran, a pesticide canceled in the United States in 2009 for most agricultural purposes but persists in the environment and remains in use in some other countries.

Conclusions: We conducted the first epidemiological study investigating the association of pesticide exposure and sleep apnea. Our results in a male agricultural population suggests that exposure to carbofuran is positively associated with sleep apnea.

Introduction

Sleep-disordered breathing is characterized by instantaneous cessations in the rhythm of breathing (apneas) or momentary or prolonged reduction in the amplitude of breathing (hypopneas).[1] Sleep apneas and hypopneas can be caused by obstruction of the upper airway (obstructive) or reduced respiratory motor neuron function (central), or reflect mixed obstructive and central etiologies.[1] Most sleep apnea-hypopnea events result from anatomical anomalies combined with a disturbance in the neurochemical control of the upper airway musculature.[1–3] The neurotransmitter acetylcholine influences the function of upper airway motor neurons that control breathing during wakefulness and sleep.[4]

Sleep apnea is a major contributor to morbidity, mortality, and reduced quality of life.[1] In men, obstructive sleep apnea prevalence has been estimated at 3.3% with highest rates at ages 45-64.[5] Risk factors include increasing age, male sex, central obesity, craniofacial and upper airway abnormalities, cardiovascular disease, and diabetes.

☆ Competing financial interests: none.

* Corresponding author at: National Institute of Environmental Health Sciences, 111 TW Alexander Dr, Rall Bldg, A306, Research Triangle Park, NC 27709. Tel.: +1 919 541 5772.
E-mail address: london2@niehs.nih.gov (S.J. London).

https://doi.org/10.1016/j.sleh.2017.08.006
2352-7218/

Central sleep apnea accounts for under 5% of patients presenting for sleep apnea evaluation.[5,6] Obstructive and central sleep apnea can co-occur, but there are distinct risk factors for central apnea including heart failure, stroke, high altitude, and opioid medication use.[6] Data on environmental contributors to sleep apnea are few. Associations with air pollutants were identified in 2 recent population-based studies[7,8]; an increased risk was reported in World Trade Center–exposed rescue or recovery workers.[9] Two smaller studies have reported associations with solvent exposure.[10,11]

Both organophosphate and carbamate pesticides act by inhibiting acetylcholinesterase, an enzyme that hydrolyzes acetylcholine. Therefore, these agents can interfere with neuronal function, including control of respiration.[4] In pesticide poisoning, respiratory depression occurs and may be fatal.[12,13] In animal studies, exposure to these pesticides elicits a spectrum of neurochemical, neurophysiological, and neurobehavioral deficits including respiratory depression and interference with sleep-wake cycles.[14] Thus, exposure to pesticides that inhibit acetylcholinesterase is potentially relevant to sleep apnea in humans. Pesticides in other chemical classes are also neurotoxic and could theoretically be relevant to sleep apnea.[15] Recent data suggest that carbamates can interact with the melatonin receptor[16] and that melatonin may play a role in sleep apnea,[16–18] providing an alternative or complementary mechanism for carbamates to impact this disorder.

No epidemiological studies exist of sleep apnea in relation to pesticide exposure. We aimed to address this gap by investigating associations between sleep apnea and pesticide exposure among male pesticide applicators in the Agricultural Lung Health Study (ALHS).

Participants and methods

Study population

The ALHS is a case-control study of current asthma nested within the prospective Agricultural Health Study (AHS). The AHS enrolled pesticide applicators applying for, or renewing, pesticide-use licenses in North Carolina and Iowa[19] along with their spouses in 1993-1997. The ALHS identified potential asthma cases and noncases among respondents to an AHS follow-up telephone interview conducted 2005-2010 (24,171 pesticide applicators, 19,959 spouses). The Institutional Review Board of the National Institute of Environmental Health Sciences approved the study. All participants provided informed consent.

Details of ALHS enrollment have been published.[20,21] Briefly, we enrolled 3301 ALHS participants between 2009 and 2013 (1223 asthma cases, response rate = 51.7%; 2078 noncases, response rate = 50.0%). We included 3 categories of asthma cases: doctor-diagnosed current asthma (n = 876), potential undiagnosed asthma based on current asthma symptoms and medication use in nonsmokers (n = 309), and overlapping diagnoses of current asthma and either chronic obstructive pulmonary disease or emphysema in nonsmokers (n = 38). Noncases were randomly selected from those without the above conditions. We analyzed only the 1596 male pesticide applicators; 97% of pesticide applicators were men.

Sleep apnea assessment

Information on physician-diagnosed sleep apnea came from the ALHS computer-assisted telephone interview. We classified participants who reported "yes" to "Have you ever been told by a doctor that you have sleep apnea?" and "yes" to 1 of 4 possible sleep apnea treatments ("CPAP," "surgery," "bi-level," or "other oral device") as sleep apnea cases (n = 236). Requiring treatment in the definition increases reliability of this self-reported outcome.[22] Participants reporting "yes" to physician-diagnosed sleep apnea but not reporting a treatment for sleep apnea were excluded from analysis (n = 49). Otherwise, individuals were classified as non-cases (n = 1360).

Assessment of pesticide exposure

On earlier AHS questionnaires (www.aghealth.nih.gov), individuals provided names of chemicals used ever in their lifetimes (Phase 1, 1993-1997), in the most recent farming season (Phase 2, 1999-2003), and since last study contact (Phase 3, 200-2010). Reported names were linked to pesticide active ingredient names using the Environmental Protection Agency (EPA) Pesticide Classification Code.[23] We analyzed the 63 pesticides reported by >1% of applicators at Phase 3 that were also reported by at least 5 (of 236) sleep apnea cases. The 63 pesticides included 40 herbicides and plant growth regulators, 19 insecticides, 3 fungicides, and 1 rodenticide.

For 22 of the 63 pesticides, we had data on lifetime days of exposure, from the AHS Phase 1 enrollment questionnaire, to assess dose-response to individual pesticides.[23] We divided lifetime days of use into approximate tertiles for comparison with never users.

Statistical analyses

Using logistic regression, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) for both ever-never pesticide exposure and lifetime days of pesticide exposure in relation to sleep apnea. Consistent with previous AHS analyses, we included continuous age and state (North Carolina or Iowa) in all models. We additionally included asthma status, the design variable for selection of ALHS participants.

We evaluated as potential covariates additional variables implicated in sleep apnea etiology from the literature including body mass index (BMI, continuous), history of diabetes, cardiovascular disease, hypertension, alcohol use (24-hour recall), caffeine intake (24-hour recall), and smoking (never, past, current, and pack-years). We calculated BMI from height and weight measured at the ALHS home visit. Individuals were classified as having cardiovascular disease if they answered "yes" to either ever experienced heart failure (asked in ALHS) or ever experienced a stroke (asked at AHS Phase 3). Final models included all the aforementioned covariates except alcohol use, caffeine intake, or smoking because they did not separately change regression coefficients by at least 10%.

Analyses included the 1569 individuals (98.3% of 1596) with complete covariate data (234 cases of sleep apnea and 1335 non-cases). A secondary analysis evaluated waist circumference, measured at the ALHS home visit, as an alternative adiposity adjustment variable to BMI (sleep apnea cases = 227, non-cases = 1307).

In additional analyses, we compared the year of first pesticide exposure to onset of sleep apnea. We also examined effect modification, and interaction, separately by asthma status and personal protective equipment use. In addition to the uncorrected *P* values presented in the tables, we calculated false discovery rate–adjusted *P* values (P_{FDR}) for the primary analysis, accounting for 63 tests using the Benjamini-Hochberg method.[24] Adjustment variables were the same as in the main analyses. We used SAS (SAS Institute Inc, Cary, NC, Version 9.3, except for tetrachoric correlations calculated using Version 9.4). Analyses used the following releases of the AHS data: P3REL201209.00, PIREL201209.00, and AHSREL201304.00.

Results

Nearly all participants were white (98.4%); few (<5%) were current smokers. Sleep apnea cases were slightly older than noncases (Table 1). As expected, BMI was higher among cases (Table 1); the adjusted OR per unit increase in BMI was 1.16 (95% CI 1.13-1.19). Sleep apnea was more common among asthmatics (Table 1): adjusted OR 2.47, 95% CI 1.87-3.27. The 234 sleep apnea cases reported the

Please cite this article as: Baumert BO, et al, Sleep apnea and pesticide exposure in a study of US farmers, Sleep Health (2017), https://doi.org/10.1016/j.sleh.2017.08.006