Serum Heavy Metals and Obstructive Lung Disease

Results From the National Health and Nutrition Examination Survey

Haala K. Rokadia, MD; and Shikhar Agarwal, MD

Background: Exposure to hazardous heavy metals such as cadmium and lead has been associated with several chronic diseases. Heavy metal exposure may contribute to increased oxidative stress and inflammation in the lungs, resulting in tissue destruction manifesting clinically as obstructive lung disease (OLD). We aimed to evaluate the association between serum cadmium and lead concentration and OLD.

Methods: Pooled cross-sectional data from the National Health and Nutrition Examination Survey 2007-2010 were used. OLD was defined as an FEV_1/FVC ratio < 0.7 by spirometry. Active smokers were defined as self-reported current smokers or those with measured serum cotinine ≥ 10 ng/mL. Serum cadmium and lead levels were measured using mass spectrometry.

Results: The prevalence of OLD was 12.4% (95% CI, 10.2%-13.6%). The mean (SE) cadmium levels in the OLD group were significantly higher in comparison with normal control subjects (0.51 [1.04] vs 0.33 [1.02], $P < .001$). Similarly, mean (SE) serum lead concentration was significantly higher in the OLD group compared with the control population (1.73 [1.02] vs 1.18 [1.0], $P < .001$). The association between OLD and smoking was significantly attenuated after adjusting for serum cadmium concentration. In addition, we demonstrated a progressive increase in serum cadmium concentrations with worsening FEV_1 % predicted values among smokers in our study population.

Conclusion: In a large representative sample of the US population, we demonstrated a significant association between OLD and serum cadmium and lead concentrations. Cadmium appeared to partially mediate the association between smoking and OLD. A dose-response effect between increasing cadmium concentration and progressively worsening lung function was observed in smokers.

CHEST 2013; 143(2):388–397

Abbreviations: NHANES = National Health and Nutrition Examination Survey; OLD = obstructive lung disease

In 2005, COPD contributed to 126,005 US deaths in individuals > 25 years old,[1] which represents an 8% increase compared with 2000.[1] Further, COPD is known to contribute to a limitation of patient functional status and increased health care expenditures.[2]

Tobacco smoke exposure,[3] occupational exposures,[4] and air pollution[5] have been associated with the development and progression of COPD. The suggested pathogenesis of COPD from environmental exposure to heavy metals involves chronic inflammation and uncontrolled oxidative stress.[6-8]

The Agency for Toxic Substances and Disease Registry 2011 identified both cadmium and lead among the top 10 environmental hazards.[9] Although small

DOI: 10.1378/chest.12-0595

observational studies[10-13] have demonstrated the association between cadmium exposure and pulmonary disease, the evidence is insufficient to support a causal relationship between cadmium and COPD. Similarly, a few small studies have demonstrated the adverse effects of lead exposure on pulmonary health.[14,15] However, a clear characterization of absolute pulmonary risk resulting from heavy metal exposure is lacking. With this background, we aimed to study the association between heavy metal exposure based on serum cadmium and lead levels and obstructive lung disease (OLD) in a large representative sample of the US population.

MATERIALS AND METHODS

Study Population

This study analyzed pooled data from the 2007-2008 and 2009-2010 National Health and Nutrition Examination Surveys (NHANES). NHANES is an ongoing cross-sectional survey of the civilian, noninstitutionalized US population.[16]

Exposure and Outcome Assessment

Cigarette smoking status was determined using serum cotinine measurements, along with questionnaire items, including "Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes?"[16] Active smokers were defined by self-reported active cigarette smoking or by measured serum cotinine ≥ 10 ng/mL.[17] All nonactive smokers by self-report were classified as former smokers and never smokers based on survey question responses. Serum lead and cadmium concentrations were assayed using plasma mass spectrometry from stored whole-blood samples from NHANES 2007-2008 and 2009-2010 participants.

Spirometric data were collected on participants aged 18 to 79 years who met strict inclusion criteria as detailed per NHANES.[16] Participants with OLD were defined as individuals with baseline spirometry with $FEV_1/FVC < 0.7$. Calculations of lower limit of normal and % predicted for FEV_1, FVC, and FEV_1/FVC were performed based on sex, race, height, and age calculations according to Hankinson et al.[18] OLD was further characterized by severity based on FEV_1 values, specifically mild ($FEV_1 \geq 80\%$ predicted) and moderate-severe ($FEV_1 < 80\%$ predicted). This definition was selected per 2004 American Thoracic Society guidelines and GOLD (Global Initiative for Obstructive Lung Disease) criteria.[19,20]

Measurement of Confounders and Mediators

We adjusted our analysis for the presence of cardiovascular disease, congestive heart failure, stroke, and chronic kidney disease and for traditional cardiovascular risk factors including age, sex, race, hypertension, hyperlipidemia, BMI, diabetes, and C-reactive protein.

Hypertension was defined as systolic BP >140 mm Hg, diastolic BP >90 mm Hg, a self-reported diagnosis of hypertension, or self-reported use of antihypertensive medication. Hyperlipidemia was defined as total blood cholesterol >200 mg/dL, a self-reported diagnosis of hyperlipidemia, or self-reported use of cholesterol-lowering medication. Diabetes was defined as a self-reported diagnosis of diabetes or self-reported use of insulin or oral agents.

The glomerular filtration rate was estimated using the modification of diet in renal disease study formula.[21,22] Serum creatinine was standardized across surveys based on calibration equations.[23] Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m². BMI was calculated from self-reported current height and weight.

Statistical Analysis

Statistical analysis was performed using Stata, version 12.0 (StataCorp LP). Data from the NHANES 2007-2008 and 2009-2010 surveys were pooled using standard methods, and subsequently, 4-year combined weights were calculated. Survey statistics traditionally used to analyze complex semirandom survey designs were employed to analyze these data. Multivariate linear regression analysis was performed with OLD as the outcome measure in the regression models to obtain adjusted effect estimates and their 95% CIs after accounting for the previously mentioned confounders.

RESULTS

Our study included 9,575 subjects, who were representative of 182,987,327 noninstitutionalized individuals in the United States. The prevalence of OLD was estimated at 12.4% (95% CI, 10.2%-13.6%). Table 1 demonstrates the demographic and clinical characteristics of the study population. In comparison with the control population, the subjects with OLD were significantly older ($P < .001$) and had a male ($P < .001$) and white ($P < .001$) predominance. We observed that the OLD group had a significantly increased prevalence of coronary artery disease, stroke, and congestive heart failure in comparison with the control population ($P < .01$ for all comparisons). There were significant differences in the smoking characteristics between the study groups. We observed that, in comparison with the control population, the OLD group had a significantly higher prevalence of active smoking (41.0% vs 26.7%) and former smoking (29.8% vs 18.8%).

Table 2 demonstrates the geometric mean of serum cadmium and lead concentrations in the study sample. The mean (SE) serum cadmium level in the OLD group was significantly higher compared with that of the control population (0.51 [1.04] μg/L vs 0.33 [1.02] μg/L, $P < .001$). Similarly, the mean (SE) serum lead level in the OLD group was 1.73 (1.02) μg/dL, which was significantly higher than that seen in the control population (1.18 [1.0] μg/dL, $P < .001$). Upon stratification by sex, the OLD group continued to have significantly increased mean serum cadmium ($P < .001$) and lead ($P < .001$) levels compared with control subjects. Interestingly, the male subjects had lower mean serum cadmium levels and higher mean serum lead levels compared with the female subjects