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Cadmium, smoking, and reduced levels of exhaled nitric oxide among US adults

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ABSTRACT

Exposure to cadmium is known to be associated with reducing nitric oxide (NO) production in experimental conditions, but few studies have examined the association between environmental cadmium exposures and exhaled NO in human. We examined the association between blood cadmium levels and exhaled NO levels in a representative sample of US adults. This investigation was a cross-sectional study of 7813 adults (≥20 years) who participated in the 2007–2008 and 2009–2010 National Health and Nutrition Examination Survey and had their exhaled NO and blood cadmium measurements recorded. The geometric means of the exhaled NO and blood cadmium levels were 13.3 ppb (95% CI: 12.7, 13.9) and 0.51 μg/dL (95% CI: 0.48, 0.54), respectively. Higher blood cadmium levels were associated with decreased exhaled NO levels after adjusting for potential confounding variables. Additionally, a two-fold increase in the blood cadmium levels was associated with a 5% decrease in the exhaled NO levels. The results were significant regardless of the subjects' smoking status or serum cotinine levels, although the percent changes in the exhaled NO levels differed depending on the extent of smoking.

Our findings suggest that blood cadmium levels may be associated with reduced levels of exhaled NO in a general sample of US adults. Moreover, cadmium may partially mediate the effect of smoking on exhaled NO production.

Introduction

Nitric oxide (NO) is an important endogenous mediator of biological functions in the airway. NO is synthesized from the amino acid L-arginine by activity of three isoforms of the NO synthase (NOS) enzyme: the constitutively expressed neuronal NOS (nNOS) and endothelial NOS (eNOS) and an inducible form of NOS (iNOS). eNOS and nNOS are regulated by calcium and calmodulin and have local regulatory role (e.g., neurotransmitter and local blood flow) whereas iNOS is independent of calcium/calmodulin and is induced by inflammatory and infectious stimuli (Asano et al., 1994; Shaul et al., 1994).

NO is normally produced and detected in the breath exhaled from the respiratory tract. Many studies have demonstrated that increases or decreases in exhaled NO can modulate pulmonary function and the pathogenesis of several airways diseases, including asthma (Barnes and Belvisi, 1993; Jorens et al., 1993; Gaston et al., 1994; Kharitonov and Barnes, 2001; Ricciardolo et al., 2004). Exposures to environmental or occupational pollutants are also associated with changes in airway-derived NO (Kim et al., 2003; Adamkiewicz et al., 2004; Olin et al., 2004; Liu et al., 2010; Sauni et al., 2012). Much attention has been paid to the effect of smoking on exhaled NO (Kharitonov et al., 1995; Yates et al., 2001; Sundy et al., 2007). For instance, cigarette smoking is known to play an important role in decreasing exhaled NO levels, and this effect is likely mediated by the down regulation of NO synthesis through the high NO concentration produced by smoking cigarettes, the inactivation of NO by oxidants in cigarettes, or toxin-induced damage to NO-producing epithelial cells (Yates et al., 2001; Rengasamy and Johns, 1993; Persson et al., 1994).

Cadmium is a highly toxic metal that can be either derived from natural sources or generated through industrial activities. Cadmium is a major toxicant of cigarette smoke, and smokers have significantly higher cadmium burdens in their bodies than non-smokers (Järup et al., 1998; Grasseschi et al., 2003). It induces oxidative stress, which is implicated in physiological damage to organs such as the kidneys, liver, and lungs (Järup et al., 1998; Cuypers et al., 2010). Exposure to cadmium is also associated with a reduction in NO production under experimental conditions (Tian and Lawrence, 1996; Demontis et al., 1998; Rodríguez-Serrano et al., 2006; Majumder et al., 2008). Thus, it is feasible that cadmium exposure could affect NO production in

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humans, although no studies to date have investigated such a link.

In this study, we evaluated the relationship between blood cadmium levels and exhaled NO concentrations in a representative sample of US adults ≥20 years of age. The study further evaluated whether the effect of cadmium on exhaled NO was dependent on cigarette smoking.

Materials and methods

Study population

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey of the non-institutionalized civilian population in the U.S. that is conducted by the Centers for Disease Control and Prevention. The NHANES study protocols were approved by the National Center for Health Statistics Institutional Review Board. Oral and written informed consent was obtained from all of the participants.

The present study investigated the exhaled NO measurements and cadmium levels in the blood and urine of NHANES participants (2007–2010). A total of 20,686 participants were included during these study periods. We initially selected 8786 participants, who were older than 20 years of age and had exhaled NO and blood cadmium measurements available to examine the association between exhaled NO and blood cadmium. We then excluded 581 participants who were missing measurements for forced expiratory volume in one second (FEV_1) and other variables of interest, which left a total of 7813 participants for this study.

Exhaled NO measurement

All of the participants aged 6–79 years were eligible to participate in the exhaled NO measurement. The examinees who had current chest pain, a physical problem with forceful expiration, or were using supplemental oxygen were medically excluded from participating.

Exhaled NO was measured using the Aerocrine NIOX MINO®, a portable, hand-held NO analyzer (Aerocrine AB, Solna, Sweden) that was approved by the FDA in 2008 (Aerocrine User Manual, NIOX MINO® Inflammation Monitor, EMD-000030-06). This device follows the American Thoracic Society and European Respiratory Society 2005 equipment recommendations for exhaled NO measurement (American Thoracic Society, 2005) in all essential aspects.

The NIOX-MINO manufacturer designed the analyzer to only accept test results for samples where the air flow rates are held constant at 50 ml/sec. The standard exhalation time specified by the manufacturer was 10 s for examinees who were at or above 130 cm in height, and 6 s for those below 130 cm in height.

The testing was conducted with participants sitting in front of a mirror so they could see display prompts on the NO analyzer screen. The participants were first asked to empty their lungs while holding the device and were the instructed to place their mouth on the disposable analyzer's filter mouthpiece and fill their lungs to capacity with NO-free air. The participants were then asked to blow all of the air out of their lungs at a constant pressure while the NO exhaled from the bronchial tree was measured. Exhaled NO measurements were always performed before spirometry because spirometric maneuvers have been shown to transiently reduce exhaled NO levels.

The NIOX MINO® monitor was cleaned and calibrated in accordance with the requirements through regularly scheduled quality control checks by the health technicians. The quality control checks were verified by supervisory staff. The ambient air was tested daily, and the temperature and humidity measurements in the respiratory health room were routinely collected. The details for the exhaled NO measurements are available at: http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/current_nhanes_07_08.htm (CDC, 2008a).

Blood cadmium levels

The whole blood specimens were stored frozen (−20 °C) until they were shipped to the National Center for Environmental Health for testing. The blood cadmium levels were measured using a multielement atomic absorption spectrometer with Zeeman background correction (SIMAA 6000 model; Perkin-Elmer, Norwalk, CT). The analytical laboratory followed extensive quality control procedures. The National Institute of Standards and Technology Standard Reference Materials (whole-blood materials) were used for external calibration. The details for the analytical procedures are available at http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/PbCd_E_met_lead_cadmium.pdf and http://www.cdc.gov/NCHS/data/nhanes/nhanes_09_10/PbCd_F_met.pdf (27-CDC, 2004).

The lower detection limit for cadmium was 0.20 μg/L from 2007–2010. For those participants with blood cadmium or lead levels below the limit of detection, a level equal to the limit of detection divided by the square root of 2 was used (Hornung and Reed, 1990).

Other variables of interests

We also evaluated other factors that may be associated with exhaled NO and exposure to cadmium, including age (20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, or 70–79 years), sex (male vs. female), race (White, Black, Hispanic or other), education (less than high school, high school graduate, or greater than high school), and family income (less than $20,000 vs. greater than $20,000). The cigarette smoking variables included self-reported smoking status and categorized into three groups: current smoker, former smoker, or never smoked. The serum cotinine levels were measured by an isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric method. The proportion of subjects with serum cotinine levels below the limit of detection was approximately one fifth of the total number of participants. Therefore, the cotinine levels were stratified into five groups (1Q, <0.015 ng/mL; 2Q, 0.015–0.031 ng/mL; 3Q, 0.032–0.127 ng/mL; 4Q, 0.128–97.8 ng/mL; 5Q, ≥97.8).

Asthma was defined through self-reporting, a physician's diagnosis or the presence of wheezing or whistling in the chest. Recent respiratory symptoms and diseases were determined according to the responses from the questionnaire, which asked if the subjects had experienced a cough, cold, phlegm, runny nose or other respiratory illness in the past 7 days.

The pulmonary function test used an Ohio 822/827 dry-rolling seal volume spirometer. The procedures were based on the current standards for pulmonary function, equipment, testing, and interpretation defined by the American Thoracic Society. The following groups of subjects were excluded prior to testing: those with current chest pain or a physical problem with forceful expiration; those taking supplemental oxygen; subjects who received recent surgery for the eyes, chest or abdomen; those with a recent heart attack, stroke or tuberculosis exposure; those with had recently coughed up blood; and those with a personal history of a detached retina or collapsed lung. The examinees were asked to blow the air out of their lungs for a minimum of 6 s. The spirometry testing continued until each individual was able to achieve a reproducible spirogram, a maximum of eight spirometry curves had been obtained, or the participant could not continue. The values used in this analysis included the forced expiratory volume in 1