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Environmental cadmium and lead exposures and age-related macular degeneration in U.S. adults: The National Health and Nutrition Examination Survey 2005 to 2008

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ABSTRACT

Age-related macular degeneration (AMD) is a complex disease resulting from the interplay of genetic predisposition and environmental exposures, and has been linked to oxidative stress and inflammatory mechanisms. Lead and cadmium can accumulate in human retinal tissues and may damage the retina through oxidative stress, and may thereby play a role in the development of AMD. We examined associations between blood lead, blood cadmium, and urinary cadmium concentrations and the presence of AMD in 5390 participants aged 40 years and older with blood lead and blood cadmium measures and a subsample of 1548 with urinary cadmium measures in the 2005–2008 National Health and Nutrition Examination Surveys. AMD was identified by grading retinal photographs with a modification of the Wisconsin Age-Related Maculopathy Grading System. The weighted prevalence of AMD was 6.6% ($n=426$). Controlling for age, gender, race/ethnicity, education and body mass index, adults in the highest blood cadmium quartile had higher odds of AMD compared to the lowest quartile (odds ratio [OR], 1.56; 95% CI, 1.02–2.40), with a significant trend across quartiles (p-trend$=0.02$). After further adjustment for pack-years of cigarette smoking, estimates were somewhat attenuated (OR, 1.43; 95% CI, 0.91–2.27; p-trend$=0.08$). Similar associations were found with urinary cadmium. The association between urinary cadmium and AMD was stronger in non-Hispanic whites (NHW) than in non-Hispanic blacks (NHB) (OR, 3.31; 95% CI, 1.37–8.01 for levels above versus below the median among NHW; OR,1.45; 95% CI, 0.40–5.32 for levels above versus below the median among NHB; p-interaction$=0.03$). We found no association between blood lead levels and AMD. Higher cadmium body burden may increase risk of AMD, particularly among non-Hispanic white individuals; however, additional studies are needed before firm conclusions can be drawn.

1. Introduction

Age-related macular degeneration (AMD) is an important cause of blindness in the United States and accounts for 54% of vision loss in whites, 4.4% in blacks, and 14.3% in individuals of Hispanic ethnicity (Congdon et al., 2004). Among white people aged 40 years and older, AMD is the number one cause of visual impairment and blindness in the U.S. (Congdon et al., 2004). Due to increasing life expectancy, the prevalence of AMD is expected to increase (National Centers for Health Statistics, 2005b).

Although the complete causal mechanisms responsible for AMD are not yet established, both genetic and environmental factors are involved. There is increasing evidence that AMD may be induced by oxidative stress and inflammation of the choroid and retina (Ambati et al., 2003; Beatty et al., 2000; Holz et al., 2004; Zarbin, 2004).

Lead and cadmium are nonessential metals that are toxic to human tissues. Studies have shown that lead and cadmium can promote chronic diseases of aging by increasing chronic oxidative stress through DNA damage, depletion of antioxidant defense systems, production of inflammatory cytokines, (Bhattacharyya et al., 2000; Hsu and Guo, 2002; Stohs and Bagchi, 1995) and by

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production of reactive oxygen species, including in retinal pigment epithelium (RPE) cells (Wills et al., 2008). The retina is susceptible to oxidative stress and free radical damage because of decreased levels of retinal antioxidant enzymes with increasing age, high polyunsaturated lipid content, and increased exposure to light (Erie et al., 2005; Wills et al., 2008).

Cells involved in the transport of trace metals such as lead and cadmium are especially vulnerable to toxicity. In the eye, the RPE can bind metals, including essential metals such as zinc, copper, and iron, but also toxic heavy metals including lead and cadmium, which have a high affinity for melanin in RPE melanosomes (Potts and Au, 1976; Ulshafer et al., 1990). Lead and cadmium ions have similar charges and are similar in size to zinc, copper, and iron. Eichenbaum and Zheng (2000) reported that lead can accumulate in the retina and choroid. More recently, Erie et al. (2005) observed an accumulation of both lead and cadmium in the pigmented ocular tissues, including neural retina and RPE/choroid of human donor eyes. Cadmium concentrations in human eyes increased with age and were higher in women compared to men and in smokers compared to nonsmokers (Erie et al., 2005; Wills et al., 2008). Lead concentrations in human retina also increase with age (Erie et al., 2005).

Limited studies have assessed the association between lead or cadmium and AMD in humans, and results are mixed. The purpose of the current study was to assess the relationship of lead and cadmium exposure with AMD in the population of individuals aged 40 years and older from the National Health and Nutrition Examination Survey (NHANES) 2005–2008 sample.

2. Materials and methods

2.1. Study population

NHANES is a cross-sectional study designed to be nationally representative of the civilian, noninstitutionalized U.S. population, with oversampling of older and minority groups. For the present study, we obtained data from the U.S. NHANES 2005/06 and 2007/08 study cycles (continuous NHANES), from which we identified 7081 persons aged 40 years and older, among which, 5604 were not missing information on the 3-level severity classification of age-related macular degeneration in at least one eye. Additionally, we excluded 173 persons who had no data on blood lead or blood cadmium. The final sample consequently consisted of 5390 persons with at least one gradeable retinal photograph, blood lead and blood cadmium measurements, and data on other important covariates (body mass index (BMI), smoking status, and education). Excluded participants tended to have higher blood lead levels ($P=0.01$) and were more likely to be older ($P<0.0001$), non-Hispanic black ($P<0.0001$), and less likely to be cigarette smokers ($P=0.02$). NHANES is a publicly available data set and all participants in NHANES provided written informed consent, consistent with approval by the National Center for Health Statistics Institutional Review Board.

By design of the study, urinary cadmium was measured in one third of randomly selected subsamples from eligible participants in NHANES 2005–2008. Of the 7081 persons aged 40 years and older, 2207 had urinary cadmium measurements and from the final sample of 5390 persons, 1808 had urinary cadmium measurements. Because chronic kidney disease may increase urinary cadmium release, 243 of the 1808 subjects with chronic kidney disease defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 were excluded and an additional 17 were excluded due to missing data. Our sample for urinary cadmium analyses included 1548 persons.

2.2. Photography and grading of age-related macular degeneration

Retinal photographs for the NHANES survey were obtained using the Canon CR6-45NM Ophthalmic Digital Imaging System and Canon EOS 10D digital camera (Canon USA, Inc, Lake Success, New York). Details of retinal imaging methods have been previously published (Klein et al., 2011; National Centers for Health Statistics, 2005b). Briefly, during the eye exam, the room was darkened to allow for pupil dilation. Each participant had two 45° nonmydriatic digital retinal images taken per eye. One image of the macula, field 2, was centered on the fovea; the second image was centered on the optic nerve. Klein et al. (2004) have previously described the capture and grading of digital images and quality control measures. Each image was graded twice using a modification of the Wisconsin Age-Related Maculopathy Grading System (Klein et al., 1991).

The primary outcome measure for this study was any AMD, which was assessed in both eyes of participants. If data were available for both eyes, data from the eye with more severe disease characteristics were used in our analyses. AMD was categorized into 3 severity levels: no AMD, early AMD, or late AMD. Early AMD was defined by the presence of drusen and/or pigmentary abnormalities. Late AMD was defined as the presence of any late lesions such as exudative AMD signs or geographic atrophy. We were not able to examine subtypes of AMD separately because a very small proportion of our study population had late AMD (0.8%).

2.3. Blood lead, blood cadmium, and urinary cadmium

Whole blood lead and cadmium and urinary cadmium concentrations were determined using inductively coupled plasma mass spectrometry (ICP-MS) at the Division of Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention. Detailed specimen collection and processing methods are available from the NHANES Laboratory Procedures Manuals (National Centers for Health Statistics, 2005a, 2007). The lower detection limit for blood cadmium was 0.20 μg/L and for urinary cadmium was 0.04 μg/L in NHANES 2005–08. The lower detection limits for lead were 0.25 μg/dL and 0.30 μg/dL in NHANES 2005–06 and 0.25 μg/dL in NHANES 2007–08. Values below the limit of detection were replaced with values equal to the detection limit divided by the square root of two. Of the 5390 observations with blood lead and cadmium measurements, 1 (0.02%) and 719 (13.34%) were below the limit of detection, respectively. Of the 1548 observations with urinary cadmium measurements, 48 (3.10%) were below the limit of detection. Lab equipment, lab methods, and lab site were the same for NHANES 2005–2008.

2.4. Other covariates

Demographic information, medical history, laboratory assessment, and physical examination were obtained via computer-assisted personal interviewing, laboratory assessment, and physical examination. Race/ethnicity was categorized as Non-Hispanic Black, Non-Hispanic White, Mexican American, and other. "Other" included other Hispanic, multiracial, and other races. Cigarette smoking status was categorized into never, former, and current smoker; and by pack-years, categorized as 0, more than 0 to less than 20, and 20 or more. Serum cotinine which is a marker of short-term exposure to tobacco smoke was also considered initially but was not included in the final model because it may not capture chronic effects and the results were robust with further adjustment for serum cotinine (data not shown). BMI was calculated from measured weight in kilograms divided by measured height in meters squared. Self-reported education level was categorized into 3 levels: less than high school degree, high school diploma, and some college or more. Self-reported frequency of weekly alcohol consumption was categorized as 0, more than 0 to less than 1, or 1 or more. Type-2 diabetes was defined as self-reported physician diagnosis or the use of insulin or diabetic pills. Hypertension was defined as self-reported physician diagnosis, the use of antihypertensive medication, systolic blood pressure $\geq$ 140 mm Hg, or diastolic blood pressure $\geq$ 90 mm Hg at the time of examination, based on the mean of the last 3 readings after disregarding the first reading. High-density lipoprotein (HDL) cholesterol and total cholesterol were measured in serum using the Roche Hitachi 717 or 912, or Roche Modular P chemistry analyzer depending on the year of collection. No adjustment of values was necessary to account for the change in instrumentation. Cholesterol values were provided in mg/dL and converted to mmol/L by multiplying by 0.02586.

2.5. Statistical analysis

NHANES uses a complex sampling survey design to over sample certain minority groups, including the elderly, Blacks, and Mexican Americans. We combined two 2-year cycles of continuous NHANES (2005–06 and 2007–08) and calculated appropriate sample weights according to the NHANES Analytic and Reporting Guidelines, which were applied when analyzing the data (National Centers for Health Statistics, 2006). Because blood cadmium and lead were measured in all participants whereas urinary cadmium was measured in a subsample (one third), the mobile examination center (MEC) exam weight (WTMEC2YR) and the MEC weights of subsample A (WTSA2YR) were used for blood cadmium/lead and urinary cadmium, respectively. We used SAS software, version 9.2, for statistical analyses (SAS Institute Inc., Cary, NC, USA).

We examined the distributions of lead and cadmium concentrations for normality. Both metal concentrations were non-normally distributed therefore survey-weighted geometric means (GMs) and 95% confidence intervals (CIs) were computed. Among the NHANES sample with a urinary cadmium measurement, we assessed the correlation between blood cadmium and urinary cadmium using Spearman correlation because the distributions of the cadmium levels were non-normal.

We used survey-weighted logistic regression models to examine the association between heavy metal levels and risk of AMD. Models contained the following covariates based on a priori knowledge of their association with AMD: model A