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Environmental cadmium and lead exposures and age-related macular degeneration in US 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 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 a 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

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Conflict of Interest

The authors declare no conflict of interest for this manuscript.

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.

Keywords

age-related macular degeneration; cadmium; lead; NHANES

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 MH, 2000; Hsu and Guo, 2002; Stohs and Bagchi, 1995) and by 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 (Eichenbaum and Zheng, 2000) reported that lead can accumulate in the retina and choroid. More recently, Erie et al. (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 7,081 persons aged 40 years and older, among which, 5,604 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 5,390 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 7,081 persons aged 40 years and older, 2,207 had urinary cadmium measurements and from the final sample of 5,390 persons, 1,808 had urinary cadmium measurements. Because chronic kidney disease may increase urinary cadmium release, 243 of the 1,808 subjects with chronic kidney disease defined as an estimated glomerular filtration rate less than 60mL/minute/1.73 m^2 were excluded and an additional 17 were excluded due to missing data. Our sample for urinary cadmium analyses included 1,548 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. (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; National Centers for Health Statistics, 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 5,390 observations with blood lead and cadmium measurements, 1(0.02%) and 719 (13.34%) were below the limit of detection, respectively. Of the 1,548 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 ≥ 140 mm Hg, or diastolic blood pressure ≥ 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 adjusted for age (linear and squared), gender, race/ethnicity, education and BMI; model B further adjusted for pack-years of cigarette smoking. We used this strategy to examine the potential confounding effect of cigarette smoking in the cadmium models because inhalation of cigarette smoke while smoking is the main source of cadmium exposure among smokers. We modeled age with linear and squared terms because the model goodness-of-fit was improved with the age squared term, suggesting the association between age and AMD is non-linear. Models for urinary cadmium were additionally adjusted for urinary creatinine to correct urine dilution. As a sensitivity analysis, we additionally adjusted for alcohol consumption, HDL cholesterol, hypertension, and diabetes and tested the robustness of the associations. Models produced odds ratios (ORs) for risk of AMD and were computed by comparing each of the upper 3 quartiles with the lowest quartile. Tests for linear trend were conducted using ordinal terms for the quartiles of each exposure variable.

We evaluated effect modification by gender, pack-years of cigarette smoking (0, >0 to <20, 20+), and race/ethnicity (non-Hispanic black, non-Hispanic White, and other) by including interaction terms between each of these covariates and lead or cadmium in the model B. We also ran separate regression models stratified by those effect modifiers as sensitivity analyses but reported the former approach because the two approaches were similar. Due to the small proportion of Mexican Americans, other Hispanics, and other race/ethnicities in our study population, we combined these categories for a total of three race/ethnicity

categories for our stratified analysis. Each exposure variable was dichotomized at the median concentrations: 1.79 μg/dL, 0.39 μg/L, and 0.35 μg/L for blood lead, blood cadmium, and urinary cadmium, respectively and adjusted odds ratios for low and high exposure were calculated for each stratum of gender, pack-years, and race/ethnicity. Measures of effect modification on the additive scale (relative excess risk due to interaction (RERI)) as well as multiplicative scale were computed as recommended by Knol and VanderWeele (Knol and VanderWeele, 2012).

3. Results

The mean age of the study population was 56.4 (SE = 0.39) years, 52.6% were female, 77.6% were non-Hispanic white, and 9.1% were non-Hispanic black. The overall prevalence of any AMD was 6.6%, including 2.8% of 40–59 year olds, and 13.4% of participants aged 60 years and older. There was no statistically significant difference in the prevalence of AMD, or in blood lead or cadmium concentrations across survey cycles (data not shown). Compared to subjects without AMD, subjects with AMD were significantly older, more likely to be non-Hispanic white, a former smoker, and have hypertension (Table 1). Among our study population, geometric means of blood lead, blood cadmium, and urinary cadmium concentrations were 1.65 (95% CI, 1.60 to 1.71) μg/dL, 0.41 (95% CI, 0.39 to 0.42) μg/L, and 0.29 (95% CI, 0.27 to 0.31) μg/L, respectively. In univariable analyses, subjects with AMD had significantly higher blood lead, blood cadmium, and urinary cadmium concentrations than those without AMD (Table 1). There was a moderate correlation between blood cadmium and urinary cadmium concentrations (Spearman correlation coefficient=0.48, $p<0.0001$, data not shown).

Both blood lead and blood cadmium concentrations were higher for older adults, non-Hispanic Blacks, persons with less education, lower income, lower body mass index, current smokers, persons with more frequent alcohol consumption, without diabetes, and for persons with any AMD (supplemental Table 1). Blood lead concentrations were higher for males than females, and those with hypertension. Blood cadmium concentrations were higher for females than for males. Urinary cadmium was higher for older adults, males, non-Hispanic Blacks, persons with less education, lower income, lower HDL, current smokers, and for persons with any AMD (supplemental Table 2).

In a univariable model, the odds of AMD increased significantly across quartiles of blood lead levels (P for trend <0.0001), but this association was not significant after controlling for demographic or other important factors (Models A and B; Table 2). Higher blood cadmium levels were significantly associated with increasing odds of AMD even after adjustment for socio-demographic factors and BMI (Model A: quartile 4 versus 1, OR = 1.56, 95% CI: 1.02 to 2.40; P for trend = 0.02). The association between blood cadmium and the odds of AMD remained suggestive after further adjusting for pack-years of cigarette smoking (Model B: quartile 4 versus 1, OR = 1.43, 95% CI: 0.91 to 2.27; P for trend = 0.08). Further adjustment for alcohol consumption, cardiovascular risk factors and diabetes slightly increased ORs but did not appreciably alter the reported findings (data not shown). For urinary cadmium, the fully adjusted ORs of AMD for quartile 4 compared to quartile 1 were 2.15 (95% CI, 0.87 to 5.53) and 2.18 (95% CI, 0.70 to 6.83) in Model A (P for trend = 0.04) and Model B (P for

trend = 0.09), respectively, but we had lower power for this exposure due to the study design.

Based on *a priori* hypotheses, we assessed effect modification by race/ethnicity, gender, and pack-years of cigarette smoking for AMD by high and low concentrations of blood cadmium and urinary cadmium (Table 3). We observed statistically significant effect modification on the multiplicative scale of the association between urinary cadmium and risk of AMD by race (non-Hispanic Black compared to non-Hispanic white, p for interaction = 0.03). Specifically, the association between urinary cadmium levels (levels above versus below the median) and AMD was strongest in non-Hispanic whites (OR=3.31, 95% CI: 1.37 to 8.01) but was not statistically significant in non-Hispanic blacks (OR=1.45, 95% CI: 0.40 to 5.32) or other race/ethnicities (OR=0.61, 95% CI: 0.21 to 1.74). Effect modification by race was not observed for the association between blood cadmium and AMD (non-Hispanic blacks compared to non-Hispanic whites, p for interaction = 0.65; non-Hispanic blacks compared to other race/ethnicities, p for interaction = 0.30). There was no significant effect modification by race on the additive scale. Further, we did not observe any significant effect modification on both multiplicative and additive scales by gender or cigarette smoking for the association between blood or urinary cadmium and AMD (each p-value for interaction > 0.05).

4. Discussion

In a representative sample of US adults from the combined 2005–2006 and 2007–2008 NHANES cycles, higher levels of blood and urinary cadmium were associated with an increased risk of AMD. These associations were somewhat attenuated after adjustment for cigarette smoking, the main source of cadmium exposure among smokers. The association between urinary cadmium and AMD was stronger in non-Hispanic whites than among non-Hispanic blacks. In contrast, there was no significant association between blood lead levels and risk of AMD.

Current levels of exposure to cadmium in the general U.S. population are still of concern, and the findings of the present study suggest that individuals with higher levels of cadmium exposure are at increased risk of AMD. A recent study using data from NHANES reported that urinary cadmium concentrations in U.S. adults from 1988–1944 to 2003–2008 decreased by 34.3% and this reduction mainly resulted from declining smoking rates and changes in exposure to tobacco smoke in both smokers and nonsmokers (Tellez-Plaza et al., 2012). However, in spite of the substantial reduction in the cadmium body burden in U.S. adults, a growing body of evidence suggests that current levels of exposure are nonetheless associated with chronic diseases such as cardiovascular disease (Tellez-Plaza et al., 2010), renal disease, (Navas-Acien et al., 2009) bone disease, (Gallagher et al., 2011) and hearing loss (Choi et al., 2012). The present study adds additional evidence that environmental cadmium exposure may be a risk factor for AMD.

Blood cadmium concentrations are a good reflection of recent exposure especially in occupationally exposed workers, whereas urinary cadmium concentrations are more indicative of the body burden over longer-term exposure (ATSDR, 2008a). Nonetheless, blood cadmium is considered a good estimate of body burden in the general population

(Jarup et al., 1998) and a better estimate than urinary cadmium for old persons because the prevalence of kidney dysfunction in older persons can increase cadmium release in urine, (Satarug et al., 2010) which may bias associations between urinary calcium levels and health outcomes in this group. There was no difference in results for subjects with and without chronic kidney disease. However, to minimize this potential source of bias, we excluded individuals with chronic kidney disease (243 subjects with an estimated glomerular filtration rate less than 60mL/minute/1.73 m^2) from our analyses of the association between urinary cadmium and AMD. Although we cannot rule out potential bias from sub-clinical kidney dysfunctions, it is less likely given that the associations for blood cadmium and urinary cadmium were consistent.

A potential biological mechanism to explain our findings is through cadmium accumulation in the retina, which produces oxidative stress and inflammation that can damage the retina. Over time, long-term cumulative exposure to cadmium may enhance risk for the development of AMD (Beatty et al., 2000; Bhattacharyya MH, 2000; Stohs and Bagchi, 1995). In support of our findings, Erie et al. (Erie et al., 2007) reported that urinary cadmium was associated with AMD in a small group of current and former smokers (N = 37) but not in non-smokers (N = 69). Additionally, Wills et al. (Wills et al., 2009; Wills et al., 2008) observed higher cadmium levels in the neural retina and RPE of eyes afflicted with AMD compared to non-AMD eyes among males. In a prospective case-control study that assessed the association between urinary cadmium concentration and AMD, 53 men and women aged 60 years and over and with AMD were age-matched to participants without AMD (Erie et al., 2007). Smokers with AMD had higher urinary cadmium concentrations compared to smokers without AMD, never smokers with AMD, and never smokers without AMD. Higher cadmium levels were associated with AMD among current and former smokers but no association was found between urinary cadmium levels and AMD among individuals who had never smoked (Erie et al., 2007).

We evaluated the impact of adjustment for cigarette smoking in the associations of cadmium biomarkers and AMD (Table 2, Model B) because cigarette smoking is a major risk factor for AMD, and also a primary source of human exposure to cadmium (ATSDR, 2008a). In these models, the associations became attenuated in both blood and urinary cadmium and the 95% CIs became wider especially for urinary cadmium. Although there was no significant effect modification by cigarette smoking (Table 3), probably due to low power, the higher OR in the association between urinary cadmium and AMD found in subjects with 20+ pack-years (4.62, 95% CI, 1.28 to 16.7)) compared with never smokers (OR=2.26, 95% CI, 0.85 to 5.97) raises the possibility that cadmium from cigarette smoke may be one mechanism by which cigarette smoking affects the risk of AMD, perhaps by acting synergistically with other components on cigarette smoke. Further investigation of such a possibility will require mechanistic studies.

We tested effect modification by race/ethnicity, gender, and cigarette smoking and found significant effect modification by race/ethnicity on the multiplicative scale, such that the effect of urinary cadmium was stronger in non-Hispanic whites compared to non-Hispanic blacks. Studies have shown melanin to have antioxidant properties, (Wang et al., 2006) and therefore a generally higher melanin concentration in the retina of non-Hispanic black

individuals compared to non-Hispanic whites could provide a reasonable explanation for the difference in effect of urinary cadmium levels on AMD observed in the present study. However, we cannot rule out the possibility that this effect modification was observed by chance because the number of AMD cases in non-Hispanic blacks was very small (n=10).

We hypothesized potential effect modification by sex given that iron plays an important role in the toxicity of divalent metals such as cadmium and lead (Gallagher et al., 2011; Wright et al., 2003) and iron body stores differ by sex (Erie et al., 2005). However, power was too low to identify anything but a very large magnitude modification, which was not present here. Because studies have indicated that iron status is associated with both cadmium body burden and AMD, (Choudhury et al., 2001; Hahn et al., 2003; Olsson et al., 2002; Wong et al., 2007) future investigations should consider iron status as a potential effect modifier between heavy metal exposure and development of AMD.

Current levels of lead exposure in U.S. adults are lower than in the past, and recent exposure levels captured by blood lead measurements may not be high enough to elevate the risk of AMD. On the other hand, blood lead concentrations are an indicator of recent exposure, reflecting exposure past 30 days (Hu et al., 2007). Although more difficult to obtain, bone lead is thought to be a better biomarker of cumulative lead body burden and may be a better measure to examine for associations with an age-related chronic disease such as AMD (Hu et al., 2007; Rabinowitz, 1991). In support of this idea, Schaumberg et al. (Schaumberg et al., 2004) found that among men age 60 years and over in a subset of the Normative Aging Study, bone lead levels were significantly positively associated with cataract, whereas there was no association between blood lead levels and cataract. Although the present study did not reveal an association between recent lead exposure and risk of AMD, it remains to be determined whether chronic low-level lead exposure may affect risk. Such a hypothesis is biologically plausible as lead accumulates over time in the RPE and choroid of the eye and can promote chronic diseases of aging by increasing chronic oxidative stress. Because retinal antioxidant enzyme levels decrease with age, the retina is susceptible to oxidative stress and free radical damage, which could lead to the development of AMD (Erie et al., 2005; Wills et al., 2008). We propose that a study of the potential relationship between bone lead and risk of AMD may provide a more sensitive test of the association between lead body burden and risk of AMD.

Despite the benefits of a large, nationally representative sample, NHANES uses a cross-sectional survey design, which may limit the validity of causal inference. Although our findings are suggestive in terms of the role of cadmium exposure as a potential AMD risk factor, residual confounding by cigarette smoking cannot be ruled out. Prospective studies of never smokers only are needed to confirm the findings. We did not assess iron status, genetic factors, vitamins, or other dietary intake factors that may be associated with AMD, lead, and cadmium body burden. Genetic factors may be particularly important to consider in future studies, as common variation in a few genes (in particular with complement factor H and ARMS2) is associated with profound differences in risk of AMD, and could plausibly interact biologically with heavy metals and their downstream consequences on inflammation and oxidative stress. About 6% of orally ingested cadmium is absorbed unchanged through the gastrointestinal tract; however, for individuals who are iron deficient, up to 9% may be

absorbed (ATSDR, 2008a). Also, the presence of elevated zinc or chromium in the diet decreases cadmium uptake (ATSDR, 2008b). Given the increasing age of the US population and exposure to toxic heavy metals through everyday food consumption, investigating the role of cadmium and lead in the pathogenesis of AMD and blindness is of significant public health importance. Since the results of this work have limitations, prospective cohort studies are needed to explore the pathological pathways involved with both AMD development and the toxic effects of lead and cadmium in choroid and RPE cells in the eye, and to establish the roles that heavy metal exposure plays in the development of AMD and other eye diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We examined the association of cadmium and lead with age-related macular degeneration (AMD) in US adults.
- Cadmium in both blood and urine was borderline significantly associated with the risk of AMD.
- Blood lead was not associated with the risk of AMD.
- The association between urine cadmium and AMD was stronger in whites than in blacks.

Table 1

Weighted mean ± standard error or weighted percentage, NHANES, 2005–2008.

Characteristics	Total Sample	AMD		p-value [A]
		Yes (N)	No (N)	
N	5390	426	4964	
Age (years)	56.4±0.39	67.8± 0.96	55.6±0.35	<.0001
Female (%)	52.6	53.0 (205)	52.5	0.83
Race (%)				
Non-Hispanic White	77.6	86.7 (304)	76.9 (2,632)	<.0001
Non-Hispanic Black	9.1	3.8 (35)	9.5 (1,017)	
Mexican American	5.4	4.1 (52)	5.5 (791)	
Other	7.9	5.4 (35)	8.1 (524)	
Education (%)				
Less than high school	17.7	21.4 (122)	17.4 (1,438)	0.21
High school diploma	26.3	27.1 (117)	26.2 (1,219)	
Some college+	56.0	51.4 (187)	56.3 (2,307)	
Cigarette smoking (%)				
Never	48.7	43.2 (190)	49.0 (2,368)	<.0001
Former	30.8	41.8 (172)	30.0 (1,564)	
Current	20.6	15.0 (62)	21.0 (1,032)	
Pack-years of cigarettes	11.6±0.61	14.5±1.43	11.4±0.63	0.04
Frequency of weekly alcohol consumption	1.2±0.07	1.1±0.10	1.2±0.7	0.34
Body mass index (kg/m^2)	29.1±0.14	28.4± 0.35	29.1±0.14	0.07
HDL cholesterol (mg/dL)	53.9±0.33	56.5± 0.69	53.7±0.35	
Hypertension (%)	47.9	61.8 (284)	47.0 (2,588)	<.0001
Diabetes (%)	11.1	12.6 (64)	11.0 (768)	0.34
Age-related macular degeneration (%)	6.6	100 (426)	0 (0)	
Blood lead (μg/dL)[B]	1.65 (1.60, 1.71)	1.86 (1.73, 2.00)	1.64 (1.58, 1.69)	0.0009
Blood cadmium (μg/L)	0.41 (0.39, 0.42)	0.47 (0.43, 0.51)	0.40 (0.39, 0.42)	0.005
Urinary cadmium (μg/L)[B]	0.29 (0.27,0.31)	0.37 (0.30, 0.45)	0.28 (0.26, 0.31)	0.04
Creatinine-adjusted urinary cadmium (μg/g)[B]	0.33 (0.31, 0.35)	0.47 (0.40, 0.54)	0.32 (0.30, 0.34)	0.0001
Chronic Kidney Disease (%)	12.0	28.6 (130)	10.8 (620)	<.0001

Abbreviation: NHANES, National Health and Nutrition Examination Survey.

[A] P-value based on the t-test for continuous variables and the Rao-Scott Chi-square test for categorical variables.

[B] Geometric mean (95% confidence interval) is presented.

Table 2

Odds Ratios (95% confidence intervals) of age-related macular degeneration by blood lead and blood cadmium (n=5390), and urinary cadmium concentrations (n=1548), NHANES, 2005–2008.

Variables	AMD/No AMD	Crude	Model A	Model B
Lead				
Blood lead quartile (μg/dL)[A]				
Quartile 1 (0.18–1.20)	78/1288	(Reference)	(Reference)	(Reference)
Quartile 2 (1.21–1.77)	101/1182	1.24 (0.85, 1.81)	0.90 (0.61, 1.32)	0.86 (0.60, 1.22)
Quartile 3 (1.78–2.61)	121/1217	1.67 (1.19, 2.34)	1.04 (0.70, 1.55)	1.00 (0.68, 1.48)
Quartile 4 (2.62–26.80)	118/1100	1.80 (1.27, 2.55)	0.92 (0.63, 1.36)	0.86 (0.59, 1.26)
p-for-trend		<.0001	0.89	0.65
Cadmium				
Blood cadmium quartile (μg/L)[A]				
Quartile 1 (0.14–0.25)	72/1256	(Reference)	(Reference)	(Reference)
Quartile 2 (0.26–0.38)	96/1218	1.41 (0.99, 2.02)	1.00 (0.67, 1.52)	1.00 (0.67, 1.51)
Quartile 3 (0.39–0.65)	134/1164	2.19 (1.53, 3.15)	1.24 (0.83, 1.85)	1.23 (0.81, 1.87)
Quartile 4 (0.66–10.80)	116/1149	1.96 (1.32, 2.90)	1.56 (1.02, 2.40)	1.43 (0.91, 2.27)
p-for-trend		<.0001	0.02	0.08
Urinary cadmium quartile (μg/L)[B]				
Quartile 1 (0.03–0.175)	26/360	(Reference)	(Reference)	(Reference)
Quartile 2 (0.176–0.352)	18/365	0.75 (0.37, 1.54)	0.74 (0.38, 1.45)	0.81 (0.39, 1.65)
Quartile 3 (0.353–0.646)	31/362	2.12 (1.00, 4.48)	2.23 (0.85, 5.94)	2.31 (0.79, 6.78)
Quartile 4 (0.648–5.35)	29/357	1.80 (0.88, 3.66)	2.15 (0.87, 5.33)	2.18 (0.70, 6.83)
p-for-trend		0.02	0.04	0.09

Abbreviation: NHANES, National Health and Nutrition Examination Survey.

[A]Model A was adjusted for age, age-squared, gender, race, education and body mass index. Model B: Model A + further adjusted for pack-years.

[B]Model A was adjusted for urinary creatinine, age, age-squared, gender, race, education and body mass index. Model B: Model A + further adjusted for pack-years.

Table 3

Effect modification of the association between blood and urinary cadmium concentrations and AMD by race/ethnicity, gender, pack-years of cigarettes in the NHANES, 2005–2008.*

	Blood Cadmium[A]					Urinary Cadmium[B]				
	Low (< 0.39 μg/L)		High (≥0.39μg/L)			Low (< 0.35 μg/L)		High(≥0.35μg/L)		
	N with/with-out AMD	OR (95 % CI)	N with/with-out AMD	OR (95 % CI)	P for interaction	N with/with-out AMD	OR (95 % CI)	N with/with-out AMD	OR (95 % CI)	P for interaction
Race/ethnicity										
Non-Hispanic Black	13/495	1.00 (Reference)	22/522	1.39 (0.75, 2.59)		4/115	1.00 (Reference)	6/186	1.51 (0.40, 5.61)	
Non-Hispanic White	119/1365	2.27 (1.26, 4.12)	185/1267	3.07 (1.69, 5.59)	0.63	27/418	1.05 (0.29, 3.75)	44/330	3.56 (0.91, 13.9)	0.03
Other	45/744	2.57 (1.28, 5.16)	42/571	2.69 (1.42, 5.11)	0.39	13/193	2.69 (0.57, 12.6)	10/202	1.66 (0.59, 4.69)	0.10
Gender										
Males	104/1408	1.0 (Reference)	117/1071	1.29 (0.87, 1.93)		21/362	1.0 (Reference)	32/388	3.51 (1.33, 9.27)	
Females	73/1196	0.87 (0.67, 1.12)	132/1289	1.17 (0.86, 1.58)	0.86	23/364	1.36 (0.68, 2.74)	28/330	2.94 (1.25, 6.92)	0.29
Pack-years										
0	106/1746	1.0 (Reference)	87/655	1.31 (0.87, 1.97)		25/409	1.0 (Reference)	21/249	2.26 (0.85, 5.97)	
0 – 19.9	44/566	1.19 (0.67, 2.13)	70/759	1.35 (0.90, 1.98)	0.43	13/200	0.86 (0.36, 2.00)	13/233	2.03 (0.90, 4.58)	0.68
20+	26/227	0.98 (0.52, 1.86)	85/834	1.59 (1.10, 2.29)	0.39	6/91	0.58 (0.16, 2.03)	25/214	2.61 (1.02, 6.63)	0.38

Abbreviations: NHANES, National Health and Nutrition Examination Survey; OR, Odds Ratio.

[A]Blood cadmium models were adjusted for age, age-squared, gender, race, education, body mass index and pack-years.

[B]Urinary cadmium models were adjusted for urinary creatinine, age, age-squared, gender, race, education, body mass index and pack-years.