Accumulated Lead Exposure and Risk of Age-Related Cataract in Men

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ALTHOUGH LEAD TOXICITY IN humans has been recognized for centuries, the 20th century has left a legacy of unprecedented lead levels spread throughout the environment. Lead continues to pose a significant public health problem in spite of substantial reductions in lead exposure in the United States in the recent past. Moreover, exposure has not been totally eliminated and most adults continue to have substantial body burdens of lead.[1]

Much of the lead taken into the body is incorporated into bone where it constantly interchanges with other tissues.[2] Recent studies suggest that accumulated lead exposure is related to several chronic disorders of aging including hypertension and cognitive decline,[1] disorders that have been associated with oxidative stress.[3,4] Several lines of evidence suggest that accumulated lead exposure could also increase the risk of another oxidative-stress–related disorder of aging, age-related cataract— the leading cause of blindness and visual impairment worldwide.[5] In the present study, the first we are aware of to investigate this hypothesis, we tested whether bone lead levels measured in both the tibia and patella were associated with age-related cataract in an ongoing study of men from the United States who were drawn from the general population surrounding Boston.

Context Low-level lead exposure may increase the risk for a number of chronic age-related diseases. Several studies have documented the presence of lead in lenses with cataract. The intrusion of lead into the lens may alter lens redox status and cause protein conformational changes that decrease lens transparency.

Objective To determine the relationship of cumulative lead exposure with the development of cataract.

Design, Setting, and Participants Tibial (cortical) and patellar (trabecular) bone lead levels were measured by K x-ray fluorescence between 1991 and 1999 in a subset of participants in the Normative Aging Study (NAS), a Boston-based longitudinal study of aging in men. Among the first 795 NAS participants to have bone lead levels measured, we reviewed eye examination data (collected routinely every 3-5 years) for the period after the bone lead measurements were taken. We limited the population to men aged 60 years and older who had sufficient eye examination information available (n=642). Blood lead levels were also measured.

Main Outcome Measures Cataract assessment was done while masked to the lead level results. A participant was considered to have cataract if there was documentation for either eye of cataract surgery or a cataract graded clinically as 3+ or higher on a 4-point scale. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as estimates of the magnitude and significance of the relationship of lead exposure with cataract, in logistic regression models.

Results The mean age of the study participants was 69 years and cataract was identified in 122 men. The age-adjusted OR (95% CI) for cataract for men in the highest vs lowest quintile of tibia lead level was 2.68 (1.31-5.50). Further adjustment for pack-years of cigarette smoking, diabetes, blood lead levels, and intake of vitamin C, vitamin E, and carotenoids resulted in an OR of 3.19 (95% CI, 1.48-6.90). For patella lead level, there was an increased risk of cataract in the highest vs lowest quintile (OR, 1.88; 95% CI, 0.88-4.02), but the trend was not significant (P=.16). Blood lead levels, more indicative of short-term exposure levels, were not significantly associated with cataract (OR, 0.89; 95% CI, 0.46-1.72; P=.73).

Conclusions These epidemiological data suggest that accumulated lead exposure, such as that commonly experienced by adults in the United States, may be an important unrecognized risk factor for cataract. This research suggests that reduction of lead exposure could help decrease the global burden of cataract.

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METHODS

Participants were drawn from the Normative Aging Study (NAS), a longitudinal study of 2280 healthy male volunteers, begun in Boston in the 1960s.[6] At the time of their initial enrollment, all NAS participants were free of heart disease, hypertension, diabetes mellitus, cancer, peptic ulcer, gout, recurrent asthma, bronchitis, or sinusitis. Study participants were predominantly white, and ranged in age from 48 to 93 years at the time of bone lead measurement. Every 3 to 5 years, participants underwent an extensive physical examination that

included a standard ocular evaluation, not always including a dilated fundus examination, with notation of any abnormalities in the lens, optic nerve, and macula. Beginning in 1991 and continuing through 1999, NAS participants were invited to undergo bone and blood lead measurements.[2,7] At the time the present study was initiated, 795 (68%) of the 1171 NAS participants who were still being monitored had completed bone lead measurements. The main reason for nonparticipation in the bone lead measurements was the inconvenience of returning to the bone lead laboratory on a separate day from the regular NAS follow-up examination. In an earlier analysis, no important differences were detected between NAS participants who did and did not have bone lead measurements taken.[8] Because we were interested in occurrence of age-related cataract, we limited our analysis to men who were at least 60 years of age at the time of measurement (n=663), and had at least one eye examination available during the period spanning the year prior to bone lead measurement and the time of this study in 2002 (n=642).

K x-ray fluorescence[9,10] was used to measure bone lead levels. Bone lead levels were measured at both the midtibial shaft and the patella. These 2 sites were chosen to represent the 2 main bony compartments: trabecular bone (patella) and cortical bone (tibia). Since trabecular bone has a higher turnover rate as compared with cortical bone, the amount of lead in trabecular bone reflects more recent exposure than the amount present in cortical bone.[10] Bone lead measurements were recorded on a continuous scale in units of µg/g.

Standard eye evaluations including a complete history, documentation of medication use, visual acuity measurement, biomicroscopy, tonometry, and ophthalmoscopy were performed and recorded at each routine NAS study visit. These examinations were generally performed by staff optometrists at the NAS examination facility. Thus, during the course of the study, several clinicians evaluated study participants but possible inter-rater differences were not in-

vestigated. For the present study, standardized forms were established for extraction of eye disease data from NAS study records. Without knowledge of the participants' bone lead results, we reviewed medical records for diagnoses and severity of cataract, and occurrence of cataract extraction between 1986 and 2002. Lens status was assessed by biomicroscopy and a participant was considered to have cataract if there was documentation for either eye of cataract surgery or a cataract (of any subtype), graded clinically as 3+ or higher on a 4-point scale, diagnosed either after or within 1 year prior to bone lead measurement.

In all analyses performed using version 8 of the SAS System (Cary, NC), we classified individuals rather than eyes, because the same examiner made assessments at the same time for both eyes of each participant, and consequently, classification of the 2 eyes was not independent. We examined relationships for categories of tibia and patella bone lead formed using quintile cutpoints. We determined the mean levels (or percentages) of baseline characteristics according to quintiles of bone lead levels, and assessed the significance of a linear trend using linear regression models for the continuous variables, and the Mantel-Haenszel χ^2 test for trend for dichotomous variables. We determined the odds ratio (OR) and 95% confidence interval (CI) for occurrence of cataract using logistic regression models. The P value of significance was <.05. In initial analyses, we obtained age- and smoking-adjusted OR of cataract by quintile of bone lead level (separately for tibia or patella). We extended these models to control for other possible risk factors including history of diabetes mellitus (yes vs no), vitamin C, carotenoids, and/or vitamin E intake, all as assessed at the time of bone lead measurement. Using interaction terms in regression models, we explored whether diabetes or cigarette smoking modified the effect of bone lead level on cataract risk.

Finally, we calculated the age-adjusted attributable fraction in the population as a measure of the amount of cataract as-

sociated with lead exposure. Since relative risks of cataract were elevated in each of the top 4 quintiles of tibia lead, relative to the first with a significant linear trend, we determined the attributable fraction associated with tibia lead above the 20th percentile (ie, considering 80% of the population to be exposed).[11]

RESULTS

The mean age of study subjects was 69 years (range, 60-93). The concentration of tibia lead ranged from 0 to 126 µg/g (median, 20 µg/g), while patella lead ranged from 0 to 165 µg/g (median, 29 µg/g). The correlation of tibia and patella lead levels was 0.68. Blood lead levels ranged from 0 to 35 µg/dL (median, 5 µg/dL), and were moderately correlated with both tibia (r=0.31) and patella (r=0.39) lead levels. Older age (P<.001), higher blood lead levels (P<.001), a greater number of pack-years of cigarette smoking (P<.001), and a history of diabetes (P=.03), were related to higher concentrations of tibia lead (TABLE 1). Older age (P<.001), higher blood lead levels (P<.001), and a greater number of pack-years of cigarette smoking (P<.001), were also associated with higher patella lead levels.

We identified 122 cases of cataract among the 642 study participants aged 60 years and older, who had bone lead measurements and sufficient eye examination data. In univariate analyses, both tibia (P for trend<.001) and patella (P for trend=.02) lead were associated with an increased risk of cataract. After controlling for age, tibia lead level remained a significant predictor of cataract (OR for highest vs lowest quintile, 2.68; 95% CI, 1.31-5.50; P for trend=.03). Additional control for pack-years of cigarette smoking, blood lead levels, diabetes, and dietary intake of vitamin C, vitamin E, and carotenoids did not alter this association (OR, 3.19; 95% CI, 1.48-6.90; TABLE 2). In contrast, there was no significant association of patella lead level with cataract after controlling for age. The age-adjusted OR (95% CI) contrasting the highest vs the lowest quintile of patella lead level was 1.44 (0.75-2.78; P for trend=.43). Additional control for other

risk factors did not alter this null finding for the trend (*P*=.16), although the OR for the top quintile of patella lead level increased to 1.88 (95% CI, 0.88-4.02).

In contrast to the findings of significant associations between bone lead levels and cataract, the risk of cataract was not different across categories of blood lead levels (*P*=.67), which were available in 630 men. After controlling for age, the OR (95% CI) contrasting the top vs bottom quintile of blood lead level was 0.88 (0.47-1.64). This finding did not change after controlling for additional risk factors (OR, 0.89; 95% CI, 0.46-1.72; **TABLE 3**).

Since tibia lead level was related to both cigarette smoking and diabetes, 2 prominent cataract risk factors, we examined whether there was any evidence that these risk factors might

Table 1. Associations of Baseline Variables With Bone Lead Levels in the Normative Aging Study*

	Quintile of Bone Lead Level					
	1	2	3	4	5	P (Trend)
			Tibia			
Range, µg/dL	0-11.0	12.0-16.0	17.0-21.0	22.0-30.0	31.0-126.0	
No. of men	125	145	121	129	122	
Age, y	67.6 (5.26)	68.2 (5.87)	69.0 (5.97)	69.8 (6.55)	71.5 (6.17)	<.001
Tibia lead, µg/g	8.3 (3.27)	15.7 (1.74)	20.9 (1.48)	27.2 (2.50)	43.3 (15.1)	<.001
Blood lead, µg/dL	4.49 (2.65)	5.78 (3.84)	5.16 (2.93)	7.24 (4.62)	7.78 (4.85)	<.001
Smoking, pack-years	12.4 (19.01)	17.3 (21.42)	24.4 (25.94)	26.3 (29.83)	28.5 (30.34)	<.001
Vitamin C, mg/d	339 (332)	266 (308)	346 (371)	281 (284)	274 (310)	.20
Carotenoids, IU/d	11 719 (14 150)	11 449 (14 713)	11 455 (8853)	9239 (7055)	10 342 (8426)	.08
Vitamin E, mg/d	98 (188)	97 (196)	104 (188)	56 (142)	93 (212)	.25
Diabetes, No. (%)	10 (8.0)	8.3	15 (12.4)	14 (10.9)	20 (16.4)	.03
			Patella			
Range, µg/dL	1.0-16.0	17.0-23.0	24.0-31.0	32.0-42.0	43.0-165.0	
No. of men	127	136	125	126	128	
Age, y	68.0 (5.41)	67.8 (5.67)	68.6 (5.56)	69.9 (6.71)	71.7 (6.35)	<.001
Patella lead, µg/g	11.9 (4.51)	21.2 (1.99)	28.8 (2.58)	38.0 (6.71)	63.1 (20.13)	<.001
Blood lead, µg/dL	4.16 (2.04)	5.09 (2.92)	6.11 (3.73)	6.43 (4.11)	8.71 (5.31)	<.001
Smoking, pack-years	13.9 (18.17)	16.3 (23.43)	22.7 (23.62)	24.4 (27.56)	31.3 (32.80)	<.001
Vitamin C, mg/d	290 (289)	313 (338)	323 (354)	308 (348)	266 (276)	.48
Carotenoids, IU/d	10 215 (6833)	11 852 (12 363)	12 641 (17 810)	9464 (6517)	9997 (8113)	.29
Vitamin E, mg/d	96 (188)	87 (171)	102 (205)	86 (183)	76 (189)	.32
Diabetes, No. (%)	9 (7.1)	19 (14.0)	17 (13.6)	10 (7.9)	16 (12.5)	.60

*Data are presented as mean (SD) unless indicated otherwise.

Table 2. Associations Between Bone Lead Levels and Risk of Cataract in the Normative Aging Study

	Odds Ratio (95% CI) Per Quintile of Bone Lead					
	1	2	3	4	5	P (Trend)
			Tibia			
Range, µg/dL	0-11.0	12.0-16.0	17.0-21.0	22.0-30.0	31.0-126.0	
No. of cases/men	13/125	26/145	23/121	22/129	38/122	
Models						
Age	1.00	1.77 (0.85-3.69)	1.73 (0.81-3.69)	1.35 (0.63-2.91)	2.68 (1.31-5.50)	.03
Age + smoking*	1.00	1.78 (0.85-3.72)	1.78 (0.85-3.75)	1.39 (0.64-3.02)	2.69 (1.29-5.62)	.04
Age, smoking, + other risk factors†	1.00	1.83 (0.87-3.88)	1.63 (0.75-3.55)	1.58 (0.72-3.48)	3.19 (1.48-6.90)	.01
			Patella			
Range, µg/dL	1.0-16.0	17.0-23.0	24.0-31.0	32.0-42.0	43.0-165.0	
No. of cases/men	19/127	23/136	22/125	23/126	35/128	
Models						
Age	1.00	1.18 (0.60-2.35)	1.14 (0.57-2.27)	0.97 (0.48-1.95)	1.44 (0.75-2.78)	.43
Age + smoking*	1.00	1.18 (0.60-2.35)	1.15 (0.57-2.30)	0.99 (0.49-2.00)	1.43 (0.73-2.82)	.46
Age, smoking, + other risk factors†	1.00	1.28 (0.62-2.65)	1.25 (0.59-2.62)	1.21 (0.57-2.57)	1.88 (0.88-4.02)	.16

Abbreviation: CI, confidence interval.
*Six men, including 1 case, were excluded from these analyses due to missing data for smoking.
†Other risk factors include blood lead levels, history of diabetes, and mean daily intake of vitamin C, vitamin E, and carotenoids. Twenty-six men, including 4 cases, were eliminated from these models because of missing covariate data.

Table 3. Associations Between Blood Lead Levels and Risk of Cataract in the Normative Aging Study

| | Odds Ratio (95% CI) Per Quintile of Blood Lead | | | | | |
	1	2	3	4	5	P (Trend)
Range, μg/dL	1.0-3.0	3.01-4.41	4.5-5.88	6.0-8.0	8.17-35.0	
No. of cases/men	30/147	18/105	22/102	27/158	22/118	
Models						
Age	1.00	0.80 (0.41-1.57)	0.93 (0.49-1.77)	0.75 (0.42-1.36)	0.88 (0.47-1.64)	.61
Age + smoking*	1.00	0.81 (0.41-1.58)	0.94 (0.49-1.78)	0.76 (0.42-1.38)	0.87 (0.46-1.66)	.60
Age, smoking, + other risk factors†	1.00	0.79 (0.40-1.57)	0.89 (0.46-1.71)	0.79 (0.43-1.46)	0.89 (0.46-1.72)	.73

Abbreviation: CI, confidence interval.
*Six men, including 1 case, were excluded from these analyses due to missing data for smoking.
†Other risk factors include history of diabetes and mean daily intake of vitamin C, vitamin E, and carotenoids. Twenty-six men, including 4 cases, were excluded from this model because of missing covariate data.

modify the associations between tibia lead level and cataract. In these models, there was no significant interaction of tibia lead level with either diabetes (*P* for interaction=.93), or cigarette smoking (*P* for interaction=.25).

Finally, after controlling for age, the attributable fraction of cataract in this population associated with lead exposure was 42%.

COMMENT

Although much progress has been made to limit lead exposure in the United States and other industrialized countries, primarily through the elimination of leaded gasoline and workplace exposures, most adults have already accumulated a substantial body burden of lead.[1] Moreover, generalized low lead exposure along with pockets of higher exposure remain commonplace, including in the United States where more than 80% of homes built before 1980 are contaminated by lead-based paint and/or leaded water pipes.[12] Results of the present study suggest that cumulative lead exposure is a risk factor for cataract, which accounts for more than 40% of all cases of blindness worldwide.[5] There was a greater than 2.5-fold increased risk of cataract in men with the highest levels of lead in the tibia, compared with men with the lowest tibia lead levels. The estimated attributable fraction of cataract in this population resulting from lead exposure was 42%. However, as expected, there was no association between blood lead levels and risk of cataract in these men.

Since blood lead levels are indicative only of recent exposures,[2,10] they are not likely to be very relevant to the development of age-related eye diseases, which take many years to develop. Approximately 95% of the total body burden of lead is present in the skeleton and, consequently, measurement of bone lead levels can provide an integrated picture of more long-term exposure. Lead stored in cortical bone has a biological half-life of more than 10 years, and lead from trabecular bone has a half-life of 1 to 5 years.[13,14] Lead is continuously mobilized from the skeleton, circulates in plasma at very low levels that are difficult to measure, and is made available for interactions with other tissues. Thus, bone lead levels are thought to be indicative not only of the magnitude of the cumulative exogenous exposure, but also of exposure from endogenous sources.[2,10] Indeed, bone lead measured by K x-ray fluorescence has recently been found to be a better biomarker of lead dose than blood lead in terms of predicting several chronic toxicity outcomes such as hypertension, decreased cognitive function, and electrocardiographic conduction disturbances in adults.[7,8,15-20]

We are interested in studying the relationship between lead exposure and cataractogenesis because lead can disrupt lens redox status, the maintenance of which is necessary to maintain lens clarity,[21] and conversely, cataract appears to be the result of accumulated oxidative damage to lens epithelial cells.[22] Furthermore, lead adversely affects glutathione metabolism in the lens[23] and increases the amount of protein-bound glutathione and cysteine. Malondialdehyde, a major lipid peroxidation product, is also increased in the lens following lead exposure.[21] Lead can interfere with the calcium homeostasis of various tissues, and normal calcium homeostasis is essential to the maintenance of lens clarity.[24]

In animal studies, lead accumulated in a time- and concentration-dependent manner in the lenses of exposed rabbits.[25] More importantly, several studies have now shown that lead may be present at higher levels in human cataractous lenses as compared with clear lenses.[23,26-29] Further, lens lead levels were inversely correlated with lens levels of the antioxidant zinc, and the intrusion of lead into the lens caused protein conformational changes that affected lens transparency.[27]

The NAS is an ongoing cohort study with high-quality data. However, ocular photographs were not taken and standardized cataract grading schemes were not used. Although some misclassification may result from our use of medical records to determine cataract status, it is unlikely that any misclassification would be differential with respect to bone lead levels; and, thus, the expected bias would be in the direction of a null finding. Furthermore, our use of cataract surgery or a relatively severe grade of cataract should have further minimized disease misclassification. Nonetheless, we were not able to examine risk as it might be related to specific types of cataract, which may have different etiologies,[30] or the risk among younger individuals (<60 years of age) as the more severe cataracts we examined were virtually nonexistent in this subgroup. Confounding by unmeasured risk factors such as sunlight exposure and use of steroid medications is an improbable explanation of our findings, since these exposures are

unlikely to be strongly correlated with bone lead levels. Although we controlled as rigorously as possible for cigarette smoking, using pack-years of exposure, residual confounding by cigarette smoking is theoretically possible since lead can be present in cigarette smoke.[31] NAS participants are fairly representative of similarly aged men in Massachusetts, with similar rates of smoking and alcohol consumption; although they tended to be slightly better educated, and with a slightly higher median income than men of comparable age in the general population of the United States.[32]

Prevention of age-related cataract remains an important public health goal. Expenditures for cataract surgery comprise the largest single line item in the Medicare budget.[33] In addition to the obvious problems of reduced vision, visual disability such as that produced by cataract can have a deleterious impact on risk of falls, fractures, quality of life, and possibly even mortality.[34-38] Lead has been spread throughout the environment, primarily through leaded gasoline and lead paint, and nearly every adult in the United States has accumulated some degree of lead in the skeleton. Moreover, lead exposure in many developing countries, where the cataract burden is even greater, continues to be high.[39-41]

These are, to our knowledge, the first data suggesting that accumulated lead exposure, such as that commonly experienced by adults in the United States, may be an important, unrecognized risk factor for cataract. This research suggests that reduction of lead exposure could help decrease the global burden of cataract.

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2004, and a reminder message was sent on April 5. Frequency distributions were computed for the 14 categorical response items.

Results. Responses were obtained from 98 (78%) of the 126 schools surveyed. The responses to the first 12 questions are shown in the TABLE. Fifty-five percent of schools report that they have modified their curriculum as a result of the Step 2 CS. Fifty percent of schools require passing scores in clinical coursework before taking the Step 2 CS and 63% require a passing score on this examination prior to graduation. Seventy-two percent of schools are taking steps to assist students with fees for taking the Step 2 CS and 54% of the schools are providing a practice examination to assist students with preparation. Faculty support for the Step 2 CS is mixed (46% positive/very positive, 29% indifferent, and 22% negative).

Comment. The addition of the Step 2 CS as a new licensure requirement has led to curricular and other modifications, including access to additional student financial aid in a majority of US medical schools. The governance of medical schools reflects the interplay of societal issues, scientific advances, faculty concerns, and regulatory requirements (eg, physician licensure and institutional accreditation). Achieving an appropriate balance among these components is a challenging task for individual schools. Making a change in one requirement appears to result in a broad investment of resources by medical schools. However, it is not clear how the educational value of this new intervention can be measured.

We believe that there should be an overarching review of this complex web of interacting bodies that affects the education of our nation's physicians.

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CORRECTIONS

Incorrect Reference Cited: In the Clinical Crossroads entitled "A 67-Year-Old Man Who e-Mails His Physician," published in the November 10, 2004, issue of *JAMA* (2004;292:2255-2261), an incorrect reference number was cited. On page 2258, in the first complete paragraph under the heading "The Medical Record Shared," "In 1970, I proposed that patients and physicians alike would benefit if medical records were declassified, shared, and developed jointly by patient and physician.[34]" should have cited reference 31 instead of 34. (Slack WV. Patient power: a patient oriented value system. In: Jacques JA, ed. *Computer Diagnosis and Diagnostic Methods: Proceedings of the Second Conference on the Diagnostic Process Held at the University of Michigan.* Springfield, Ill: Charles C Thomas; 1972: 3-7.)

Incorrect Measurement Units: In the Original Contribution entitled "Accumulated Lead Exposure and Risk of Age-Related Cataract in Men," published in the December 8, 2004, issue of *JAMA* (2004;292:2750-2754), an incorrect unit of measure was used. On page 2752, in Table 1 and Table 2, Range, µg/dL should have read Range, µg/g.