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Association of Cadmium and Lead Exposure With the Incidence of Contrast Sensitivity Impairment Among Middle-aged Adults

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IMPORTANCE Contrast sensitivity (CS) is an important indicator of visual function that affects daily life, including mobility, visually intensive tasks, safety, and autonomy. Understanding the risk factors for CS impairment could prevent decreases in visual function.

OBJECTIVE To determine the incidence of and factors associated with CS impairment in a large cohort.

DESIGN, SETTING, AND PARTICIPANTS The Beaver Dam Offspring Study is an ongoing longitudinal cohort study of aging involving adults in Beaver Dam, Wisconsin. Participants who were free of CS impairment in both eyes at baseline were included (N = 1983). Baseline data collection occurred from June 8, 2005, through August 4, 2008, when the participants ranged from 21 to 84 years of age. Two follow-up examinations occurred at 5-year intervals: one was conducted between July 12, 2010, and March 21, 2013, and the other between July 1, 2015, and November 13, 2017. Data analysis was performed from November 27, 2017, to February 27, 2018.

MAIN OUTCOMES AND MEASURES Contrast sensitivity testing was conducted with Pelli-Robson letter sensitivity charts, and incident impairment was defined as a log CS score less than 1.55 in either eye at any follow-up examination. Cadmium and lead levels were measured in whole blood with inductively coupled plasma mass spectrometry. Associations between baseline characteristics and CS impairment incidence were examined using Cox proportional hazard models and quantified as hazard ratios (HRs) with 95% CI.

RESULTS Of the 1983 participants included, 1028 (51.8%) were female and 955 (48.2%) were male, with a mean (SD) age of 48 (9.3) years. The 10-year cumulative incidence of CS impairment was 24.8% (95% CI, 22.9-26.8), similar in women (24.9%) and men (24.6%), and highest in the oldest age group (65-84 years) at 66.3%. In multivariable models, cadmium level in the highest quintile (HR, 1.35; 95% CI, 1.02-1.78), older age (HR, 1.36; 95% CI, 1.25-1.47), larger waist circumference (HR, 1.06; 95% CI, 1.01-1.11), and more plaque sites (1-3 sites: HR, 1.43; 95% CI, 1.07-1.92; 4-6 sites: HR, 2.75; 95% CI, 1.26-6.05) were among the factors associated with increased risk, while male sex (HR, 0.77; 95% CI, 0.60-0.98) and any alcohol consumption (HR, 0.61; 95% CI, 0.43-0.88) were associated with decreased risk. Results were similar when smoking status replaced cadmium exposure in the models. Lead level was not associated with increased risk.

CONCLUSIONS AND RELEVANCE This study's findings suggest that incident CS impairment was common in the 10-year follow-up, with cadmium, but not lead, exposure associated with increased risk. The associations of diminished CS with other modifiable risk factors found appear to imply that changes in behavior may reduce future incidence of CS impairment.

Invited Commentary
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Contrast sensitivity (CS) is an important indicator of visual function that measures aspects of vision not captured by the more commonly measured and reported distance visual acuity (VA). Specifically, CS is a measure of how well an object is seen against its background, and low-contrast conditions simulate low light, fog, or glare. As a result, CS may be diminished even in those with good VA.[1,2]

The prevalence of CS impairment varies by age and is more common in older adults. In the Beaver Dam Offspring Study (BOSS), whose participants had a mean age of 49 years, the prevalence of CS impairment was 7.8%, whereas in the Beaver Dam Eye Study, whose participants had a mean age of 65 years, the prevalence was 26%.[3,4] Contrast sensitivity is associated with the ability to function in daily life as well as with safety and autonomy. Earlier studies found that diminished CS was associated with lower scores on the Activities of Daily Vision Scale (score range: 0-100, with the highest score indicating no difficulty with daily activities),[5] independent of visual acuity and glare sensitivity, as well as poor performance on tasks of everyday life, including mobility, inserting keys into locks, and reading.[6,7] Similarly, the Beaver Dam Eye Study found that poorer CS was associated with worse self-reported general visual function, more limitations with vision-dependent activities such as reading small print, and a slower gait time.[3,8] In the Longitudinal Aging Study Amsterdam, the investigators found that those with decreased CS had a higher probability of recurrent falls.[9] Studies aiming to determine the effects of VA and CS on driving performance found that CS, but not VA, was associated with a driver's recognition abilities; those with better CS were more likely to drive at night; and older drivers with impaired CS had a 42% increased risk for motor vehicle collision compared with drivers without CS impairment.[10-12] In addition, CS has been associated with other disorders, including Alzheimer disease,[13] cognitive function and impairment,[4,14] diabetes,[15] and multiple sclerosis.[16,17]

Cadmium and lead are neurotoxic heavy metals with multiple points of exposure, including the home environment. Cadmium exposure typically occurs through inhalation of cigarette smoke and consumption of green leafy vegetables, rice, and shellfish. Lead exposure occurs frequently from air pollution and old paint or water pipes.[18] Both cadmium and lead are associated with impairments in multiple sensory systems and accumulate in ocular tissues, including the retina, during aging.[19-23] The neurotoxic effects of cadmium and lead may play a role in the development of CS impairment through multiple mechanisms such as increased oxidative stress[20,24]; neuronal apoptosis[25]; increased inflammation; disruption of metabolism of critical elements, such as zinc and copper[18,26-28]; and interference of cell signaling.[29] Cadmium and lead are implicated in the pathogenesis of age-related macular degeneration (AMD)[19,30-35] and cataract formation.[36-39] The potential implications of these heavy metals for CS are relatively unknown.

Little is known about other potential risk factors for CS impairment. A study of older adults found that smoking, not consuming any alcohol in the past year, and sedentary behavior were associated with larger decreases in VA over a 20-year period.[40] Similar associations may exist between behavioral factors and development of CS impairment. The association of atherosclerosis with CS is unknown, although atherosclerosis affects other sensory systems and cognition, which may diminish neuronal health and signaling between sensory organs and the brain.[41-43] Inflammation may play a similar role and have negative associations with sensory health, including vision. Inflammation is associated with incident AMD and may similarly affect CS.[40]

Given the importance of CS to visual function and everyday function, the factors that contribute to a decrease in CS must be identified and understood. Studying these potential risk factors in middle-aged adults may present opportunities for early intervention to preserve good visual function in aging populations.

Key Points

Question What is the association of blood cadmium and lead levels with the 10-year incidence of contrast sensitivity impairment in a cohort of middle-aged adults?

Findings In this longitudinal cohort study of 1983 adults, exposure to cadmium, but not lead, and smoking were associated with increased risk for contrast sensitivity impairment in the 10-year follow-up period.

Meaning Reducing exposure to cadmium, smoking, or both may reduce the burden of contrast sensitivity impairment in middle-aged adults.

Methods

Participants

Recruitment details of the BOSS have been previously reported.[44] Briefly, the BOSS is an ongoing cohort study of aging in Beaver Dam, Wisconsin, involving the adult children of the participants in the population-based Epidemiology of Hearing Loss Study.[45] Baseline data collection occurred from June 8, 2005, through August 4, 2008, when the participants ranged from 21 to 84 years of age. Two follow-up examinations occurred at 5-year intervals: one was conducted between July 12, 2010, and March 21, 2013, and the other between July 1, 2015, and November 13, 2017. At baseline with at least 1 follow-up examination, 1983 participants were found at risk for CS impairment. Study approval was granted by the Health Sciences Institutional Review Board of the University of Wisconsin-Madison. Informed written consent was obtained from all participants prior to each examination.

CS Measurement

Contrast sensitivity testing was conducted using the Pelli-Robson letter sensitivity chart.[46] Participants viewed this chart at a distance of 1 m and were tested monocularly while wearing trial frames with the appropriate distance correction, as determined by autorefractor (WR-5001K; Grand Seiko) readings and refined by subjective refraction when VA was worse than 20/40. Each of the 2 charts (1 for each eye) consisted of 16 letter triplets, and the contrast in each successive triplet decreased by a factor of 0.15 log unit. Participants were encour-

aged to progress as far as possible, making a best guess if they were unsure about a particular letter. The last triplet in which a participant correctly identified at least 2 of the 3 letters was used to assign a log CS score. A log CS score less than 1.55 was considered impaired, and cases were defined when either eye was impaired at the follow-up examination.

Cadmium and Lead Level Measurement

Cadmium and lead levels were measured in whole blood samples obtained during the BOSS baseline examination. Blood samples were stored at -80°C until the 2015 to 2016 testing by the Wisconsin State Laboratory of Hygiene. Inductively coupled plasma mass spectrometry was used to measure both metals. The limits of detection for cadmium level were 0.21 µg/L (to convert to nanomoles per liter, multiply by 8.896) and for lead level were 0.20 µg/dL (to convert to micromoles per liter, multiply by 0.0483). The samples used for quality control had to be within 10% of the target value to be considered acceptable, and 10% of samples were retested to ensure they met acceptability criteria.

Covariates

Baseline factors potentially associated with the risk for cumulative incidence of impaired CS were evaluated. Blood pressure, height, weight, and waist circumference were measured following standard protocols. Hypertension was defined as a measured systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or physician diagnosis with current blood pressure medication. Body mass index (weight in kilograms divided by height in meters squared) was calculated and classified as normal (<25), overweight (25-29), or obese (≥30).

Retinal photographs were taken with a fundus camera (Dgi-45NM; Canon), lens images were taken with a slitlamp (SL-D7; Topcon Medical Systems) and camera back (DG-1; Topcon Medical Systems), and retroillumination lens images were taken with a cataract screener (Neitz CT-S; Neitz Instruments Co Ltd). The presence of AMD was determined by fundus image grading by the University of Wisconsin Ocular Epidemiology Reading Center using the Wisconsin Age-Related Maculopathy Grading System, and the presence of cataract (cortical, nuclear sclerosis, or posterior subcapsular) was determined by slitlamp and retroillumination lens image grading.[47,48] Visual acuity was measured monocularly using the Early Treatment Diabetic Retinopathy Study charts and protocol. Impaired visual acuity was defined as an equivalent Snellen value of 20/40 or worse. Carotid artery ultrasound scans were used to measure intima-media thickness (mean of up to 12 wall thicknesses in the carotid arteries) and count of plaque in the carotid arteries (0 to 6 sites: common carotid, carotid bulb, and internal carotid, right and left sides).[49] Whole blood glycated hemoglobin A_{1C} level was measured using an automated high-performance liquid chromatography method (Tosoh A_{1C} G7 Glycohemoglobin Analyzer; Tosoh Medics). Diabetes was defined by a hemoglobin A_{1C} level of 6.5 or higher or a physician diagnosis of borderline diabetes with current treatment. Inflammatory markers were measured in stored serum samples by the University of Minnesota Advanced Research and Diagnostic Laboratory. Interleukin 6, tumor necrosis factor, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1 were measured by a quantitative sandwich enzyme technique (ELISA QuantiKine High Sensitivity kit; R&D Systems), and the human tumor necrosis factor, soluble intercellular adhesion molecule 1, and soluble vascular cell adhesion molecule 1 were measured with high-sensitivity immunoassays (QuantiKine; R&D Systems). C-reactive protein level was measured using a latex particle-enhanced immunoturbidimetric assay (Roche Diagnostics).

Age, sex, socioeconomic status (household income and educational level), smoking status (never, past, or current), household information (urban or rural and source of drinking water), exercise (at least once a week), employment type (professional, managerial, technical, or sales vs farming, forestry, production, fabrication, or labor), work-related exposures (heavy metals or solvents), and alcohol consumption (none or any in past year) were assessed by in-person interview or reported via a self-administered questionnaire following standard protocols. Use of medications, including statins and multivitamins, was documented.

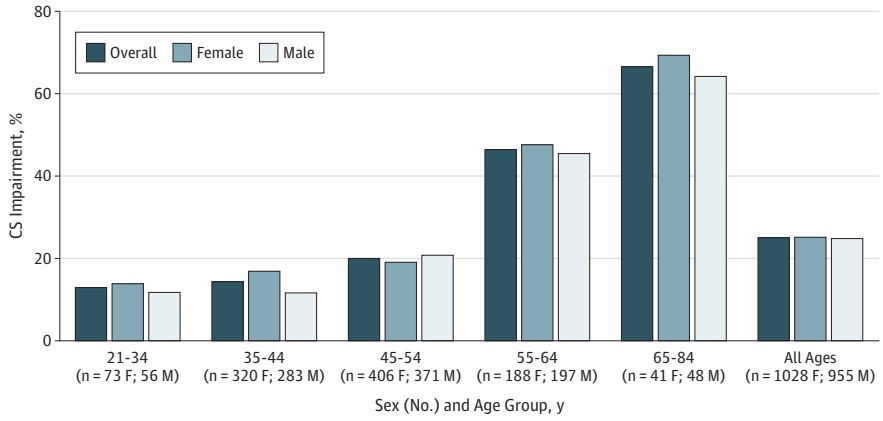
Statistical Analysis

Cadmium and lead levels were divided into quintiles, and exposure was modeled with quintiles 1 through 4 as the reference group. A dose-response relationship was also investigated using indicator variables for cadmium and lead levels and by analyzing the doubling of levels. Potential risk factors were first assessed with age- and sex-adjusted Cox proportional hazards models. Multivariable models were built with a manual backward elimination approach, beginning with associated variables in age- and sex-adjusted models. Variables that remained associated in the larger multivariable model or were suggestive of associations were considered for the final model, which was confirmed using a stepwise selection procedure. Because smoking is a major source of cadmium exposure, models with either smoking or cadmium excluded were constructed and a sensitivity analysis was conducted among nonsmokers to examine this relationship. In addition, the final cumulative incidence models were repeated that excluded all participants with AMD, cataract, or VA impairment at any examination to check the consistency of results because these conditions are known to be strong factors in CS impairment.[1] All analyses were completed with the SAS software, version 9.4 (SAS Institute, Inc). Data analysis was performed from November 27, 2017, to February 27, 2018. Statistical significance was defined as $P < .05$ (2-sided).

Results

Participants who were free of CS impairment in both eyes at baseline were included in the present study (N = 1983). Of the 1983 participants, 1028 (51.8%) were female and 955 (48.2%) were male, with a mean (SD) age of 48 (9.3) years. The 10-year cumulative CS impairment incidence was 24.8% (95% CI, 22.9-26.8) and was similar in women (24.9%) and men (24.6%). The **Figure** displays incidence by age and sex. Incidence was

Figure. 10-Year Cumulative Incidence of Contrast Sensitivity (CS) Impairment by Sex and Baseline Age



F indicates female; M, male.

highest (66.3%) in the 65-to-84-years age group, which comprised 41 women and 48 men. Four hundred six (87.1%) of the 466 incident cases occurred in participants who did not have a measured VA worse than Snellen 20/40 at any time point.

Age- and sex-adjusted hazard ratios (HRs) for baseline characteristics and incident CS impairment can be found in **Table 1**. Blood cadmium level in quintile 5 was associated with an increased risk for CS impairment (HR, 1.40; 95% CI, 1.09-1.81), although a similar association did not exist for lead level (HR, 0.91; 95% CI, 0.69-1.18). In addition, lower household income (HR, 1.34; 95% CI, 1.07-1.67), current smoking (HR, 1.55; 95% CI, 1.18-2.03), more carotid artery sites with plaque (1-3 sites: HR, 1.55; 95% CI, 1.20-2.00; 4-6 sites: HR, 2.67; 95% CI, 1.36-5.23), thicker intima-media thickness (HR, 1.19; 95% CI, 1.10-1.29), higher interleukin 6 values (tertile 3: HR, 1.54; 95% CI, 1.19-2.01), higher C-reactive protein levels (>3: HR, 1.46; 95% CI, 1.11-1.91), cataract (HR, 1.97; 95% CI, 1.27-3.07), VA impairment (HR, 2.58; 95% CI, 1.32-5.01), diabetes (HR, 2.06; 95% CI, 1.37-3.10), and larger waist circumference (HR, 1.07; 95% CI, 1.04-1.11) were associated with increased risk for developing CS impairment. Consumption of alcohol in the previous year was the only factor inversely associated with incident CS impairment (HR, 0.62; 95% CI, 0.46-0.85), although a history of heavy drinking (>4 drinks per day) was not associated with incident impairment (HR, 0.99; 95% CI, 0.76-1.31).

In the multivariable model, older age (HR, 1.36; 95% CI, 1.25-1.47), larger waist circumference (HR, 1.06; 95% CI, 1.01-1.11), more carotid plaque sites (1-3 sites: HR, 1.43; 95% CI, 1.07-1.92; 4-6 sites: HR, 2.75; 95% CI, 1.26-6.05), VA impairment (HR, 3.61; 95% CI, 1.61-8.10), and cataract (HR, 1.99; 95% CI, 1.21-3.28) were associated with greater risk for CS impairment incidence, but male sex (HR, 0.77; 95% CI, 0.60-0.98) and any alcohol consumption in the past year were associated with decreased risk (HR, 0.61; 95% CI, 0.43-0.88) (**Table 2**). In this model, neither cadmium level nor smoking was associated with CS impairment incidence. Because of a strong collinear relationship between smoking and cadmium, as 233 (75.4%) of 309 participant smokers were in quintile 5 and as 233 (64.5%) of 361 in quintile 5 were smokers, separate reduced models with cadmium level or smoking were run. In these models, estimates for most covariates remained unchanged, although the association with quintile 5 cadmium level (HR, 1.35; 95% CI, 1.02-1.78) and smoking (HR, 1.46; 95% CI, 1.09-1.95) strengthened in their respective models (Table 2). In the sensitivity analysis, among nonsmokers, the association with quintile 5 cadmium level was attenuated (HR, 1.10; 95% CI, 0.72-1.70).

In the sensitivity analysis, excluding those with ocular comorbidities, estimates for age, sex, alcohol consumption, and waist circumference were similar (Table 2). The increased risk from quintile 5 cadmium level (HR, 1.72; 95% CI, 1.26-2.35) and smoking (HR, 1.73; 95% CI, 1.26-2.39) was higher in the group without AMD, cataract, or VA impairment. The association between carotid artery plaque and CS impairment incidence was inconsistent in these reduced models with fewer participants.

Discussion

Nearly a quarter of BOSS participants developed CS impairment in the 10-year follow-up period, suggesting that CS impairment is relatively common among aging adults. Previous studies found that poor CS occurs in individuals without ocular comorbidities and in those with good VA. More than 87% of incident cases had normal VA in the BOSS. Contrast sensitivity impairment has been associated with problems with daily activities; lower autonomy, including driving; and higher risk for falls.[3,6-12] With a large proportion of middle-aged adults experiencing a decrease in CS, better understanding of risk factors to potentially prevent this decrease is an important target for public health.

Cadmium exposure and smoking were associated with an increased risk for CS impairment in separate models. Because smoking is a main source of cadmium, these 2 risk factors had a high level of collinearity, making it impossible to discern which factor was ultimately responsible for the increased risk in this study. In the analysis limited to nonsmokers that greatly reduced the number of participants in the highest quintile of exposure, the association with cadmium exposure was attenuated. This outcome may indicate a lack of power rather than a lack of association. Some other components of cigarette smoke may also be involved in the development of CS

Table 1. Risk for Incident Contrast Sensitivity Impairment by Baseline Characteristics

Variable	Incident CS Impairment, No. (%)		Age- and Sex-Adjusted Hazard Ratio (95% CI)
	No (n = 1517)	Yes (n = 466)	
Heavy Metals			
Cadmium level, μg/L			
Quintiles 1-4: <0.52	1143 (81.6)	331 (76.1)	1 [Reference]
Quintile 5: >0.52	257 (18.4)	104 (23.9)	1.40 (1.09-1.81)
Lead level, μg/L			
Quintiles 1-4: <2.06	1125 (80.4)	338 (77.7)	1 [Reference]
Quintile 5: ≥2.06	275 (19.6)	97 (22.3)	0.91 (0.69-1.18)
Demographics			
Educational level, y			
<16	963 (63.8)	312 (67.2)	1 [Reference]
>16	546 (36.2)	152 (32.8)	0.96 (0.77-1.19)
Household income, US $			
<50 000	415 (28.1)	168 (37.8)	1.34 (1.07-1.67)
>50 000	1064 (71.9)	277 (62.2)	1 [Reference]
Home Environment			
Location of home			
Town or city	1041 (68.6)	307 (65.9)	1 [Reference]
Country	476 (31.4)	159 (34.1)	0.99 (0.79-1.22)
Municipal drinking water			
No	538 (35.5)	173 (37.1)	1 [Reference]
Yes	979 (64.5)	293 (62.9)	1.0 (0.84-1.28)
Employment Type			
Farming, forestry, production, fabrication, or labor job			
No	1006 (75.3)	281 (77.4)	1 [Reference]
Yes	330 (24.7)	82 (22.6)	0.88 (0.66-1.18)
Metal exposure at work			
No	1421 (94.4)	447 (96.5)	1 [Reference]
Yes	85 (5.6)	16 (3.5)	0.68 (0.40-1.15)
Behavioral Factors			
Regular exercise, at least once/wk			
No	556 (36.7)	190 (40.9)	1 [Reference]
Yes	959 (63.3)	275 (59.1)	0.96 (0.78-1.20)
Current smoker?			
No	1267 (83.6)	378 (81.1)	1 [Reference]
Yes	249 (16.4)	88 (18.9)	1.55 (1.18-2.03)
Alcohol consumption in previous year			
None	127 (8.4)	67 (14.4)	1 [Reference]
Any	1389 (91.6)	389 (85.6)	0.62 (0.46-0.85)
Medication Use			
Multivitamins			
No	805 (53.1)	235 (50.4)	1 [Reference]
Yes	712 (46.9)	231 (49.6)	0.85 (0.69-1.05)
Statins			
No	1340 (88.3)	378 (81.1)	1 [Reference]
Yes	177 (11.7)	88 (18.9)	1.02 (0.77-1.36)
Vascular Factors			
Hypertension			
No	1064 (70.2)	263 (56.4)	1 [Reference]
Yes	452 (29.8)	203 (43.5)	1.19 (0.95-1.48)

(continued)

Table 1. Risk for Incident Contrast Sensitivity Impairment by Baseline Characteristics (continued)

Variable	Incident CS Impairment, No. (%)		Age- and Sex-Adjusted Hazard Ratio (95% CI)
	No (n = 1517)	Yes (n = 466)	
No. of plaque sites			
0	1189 (82.5)	276 (64.6)	1 [Reference]
1-3	239 (16.6)	134 (31.4)	1.55 (1.20-2.00)
4-6	13 (0.9)	17 (4.0)	2.67 (1.36-5.23)
Carotid IMT, mean (SD), mm	0.63 (0.12)	0.71 (0.18)	1.19 (1.10-1.29)[a]
Inflammatory Markers			
Interleukin 6, pg/mL			
Tertile 1: <1.27	541 (37.5)	118 (26.6)	1 [Reference]
Tertile 2: 1.27 to <2.28	501 (34.7)	140 (31.6)	0.99 (0.76-1.30)
Tertile 3: ≥ 2.28	400 (27.7)	185 (41.8)	1.54 (1.19-2.01)
ICAM-1, ng/mL			
Tertile 1: <190.1	504 (34.9)	139 (31.2)	1 [Reference]
Tertile 2: 190.1 to <238.5	505 (34.9)	155 (34.7)	1.00 (0.77-1.29)
Tertile 3: ≥238.5	436 (30.2)	152 (34.1)	1.04 (0.80-1.35)
CRP, mg/L			
<1.0	620 (42.8)	150 (33.3)	1 [Reference]
1.0-3.0	537 (37.1)	175 (38.8)	1.10 (0.86-1.41)
>3.0	292 (20.1)	126 (27.9)	1.46 (1.11-1.91)
TNF, pg/mL			
Tertile 1: <.358	515 (35.5)	138 (30.6)	1 [Reference]
Tertile 2: .358 to <.613	479 (33.1)	161 (35.7)	1.12 (0.87-1.45)
Tertile 3: ≥.613	455 (31.4)	152 (33.7)	1.10 (0.85-1.43)
VCAM-1, ng/mL			
Tertile 1: <497	520 (35.9)	143 (31.7)	1 [Reference]
Tertile 2: 497 to <635	491 (33.9)	142 (31.5)	0.92 (0.71-1.19)
Tertile 3: ≥635	438 (30.2)	166 (36.8)	1.05 (0.81-1.37)
Visual Health Factors			
AMD[b]			
No	1459 (97.1)	433 (95.8)	1 [Reference]
Yes	44 (2.9)	19 (4.2)	1.12 (0.65-1.92)
Cataract[c]			
No	1459 (97.8)	410 (90.9)	1 [Reference]
Yes	32 (2.2)	41 (9.1)	1.97 (1.27-3.07)
VA impairment (worse eye)			
No	1499 (98.8)	452 (97.0)	1 [Reference]
Yes	18 (1.2)	14 (3.0)	2.58 (1.32-5.01)
Other Health Factors			
Diabetes			
No	1436 (96.8)	414 (90.6)	1 [Reference]
Yes	47 (3.2)	43 (9.4)	2.06 (1.37-3.10)
BMI			
<25.0	350 (23.3)	78 (16.9)	1 [Reference]
25.0 to <30.0	532 (35.4)	141 (30.5)	0.98 (0.72-1.34)
≥30.0	622 (41.4)	243 (52.6)	1.28 (0.96-1.72)
Waist circumference, mean (SD), cm	98.2 (15.8)	103.5 (17.2)	1.07 (1.04-1.11)

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; CS, contrast sensitivity; ICAM-1, intercellular adhesion molecule 1; IMT, intima-media thickness; TNF, tumor necrosis factor; VA, visual acuity; VCAM-1, vascular cell adhesion molecule 1.

SI conversion factors: To convert cadmium level to nanomoles per liter, multiply by 8.896; lead level to micromoles per liter, multiply by 0.0483; CRP level to nanomoles per liter, multiply by 9.524.

[a] Based on increase in carotid IMT of 0.1 mm.

[b] Based on graded retinal fundus images.

[c] Based on graded slitlamp and retroillumination lens images.

impairment, and cadmium level and smoking could be acting as proxies for that unmeasured exposure. However, blood cadmium level and smoking remain associated with increased risk.

To our knowledge, this is the first study to find cadmium exposure to be associated with CS; previous studies have reported cadmium level and smoking to be associated with other ocular diseases, such as AMD and cataract.[19,30-39,50] In turn, both of these pathologies have been associated with lower CS.[51-55] A study using data from the National Health and Nutrition Examination Survey found that more than 50% of the

Table 2. Multivariable Models of the Risk for Incident Contrast Sensitivity Impairment

Variable	Hazard Ratio (95% CI)				
	All Participants			Sensitivity Analysis (n = 1434)[a]	
	Full Model	Reduced Model With Smoking	Reduced Model With Cadmium	Reduced Model With Smoking	Reduced Model With Cadmium
Age per 5 y	1.36 (1.25-1.47)	1.36 (1.26-1.46)	1.34 (1.25-1.44)	1.31 (1.21-1.42)	1.28 (1.18-1.39)
Male sex	0.79 (0.61-1.04)	0.76 (0.60-0.97)	0.77 (0.60-0.98)	0.64 (0.49-0.84)	0.65 (0.49-0.86)
Household income, <US $50 000	1.16 (0.89-1.51)	NA	NA	NA	NA
Current smoker	1.23 (0.81-1.85)	1.46 (1.09-1.95)	NA	1.73 (1.26-2.39)	NA
Any alcohol consumption	0.61 (0.43-0.88)	0.61 (0.44-0.85)	0.54 (0.39-0.76)	0.59 (0.40-0.86)	0.56 (0.38-0.83)
Current multivitamin use	1.05 (0.82-1.34)	NA	NA	NA	NA
Hypertension	0.89 (0.67-1.17)	NA	NA	NA	NA
Diabetes	1.40 (0.82-2.37)	NA	NA	NA	NA
Waist circumference per 5 cm	1.06 (1.01-1.11)	1.06 (1.02-1.10)	1.06 (1.02-1.10)	1.07 (1.03-1.11)	1.06 (1.01-1.10)
No. of plaque sites					
1-3	1.43 (1.07-1.92)	1.43 (1.10-1.87)	1.37 (1.03-1.81)	1.40 (1.02-1.91)	1.33 (0.96-1.85)
4-6	2.75 (1.26-6.05)	2.59 (1.25-5.35)	2.63 (1.26-5.48)	1.67 (0.65-4.31)	1.79 (0.69-4.65)
Cadmium level, quintile 5 vs all other quintiles	1.14 (0.79-1.65)	NA	1.35 (1.02-1.78)	NA	1.72 (1.26-2.35)
Interleukin 6					
Tertile 1: <1.27	1 [Reference]	NA	NA	NA	NA
Tertile 2: 1.27 to <2.28	0.74 (0.54-1.02)	NA	NA	NA	NA
Tertile 3: ≥2.28	0.94 (0.65-1.36)	NA	NA	NA	NA
CRP, mg/L					
<1	1 [Reference]	NA	NA	NA	NA
1-3	1.01 (0.75-1.35)	NA	NA	NA	NA
≥3	1.04 (0.72-1.52)	NA	NA	NA	NA
VA impairment	3.61 (1.61-8.10)	3.32 (1.59-6.93)	3.05 (1.42-6.52)	NA	NA
Cataract	1.99 (1.21-3.28)	2.11 (1.34-3.33)	2.08 (1.30-3.34)	NA	NA
AMD	0.91 (0.50-1.67)	0.92 (0.51-1.66)	0.97 (0.53-1.75)	NA	NA

Abbreviations: AMD, age-related macular degeneration; CRP, C-reactive protein; NA, applicable; VA, visual acuity.

SI conversion factor: To convert CRP level to nanomoles per liter, multiply by 9.524.

[a] Sensitivity analysis excluded participants with VA impairment, cataract, or AMD.

risk posed by smoking on cataract development could be attributed indirectly to cadmium.[37] The same may be true of the association of smoking and cadmium level with incident CS impairment. The biological mechanism by which cadmium exposure diminishes CS cannot be discerned in this study, but potential mechanisms include increases in inflammation, reactive oxygen species, apoptosis, and metabolic disruption of key elements.[18,20,24-29]

In the BOSS study, cataract and VA impairment at baseline displayed strong associations with CS impairment incidence, justifying the need for a sensitivity analysis. Although baseline AMD did not demonstrate the same association, it was likely to be in early stages, given that this is a relatively young cohort. A recent study found that CS may not differ between patients with early-stage AMD and healthy controls.[55] In the follow-up period, these baseline cases would be expected to progress and could confound the association. Baseline cases of AMD were then excluded from this sensitivity analysis, allowing the measurement of cadmium-induced changes in eyes without these comorbidities. In this sensitivity analysis that excluded anyone with AMD, cataract, or impaired VA during follow-up, cadmium level and smoking remained significantly associated with CS impairment. This finding suggests the mechanism by which cadmium level and smoking affect CS could be independent of the mechanisms by which comorbid eye conditions affect CS. In addition, the associations between CS and measures of adiposity, intima-media thickness, plaque, and alcohol consumption demonstrate that the risk is potentially modifiable.

Lead levels were not associated with increased risk for CS impairment in the BOSS cohort. However, exposure was generally low in this population, as only 29 participants displayed a level of 5 µg/dL or higher, the cut point currently considered to indicate elevated blood lead level in adults, and only 6 participants had a reading of 10 µg/dL or higher.[56] No level of circulating lead is considered safe, but most of those in quintile 5 still had relatively low levels. If a higher lead toxicity level is required before changes begin to occur in the retina, then the BOSS population would not have had the exposure necessary to detect a difference in the rate of CS impairment.

Strengths and Limitations

The strengths of this study include the large sample size, standardized measurement of key variables, and longitudinal de-

sign. The sample size provides the power to detect potential differences in risk, the standardized measurements allow for confidence in found associations, and the longitudinal design means exposure proceeds disease. A limitation of this study is that the population is racially and ethnically homogenous. The direct generalizability of these findings to other racial/ethnic groups is limited. However, we believe the mechanism by which heavy metals affect vision, specifically CS, likely does not differ by race/ethnicity. As noted, cadmium exposure and cigarette smoking were closely linked and, as such, no definitive conclusions can be drawn on whether 1 or both are responsible for the observed increased risk for CS impairment. Further study into this association is needed. Finally, cadmium and lead levels in blood were measured, and heavy metals in blood are generally accepted to indicate recent acute exposure. However, overall body burden also contributes to higher circulating levels.[18,57]

Conclusions

Contrast sensitivity impairment incidence was high, with about 1 in 4 participants in the BOSS developing impairment in the 10 years of follow-up. Cadmium, but not lead, exposure was associated with an increased risk for incident CS impairment, although the observed association may be due to some other component of cigarette smoke exposure. Changes in modifiable factors, including cadmium exposure and smoking, and improvement of adiposity or vascular factors could potentially reduce the burden of CS impairment in the population.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Paulsen, Johnson, Pinto.
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