NeuroToxicology 32 (2011) 110–115

Contents lists available at ScienceDirect

NeuroToxicology

Blood lead levels in relation to cognitive function in older U.S. adults

Edwin van Wijngaarden [a,*], Paul C. Winters [b], Deborah A. Cory-Slechta [c]

[a] Department of Community and Preventive Medicine, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Box 644, Rochester, NY 14642, United States
[b] Department of Family Medicine, University of Rochester, 1381 South Avenue, Rochester, NY 14620, United States
[c] Department of Environmental Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642, United States

ARTICLE INFO

Article history:
Received 14 June 2010
Accepted 2 November 2010
Available online 17 November 2010

Keywords:
Aging
Blood lead levels
Cognition
Epidemiology
NHANES

ABSTRACT

Studies suggest that cumulative exposure to lead, as measured in the bone, is associated with accelerated cognitive decline at older age. It is presently unclear, however, whether current blood lead levels (BLLs) are adversely related to cognitive functioning in older adults. We evaluated BLLs in relation to cognition in the continuous National Health and Nutrition Examination Survey (NHANES). The current study was limited to adults age 60 and older. We examined two measures of cognitive functioning: self-reported functional limitation due to difficulty remembering or periods of confusion (NHANES 1999–2008; $n = 7277$) and performance on the Digit Symbol Substitution Test (DSST; NHANES 1999–2002; $n = 2299$). We evaluated quintiles of BLL (<1.30, 1.79–<2.30, 2.30–<3.20, and ≥3.20 μg/dL) in relation to cognitive functioning using logistic (functional limitation) and linear (DSST scores) regression in SUDAAN, adjusting for age, sex, race, poverty–income ratio, education, and self-reported general health status. BLLs were not associated with self-reported confusion or memory problems in crude and adjusted analyses, with adjusted odds ratios and 95% confidence intervals (CI) of 1.0 (ref.), 0.9 (CI = 0.7–1.3), 0.8 (CI = 0.6–1.2), 1.0 (CI = 0.7–1.3), 1.0 (CI = 0.7–1.4), respectively, in increasing quintiles. Similarly, there was no clear association between performance on the DSST and BLL after accounting for all covariates. Our findings add to the inconsistent evidence regarding the association between concurrent BLLs and cognitive function in older adults. Early-life or long-term, accumulated lead exposures may be etiologically more relevant to accelerated cognitive decline at older age.

1. Introduction

Lead is a heavy, low melting, bluish-gray metal that occurs naturally in various mineral forms in the earth's crust. Exposure to lead is predominantly due to anthropogenic activity. Although the highest levels of exposure have been experienced by workers in the smelting and battery manufacturing industries, the largest source of environmental lead exposure in the United States has been through inhalation and ingestion of air, dust, soil, water and food contaminated from the use of lead in pipes, paints, food and drink cans, and gasoline. These uses have been phased out in the United States, and geometric mean blood lead levels among adults in the United States have correspondingly declined from 13.1 μg/dL (0.63 μmol/L) in the late 1970s to 1.64 μg/dL (0.08 μmol/L) in 1999–2002 (Muntner et al., 2005). Despite this declining trend in environmental lead exposure, however, many communities continue to be exposed to excessive amounts of lead (Muntner et al., 2005), in particular in urban settings (Chadha et al., 1998; Gasana and Chamorro, 2002; Lanphear et al., 1998; Leighton et al., 2003; Maas et al., 2005; Meyer et al., 2003; Mielke and Reagan, 1998; Roberts et al., 2003).

Lead accumulates in bones and may be released long after the exposure has ceased due to age-related increases in the rate of bone breakdown, most prominent in diseases such as osteoporosis (Hu et al., 1996, 1998; Rabinowitz, 1991). Animal studies have shown that mobilization of lead from bone co-occurs with increased levels in the brain (Cory-Slechta, 1990). Therefore, past lead exposure continues to be a concern for lead exposure later in life even in the absence of concurrent external exposure sources (Weuve et al., 2009). Indeed, blood lead levels in adults have been shown to increase with increasing age, with average levels of 3.61 and 3.75 μg/dL individuals between 60 and 74 and over the age 75, respectively, as compared to 2.21 μg/dL in 18–39 year-olds in NHANES III (1988–1994). Average blood lead levels declined to 1.28, 2.17 and 2.32 μg/dL in 18–39, 60–74 and 75+ year-olds, respectively, in NHANES 1999–2002 (Muntner et al., 2005).

There is increasing evidence that lead exposure may contribute to age-related cognitive deficits, and this relationship has received considerable attention in the epidemiologic literature (Shih et al.,

* Corresponding author. Tel.: +1 585 275 1985; fax: +1 585 461 4532.
E-mail address: edwin_van_wijngaarden@urmc.rochester.edu (E. van Wijngaarden).

0161-813X/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuro.2010.11.002

2007). Studies suggest that cumulative exposure to lead, as measured in the bone, is associated with accelerated cognitive decline at older age (van Wijngaarden et al., 2009; Weisskopf et al., 2007, 2004; Weuve et al., 2009; Wright et al., 2003). However, the evidence for an effect of lead on cognitive function in adults appears to be more consistent for markers of cumulative dose than for blood lead levels (BLLs) (Shih et al., 2007).

In adults age 60 and older who participated in the continuous National Health and Nutrition Examination Survey (NHANES), we examined BLLs in relation to two measures of cognitive functioning: self-reported functional limitation due to difficulty remembering or periods of confusion (NHANES 1999–2008) and performance on the Digit Symbol Substitution Test (DSST; NHANES 1999–2002).

2. Methods

2.1. Subjects

NHANES is a complex, multi-stage survey of non-institutionalized civilians of the U.S. population that collects information about health, nutrition, demographic, and socioeconomic factors (Centers for Disease Control and Prevention (CDC), 2009). The survey is conducted by trained physicians, medical and health technicians, and dietary and health interviewers. Data are collected in the form of standardized home interviews and an examination component consisting of a medical, dental, and laboratory test evaluation conducted in Mobile Examination Centers. Approximately 5000 individuals from 15 counties across the country are surveyed each year. Persons over 60, African-Americans, and Hispanic individuals are over-sampled, and weights are computed correspondingly to arrive at a sample that is representative of the U.S. population. We included adults ages 60 and older from NHANES 1999–2008 (for self-reported confusion and memory problems, $n = 9331$) and NHANES 1999–2002 (for DSST, $n = 3706$) in our analysis. Our primary analyses were based on 7277 and 2299 individuals with complete information on self-reported cognitive functional limitation and DSST scores, respectively, and all covariates.

2.2. Cognitive assessment

Information on self-reported limitation in cognitive functioning was obtained by asking participants the following question: "{Are you/Is SP} limited in any way because of difficulty remembering or because {you/s/he} experience{s} periods of confusion?" Response categories included "yes", "no", "refused" and "don't know". There were no subjects who responded "don't know", and the nine subjects over the age of 60 who refused to answer this question were excluded from the analysis of self-reported confusion or memory problems. A subjective complaint of memory loss by a patient or family member is an initial step towards identifying individuals at risk of mild cognitive impairment or dementia (Chertkow et al., 2008; Feldman et al., 2008). Similar information has been previously used to classify someone as having a disability (Brophy et al., 2008) and to obtain nationally representative estimates of the prevalence of cognitive impairment (Bernstein and Remsburg, 2007).

In addition, the DSST was administered in NHANES 1999–2002 to participants age 60 and older (http://www.cdc.gov/nchs/data/nhanes/nhanes_01_02/cfq_b_doc.pdf). This is a subtest of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) (Wechsler, 1997). The DSST consists of a table showing pairs of digits and symbols, and rows of boxes with a digit in the top section and an empty space in the bottom section of each box. Participants copy symbols that are paired with numbers, resulting in a score indicating the number of correct symbols drawn within a period of 120 s, with a maximum score of 133. Sample items were provided for initial practice; participants who were unable to complete any of the sample items did not continue with the remainder of the test. A small percentage (1.9%) of participants was not able to complete the sample exercise due to cognitive limitations.

2.3. Measurement of blood lead levels (BLLs)

Non-fasting blood samples (minimum of 0.25 mL per vial) were collected from participants by venipuncture in pre-screened vials or vacuum tubes. After collection, samples were kept at a temperature of 4 °C until receipt by the processing laboratory, after which the samples were kept at −20 °C until time for processing. Whole blood lead concentrations were determined using atomic absorption spectroscopy at 283.3 nm while employing Zeeman background correction (NHANES 1999–2002), or using inductively coupled plasma mass spectrometry (NHANES 2003–2008). Lower detection limits were reported to be 0.6 μg/dL (NHANES 1999–2002), 0.025 μg/dL (NHANES 2003–2004), 0.25 or 0.30 μg/dL (NHANES 2005–2006), and 0.25 μg/dL (2007–2008). For values below the detection limit ($n = 7$ and $n = 4$ in 1999–2008 and 1999–2002 datasets, respectively), the NHANES public use data included the detection limit divided by square root of two as an estimate of the BLL.

2.4. Potential confounders

The following covariates were included *a priori* as they were suspected to be associated with both BLLs and cognition: age (continuous), sex (male as reference), education level (<high school, high school, >high school (reference)), ethnicity (Mexican American, Other Hispanic, Non-Hispanic White (reference), Non-Hispanic Black, Other Race – Including Multi-Racial), and poverty–income ratio (PIR; ratio of family income to poverty threshold <1.0, 1–<2.0, and ≥2.0 (reference)), and self-reported general health status (poor, fair, good, very good, excellent (reference)) as a global measure of possible co morbid conditions which has been shown to be correlated with mortality risk (Idler and Benyamini, 1997).

2.5. Statistical analyses

We used SAS 9.2 (SAS Institute, Cary, NC) and SAS-callable SUDAAN 10 (Research Triangle Institute, Research Triangle Park, NC), applying NHANES cluster design variables (SDMVSTRA, SDMVPSU) and medical examination weights (original WTMEC4YR for 1999–2002, or newly derived WTMEC for 1999–2008 based on medical examination weights provided for individual cycles) to all analyses. The new weights for the 1999–2008 analyses were calculated in accordance with NHANES documentation (http://www.cdc.gov/nchs/tutorials/Nhanes/SurveyDesign/Weighting/intro.htm); for 1999–2002, the 4-year medical examination weights were multiplied by 2/5 and the 2-year medical examination weights for 2003–2008 were multiplied by 3/5.

Initially we computed descriptive statistics for our study population, including proportions, means and percentiles. Subsequently, we evaluated quintiles of BLL (<1.30, 1.30–<1.79, 1.79–<2.30, 2.30–<3.20, and ≥3.20 μg/dL) in relation to cognitive functioning using logistic (self-reported confusion/memory problems) and linear (DSST scores) regression in SUDAAN, adjusting for age, sex, race, poverty–income ratio, education, and self-reported general health status. In addition, we assessed the $\log_{10}$ of BLL as a continuous variable in relation to cognitive functioning. We repeated these analyses removing self-reported general health status from the adjusted model because this may be an