Blood Lead Levels and Decreased Kidney Function in a Population-Based Cohort

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Background: Environmental lead exposure has been associated with decreased kidney function, but evidence from large prospective cohort studies examining low exposure levels is scarce. We assessed the association of low levels of lead exposure with kidney function and kidney disease.

Study Design: Prospective population-based cohort.

Setting & Participants: 4,341 individuals aged 46 to 67 years enrolled into the Malmö Diet and Cancer Study-Cardiovascular Cohort (1991-1994) and 2,567 individuals subsequently followed up (2007-2012).

Predictor: Blood lead concentrations in quartiles (Q1-Q4) at baseline.

Outcomes: Change in estimated glomerular filtration rate (eGFR) between the baseline and follow-up visit based on serum creatinine level alone or in combination with cystatin C level. Chronic kidney disease (CKD) incidence (185 cases) through 2013 detected using a national registry.

Measurements: Multivariable-adjusted linear regression models to assess associations between lead levels and eGFRs at baseline and follow-up and change in eGFRs over time. Cox regression was used to examine associations between lead levels and CKD incidence. Validation of 100 randomly selected CKD cases showed very good agreement between registry data and medical records and laboratory data.

Results: At baseline, 60% of study participants were women, mean age was 57 years, and median lead level was 25 (range, 1.5-258) μg/L. After a mean of 16 years of follow-up, eGFR decreased on average by 6 mL/min/1.73 m^2 (based on creatinine) and 24 mL/min/1.73 m^2 (based on a combined creatinine and cystatin C equation). eGFR change was higher in Q3 and Q4 of blood lead levels compared with Q1 (*P* for trend = 0.001). The HR for incident CKD in Q4 was 1.49 (95% CI, 1.07-2.08) compared with Q1 to Q3 combined.

Limitations: Lead level measured only at baseline, moderate number of CKD cases, potential unmeasured confounding.

Conclusions: Low-level lead exposure was associated with decreased kidney function and incident CKD. Our findings suggest lead nephrotoxicity even at low levels of exposure.

Complete author and article information provided before references.

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Environmental exposure to lead remains a public health problem. Although lead exposure has decreased in the last couple of decades,[1,2] there is evidence of health effects in children and adults even at low lead levels.[1] Exposure occurs through ingestion of contaminated food, drinking water, and dust, as well as smoking and inhalation of polluted air in areas with heavy traffic or industrial emissions.[2,3] The most important dietary contributors in the United States and Europe are cereals, leafy vegetables, potatoes, and tap water.[3] More than 90% of absorbed lead is stored in bones,[2,4,5] so bone lead level reflects long-term exposure and body burden. Lead in blood reflects more recent exposure, but also whole-body burden, and is the most commonly used biomarker of lead exposure.[2,6]

The kidney is one of the target organs for lead toxicity.[2] Lead has long been known to be nephrotoxic at high-level occupational exposure,[7] but nephrotoxicity at low-level lead exposure has been discussed more recently. A review by the US National Toxicology Program concluded that there is sufficient evidence of decreased kidney function in humans at lead levels < 50 μg/L.[1] However, this conclusion was mostly based on cross-sectional studies[8-18] and only 3 prospective studies evaluating kidney function in relation to environmental lead exposure.[19-21] Three later cross-sectional studies also provide evidence for an impact of low-level lead exposure on kidney function,[22-24] whereas another found no associations.[25] A later case-control study found associations between erythrocyte lead levels and increased risk for end-stage kidney disease, whereas 2 prospective studies of occupational lead exposure and chronic kidney disease (CKD) and end-stage kidney disease found no associations.[26-28]

All except 2 of these studies used serum creatinine (Scr) or Scr-based estimated glomerular filtration rate (eGFR) equations as markers of kidney function.[22,26] Recently developed equations based on a combination of Scr and serum cystatin C levels have been suggested to provide a better estimation of GFR,[29] but no prospective studies estimated kidney function in relation to lead exposure based on these new equations.

The present study aimed at elucidating whether environmental low-level lead exposure is associated with kidney function, estimated using eGFR equations based on Scr and the combination of Scr and cystatin C levels, and with incident CKD. Analyses were performed in a large prospective population-based cohort study with a mean

follow-up of 16 years for kidney function and 19 years for diagnosis of CKD.

Methods

Study Population

This study was based on the cardiovascular cohort of the Malmö Diet and Cancer Study (MDCS-CC),[30,31] which is a random sample of the larger prospective population-based study (MDCS).[32,33] The MDCS-CC includes 6,103 individuals (aged 46-67 years) living in Malmö, Sweden, between 1991 and 1994,[30] here referred to as "baseline" (Fig 1). Those who were still alive and had not emigrated (n = 4,924) were invited to a follow-up examination in 2007 to 2012,[31] and 3,734 attended.

The present study included all individuals with data available for smoking habits and lead levels at baseline (n = 4,341; Fig 1). All of these were analyzed for incident CKD. For analyses of kidney function, we excluded those without data for Scr and cystatin C levels (n = 361) at baseline. Of the remaining 3,980 individuals, 2,567 (65%) had complete data at follow-up and were used for the analyses of eGFR change from baseline to follow-up (Fig 1).

At baseline and follow-up, participants completed self-administered questionnaires concerning lifestyle, socioeconomic status, health, and medication and underwent medical examination.[30,31] In addition, venous blood samples were collected after an overnight fast and centrifuged to separate serum and erythrocytes.

The study followed the Declaration of Helsinki. All participants provided written informed consent, and the different parts of the study were approved by the Regional Ethics Board at Lund University, Sweden (no. 166-2007).

Analyses of Lead Levels in Blood at Baseline

Lead is present mostly in red blood cells, with <1% found in plasma,[2,3] so lead was measured in erythrocytes in baseline samples. Whole-blood lead concentrations were calculated by multiplying the metal concentrations in erythrocytes by hematocrit.

Analysis of lead in erythrocytes was performed using inductively coupled plasma mass spectrometry with an octopole reaction system in helium mode (Agilent 7700x ICP-MS; Agilent Technologies), as described previously.[34,35] The method is further described in Item S1. None of the samples had lead levels below the limit of detection, which was 0.16 μg/L. Analyses of external quality control samples with low lead levels were included in all analytical rounds and showed satisfactory results.[35]

Markers of Kidney Function at Baseline and Follow-up

The potential association of lead levels with kidney function was assessed based on the change in kidney function between baseline and follow-up. We estimated GFR using CKD-EPI (CKD Epidemiology Collaboration) equations: the Scr-based equation, cystatin C–based equation, and the combined Scr and cystatin C equation[29] and calculated eGFR change as the difference between eGFR at follow-up and at baseline.

In baseline samples from 1991 to 1994, Scr was analyzed using a modified Jaffé method (Beckman Synchron LX20–4; Beckman-Coulter). In follow-up samples from 2007 to 2012, Scr was analyzed using an enzymatic method (Cobas autoanalyzer; Roche Diagnostics) calibrated using isotope-dilution mass spectrometry–traceable Scr.[36] Method comparisons at the chemical laboratory where analyses were performed have shown that the Jaffé

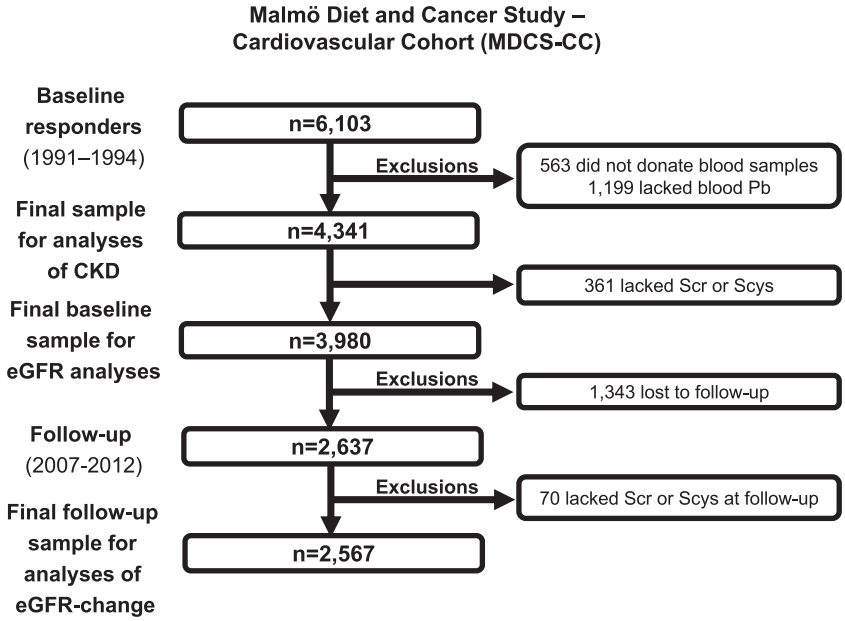

Figure 1. Overview of the Malmö Diet and Cancer Study (cardiovascular cohort) at baseline and follow-up. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Pb, lead; Scr, serum creatinine; Scys, serum cystatin C.

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