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SUPPLEMENTARY MATERIALS

Two-year responses of renal function to first occupational lead exposure

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Methods

Clinical measurements

At the study sites, trained nurses measured the workers' anthropometric characteristics and applied current guidelines to measure office blood pressure at the brachial artery. After the workers had rested for 5 minutes in the sitting position, the nurses obtained five consecutive blood pressure readings to the nearest 2 mm Hg by auscultation of the Korotkoff sounds, using standard mercury sphygmomanometers. For analysis, the five readings were averaged. Mean arterial pressure was diastolic blood pressure plus one third of pulse pressure (the difference between systolic and diastolic blood pressure). Blood pressure was categorised according to the 2017 ACC/AHA guideline.[1] If systolic and diastolic blood pressure were in different categories, the highest value was used to classify participants. Body mass index was body weight in kilograms divided by height in meters squared. The study nurses administered the validated[2] questionnaire at baseline and follow-up, to collect information about each worker's medical history, exposure to heavy metals, smoking and drinking habits, intake of medications and life style. Diabetes mellitus was a self-reported diagnosis, a fasting blood glucose of 126 mg/dl (7.0 mmol/l) or higher, or use of antidiabetic drugs.

Biochemical measurements

Venous blood samples were obtained after 8 to 12 hours of fasting. BL was determined on whole blood by inductively coupled plasma mass spectrometry at an analytical laboratory certified for BL analysis in compliance with the provisions of the OSHA Lead Standard, 29CFR 1910.1025 (Occupational Safety and Health Administration [www.osha.gov]). Prior to analysis, the specimens were digested with nitric acid and spiked with an iridium internal standard. The BL detection limit was 0.5 µg/dl. The accuracy of the BL tests was verified by

use of proficiency samples purchased from the College of American Pathologists (CAP) and the Pennsylvania Department of Blood Lead Programs.[3] Proficiency testing was performed in six separate trial runs, including in total 30 test samples annually. All survey materials were handled in the same manner as the study samples and processed with the normal workflow utilising the same repeat/dilution protocols and calibration and quality control frequency.[3] Compliance with Clinical Laboratory Improvement Amendments (CLIA), CAP and New York State accreditation and regulatory requirements was verified routinely with test level review of the laboratory services by external auditors. Calibrators with certified accuracy (National Institute of Standards and Technology [htpps://www.nist.gov]) were included in each batch of study samples and spanned the range of the analytical measurement range. Accuracy was evaluated on Westgard Rules[4] and defined within the total allowable error established with review of the CAP, Centers for Disease Control and Prevention, CLIA 88,[5] and OSHA guidelines. Accuracy, defined as the deviation from known BL standards ran along with the study samples, was within 10%. The bias determined according to the Bland and Altman approach[6] in 30 spilt blood samples with BL concentrations (average in duplicate samples) ranging from 0.70 to 27.9 μg/dl, was 0.08 μg/dl (95% confidence interval [CI], -0.01 to 0.18, $P = 0.07$).[7] The repeatability coefficient, defined as twice the standard deviation (SD) of the signed differences between duplicate measurements,[6] was 0.52. Expressed as a percentage of mean BL or as a percentage of near maximal BL variation (four times the SD of the logarithmically transformed distribution), the repeatability coefficient was 6.7% and 1.9%, respectively. Lower values indicate better repeatability.

Total and high-density (HDL) lipoprotein serum cholesterol, serum creatinine, serum cystatin C, γ-glutamyltransferase (an index of alcohol intake), blood urea nitrogen, and blood glucose were measured by automated enzymatic methods, serum insulin by ELISA, and

serum sodium by flame photometry. Serum creatinine was measured, using Jaffe's method with modifications in a single certified laboratory that applied isotope-dilution mass spectrometry for calibration.[8] eGFR was derived from serum creatinine, serum cystatin C and both, using the Chronic Kidney Disease Epidemiology Collaboration equations (Table S1).[9] CKD stages were categorised according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guideline.[10] Serum osmolality (mOsm/kg) was computed as 2 × (serum Na^+ [mmol/L]) + (blood glucose [mg/dl] / 18) + (blood urea nitrogen [mg/dl] / 2.8).[11] Fresh urine samples were analysed for specific gravity and the albumin-to-creatinine ratio (ACR) defined as the urinary albumin in milligrams divided by urine creatinine in grams. Over three evaluations, the laboratory obtained a proficiency score of 100% for the BL measurements and 100% for routine biochemistry.

Haematological measurements

Haemoglobin and the red blood cell (RBC) count were measured, using the fully automated UniCel DxH800 haematology analyser (Beckman Coulter, Brea, CA, USA). In the RBC chamber of the instrument, RBCs are counted and discriminated by electrical impedance as the cells are pulled through each of three sensing apertures (50 μm in diameter and 60 μm in length). Electrical pulses generated in the counting cycles are sent to the analyser for editing, coincidence correction, and digital conversion. Two of the three RBC counts obtained must match within specified limits for the counts to be accepted by the instrument. This multiple counting procedure prevents data errors resulting from aperture obstructions or statistical outliers and allows for excellent reproducibility. The haematocrit, mean corpuscular volume (MCV), mean cell haemoglobin (MCH), and mean cell haemoglobin concentration (MCHC) are calculated from measured and derived values. MCV is obtained by multiplying a volume of blood by the proportion of blood that is cellular (the haematocrit),

and dividing that product by the number of RBCs. MCH is average quantity of haemoglobin in a single RBC. MCHC is the average amount of haemoglobin per RBC, relative to the size of the cell. The RBC distribution width is derived directly from the histogram as the coefficient of variation of the RBC volume distribution.

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Table S1 | Chronic Kidney Disease Epidemiology Collaboration equations for estimating glomerular filtration rates derived from serum creatinine, serum cystatin C and both

Variable	Sex	Serum creatinine (mg/dl)	Serum cystatin C (mg/l)	Equation for estimating GFR
eGFRcrt	Female	≤ 0.7		$144 \times (Scr / 0.7)^{-0.329} \times 0.993^{Age}$ [× 1.159 if black]
		> 0.7		$144 \times (Scr / 0.7)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
	Male	≤ 0.9		$144 \times (Scr / 0.7)^{-0.411} \times 0.993^{Age}$ [× 1.159 if black]
		> 0.9		$144 \times (Scr / 0.7)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
eGFRcys	Female or male		≤ 0.8	$133 \times (Scys / 0.8)^{-0.499} \times 0.996^{Age}$ [× 0.932 if female]
			> 0.8	$133 \times (Scys / 0.8)^{-1.328} \times 0.996^{Age}$ [× 0.932 if female]
eGFRcc	Female	≤ 0.7	≤ 0.8	$130 \times (Scr / 0.7)^{-0.248} \times (Scys / 0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
			> 0.8	$130 \times (Scr / 0.7)^{-0.248} \times (Scys / 0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
		> 0.7	≤ 0.8	$130 \times (Scr / 0.7)^{-0.601} \times (Scys / 0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
			> 0.8	$130 \times (Scr / 0.7)^{-0.601} \times (Scys / 0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
	Male	≤ 0.9	≤ 0.8	$135 \times (Scr / 0.7)^{-0.207} \times (Scys / 0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
			> 0.8	$135 \times (Scr / 0.7)^{-0.207} \times (Scys / 0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
		> 0.9	≤ 0.8	$135 \times (Scr / 0.7)^{-0.601} \times (Scys / 0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
			> 0.8	$135 \times (Scr / 0.7)^{-0.601} \times (Scys / 0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]

eGFRcrt, eGFRcys, and eGFRcc refer to the glomerular filtration rate estimated from serum creatinine, serum cystatin C or both. To convert serum creatinine to µmol/l, multiply by 88.42; to convert cystatin C from mg/l to nmol/l, multiply by 74.9. This table is reproduced from *N Engl J Med.* 2012;367:20-29 (reference 9).

Table S2 | Baseline characteristics of workers followed up and not followed up

Characteristic	N (%)		Characteristic	Mean **(SD/IQR)**	
	Analysed	**Not analysed**		**Analysed**	**Not analysed**
Male	230 (91.6)	218 (85.5)	Age, years	29.7 (9.8)	27.8 (10.0)
White ethnicity	122 (48.6)	110 (43.1)	Body mass index, kg/m^2	28.9 (6.1)	29.0 (6.8)
Hispanic ethnicity	107 (42.6)	122 (47.8)	Systolic blood pressure, mm Hg	120.0 (10.2)	120.3 (10.5)
Black ethnicity	12 (4.8)	10 (4.0)	Diastolic blood pressure, mm Hg	79.7 (8.8)	81.1 (8.4)
Other ethnicity	10 (4.0)	13 (5.1)	Mean arterial pressure, mm Hg	93.1 (8.7)	94.2 (8.3)
Current smokers	67 (27.0)	75 (29.4)	Total cholesterol, mg/dl	171.8 (37.8)	170.6 (37.9)
Alcohol intake	110 (44.4)	100 (39.2)	HDL cholesterol, mg/dl	46.3 (12.0)	47.7 (12.3)
Hypertension stage ≥1	125 (49.8)	161 (63.1)*	Total-to-HDL cholesterol ratio	3.91 (1.3)	3.82 (1.3)
Hypertension stage ≥2	46 (18.3)	35 (13.7)	Blood glucose, mg/dl	94.3 (15.8)	92.7 (11.5)
Treated hypertension	17 (6.8)	8 (3.1)	γ-glutamyltransferase, U/l	22.6 (16.0, 33.0)	21.8 (15.0, 30.0)
Diabetes mellitus	12 (4.8)	2 (0.78)*	Blood lead, μg/dL	4.13 (2.40, 7.80)	4.04 (2.20, 8.40)

Values are number of participants (%), arithmetic mean (SD) or geometric mean (IQR). Blood pressure was the average of five readings. Hypertension was categorised according to the 2017 ACC/AHA guideline, irrespective of treatment status. Mean arterial pressure was diastolic blood pressure plus one third of pulse pressure. Diabetes mellitus was a self-reported diagnosis, a fasting blood glucose of ≥7 mmol/l, or use of antidiabetic drugs. To convert total or high-density lipoprotein (HDL) serum cholesterol to mmol/l, multiply by 0.0259; to convert blood glucose to mmol/l, multiply by 0.0559. An asterisk indicates a significant between-group difference.

Table S3 | Red blood cell biomarkers changes from baseline to last follow-up by quartiles of the distribution of the follow-up-to-baseline blood lead concentration ratio

Characteristic	<1.91	1.91-3.45	3.45-5.66	≥5.66	*P* value
Number in group	62	63	63	63	…
Haemoglobin, g/dl	-0.19 (-0.39, 0.00)	-0.06 (-0.26, 0.14)	-0.07 (-0.26, 0.11)	-0.23 (-0.41, -0.05)	0.77
Haematocrit, %	-0.01 (-0.02, -0.00)	-0.01 (-0.01, -0.00)	-0.01 (-0.01, -0.00)	-0.01 (-0.02, -0.00)	0.88
RBC count, $\times 10^{12}$ /l	-0.14 (-0.21, -0.07)	-0.15 (-0.20, -0.09)	-0.10 (-0.17, -0.03)	-0.15 (-0.21, -0.09)	0.97
RDW, %	15.8 (15.1, 16.4)	15.5 (14.6, 16.4)	15.6 (14.9, 16.3)	16.2 (15.8, 16.7)	0.33
MCV, fl	0.47 (-0.19, 1.14)	0.90 (0.19, 1.61)	0.41 (0.00, 0.82)	0.64 (-0.03, 1.31)	>0.99
MCH, pg	0.66 (0.13, 1.19)	0.85 (0.34, 1.35)	0.69 (0.31, 1.07)	0.37 (0.05, 0.70)	0.31
MCHC, g/dl	0.33 (0.12, 0.54)	0.45 (0.29, 0.62)	0.37 (0.15, 0.58)	0.23 (-0.04, 0.50)	0.43

RBC, RDW, MCV, MCH, MCHC indicate red blood cell, red cell distribution width, mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration, respectively. Within-group changes are arithmetic mean (SD) or geometric mean (IQR). P values denote the significance of the between-group differences.

Table S4 | Renal function at baseline by quartiles of the distribution of the follow-up-to-baseline blood lead ratio

Characteristic	<1.91	1.91-3.45	3.45-5.66	≥5.66	*P* value
Number in group	62	63	63	63	…
Serum creatinine, mg/dl	0.932 (0.173)	0.955 (0.157)	0.988 (0.186)	0.955 (0.152)	0.28
Serum cystatin C, mg/l	0.671 (0.114)	0.680 (0.103)	0.678 (0.104)	0.675 (0.107)	0.86
eGFRcrt, ml/min/1.73 m^2	106.2 (18.1)	106.4 (17.5)	102.9 (16.2)	106.1 (16.2)	0.69
eGFRcys, ml/min/1.73 m^2	124.6 (15.1)	125.1 (12.5)	125.5 (12.3)	125.2 (13.4)	0.77
eGFRcc, ml/min/1.73 m^2	115.5 (16.7)	115.0 (13.9)	113.2 (12.6)	115.2 (14.2)	0.75
Serum osmolality, mOsm/kg	287.1 (3.4)	286.3 (4.0)	287.0 (4.1)	286.7 (3.6)	0.77
Serum sodium, mmol/l	138.4 (1.7)	138.1 (1.8)	138.4 (1.9)	138.2 (1.7)	0.83
Blood glucose, mg/dl	95.1 (14.4)	92.3 (10.5)	94.9 (22.5)	94.7 (13.5)	0.85
Serum insulin, U/l	6.94 (4.00, 12.9)	7.87 (3.60, 14.6)	6.84 (3.60, 11.0)	7.25 (3.50, 13.2)	0.99
Blood urea nitrogen, mg/dl	14.1 (3.9)	14.0 (3.8)	14.0 (3.3)	13.9 (3.1)	0.70
BUN-to-SCRT ratio	15.5 (4.6)	14.8 (3.9)	14.3 (3.5)	15.0 (4.5)	0.38
Urine specific gravity,	1.017 (0.0080)	1.020 (0.0075)	1.021 (0.0079)	1.019 (0.0073)	0.15
ACR, mg/g	4.54 (2.92, 6.70)	4.42 (3.12, 6.18)	4.37 (2.65, 6.55)	4.63 (2.93, 5.93)	0.90

eGFRcrt, eGFRcys, and eGFRcc refer to the glomerular filtration rate estimated from serum creatinine, serum cystatin C or both. BUN-to-SCRT ratio is the ratio of blood urea nitrogen (mg/dl) to serum creatinine (mg/dl). Values are arithmetic mean (SD) or geometric mean (IQR). *P* values are for trend across increasing categories of the follow-up-to-baseline blood lead concentration ratio. To convert serum creatinine to µmol/l, multiply by 88.42; to convert cystatin C from mg/l to nmol/l, multiply by 74.9; to convert blood glucose to mmol/l, multiply by 0.0559; to convert blood urea nitrogen to mmol/l, multiply by 0.3571.

Table S5 | Renal function at last follow-up by quartiles of the distribution of the follow-up-to-baseline blood lead ratio

Characteristic	<1.91	1.91-3.45	3.45-5.66	≥5.66	*P* value
Number in group	62	63	63	63	…
Serum creatinine, mg/dl	0.994 (0.210)	1.038 (0.157)	1.022 (0.178)	1.019 (0.156)	0.56
Serum cystatin C, mg/l	0.693 (0.164)	0.704 (0.148)	0.722 (0.165)	0.720 (0.143)	0.26
eGFRcrt, ml/min/1.73 m^2	98.9 (19.1)	97.0 (15.9)	98.0 (16.3)	98.4 (16.0)	0.97
eGFRcys, ml/min/1.73 m^2	121.5 (20.2)	121.4 (18.1)	120.3 (20.2)	119.2 (18.8)	0.46
eGFRcc, ml/min/1.73 m^2	109.6 (17.9)	108.1 (14.9)	107.7 (14.8)	107.7 (16.1)	0.49
Serum osmolality, mOsm/kg	289.5 (5.9)	288.8 (4.5)	289.0 (3.9)	289.1 (3.4)	0.76
Serum sodium, mmol/l	139.5 (2.8)	139.0 (2.0)	139.3 (1.9)	139.4 (1.7)	0.98
Blood glucose, mg/dl	90.3 (19.4)	87.3 (16.3)	86.5 (16.9)	89.3 (21.2)	0.71
Insulin U/l	9.50 (5.20, 20.7)	8.57 (3.90, 19.2)	8.16 (4.30, 14.7)	9.28 (4.00, 17.2)	0.84
Blood urea nitrogen, mg/dl	15.2 (3.3)	16.4 (4.7)	15.4 (3.0)	15.1 (3.7)	0.52
BUN-to-SCRT ratio	15.8 (4.0)	15.7 (3.8)	15.3 (3.0)	15.1 (3.8)	0.21
Urinary specific gravity,	1.022 (0.0068)	1.023 (0.0077)	1.021 (0.0070)	1.022 (0.0067)	0.89
ACR, mg/g	4.45 (2.82, 7.77)	4.51 (2.63, 6.25)	4.83 (2.89, 7.19)	4.65 (2.86, 6.17)	0.68

eGFRcrt, eGFRcys, and eGFRcc refer to the glomerular filtration rate estimated from serum creatinine, serum cystatin C or both. BUN-to-SCRT ratio is the ratio of blood urea nitrogen (mg/dl) to serum creatinine (mg/dl). Values are arithmetic mean (SD) or geometric mean (IQR). *P* values are for trend across increasing categories of the follow-up-to-baseline blood lead concentration ratio. To convert serum creatinine to µmol/l, multiply by 88.42; to convert cystatin C from mg/l to nmol/l, multiply by 74.9; to convert blood glucose to mmol/l, multiply by 0.0559; to convert blood urea nitrogen to mmol/l, multiply by 0.3571.

Table S6 | Association between changes in red blood cell biomarkers and in blood lead

Variable	Unadjusted		Adjusted		Fully adjusted	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Haemoglobin, g/dl	0.00 (-0.03, 0.03)	0.87	0.01 (-0.02, 0.04)	0.63	0.01 (-0.02, 0.04)	0.65
Haematocrit, %	0.01 (-0.08, 0.10)	0.90	0.03 (-0.06, 0.12)	0.56	0.03 (-0.07, 0.12)	0.57
RBC count, $\times 10^{12}$ /l	-0.00 (-0.01, 0.00)	0.70	-0.00 (-0.01, 0.01)	0.95	-0.00 (-0.01, 0.01)	0.84
RDW, %	-0.63 (-5.13, 3.86)	0.78	0.04 (-0.23, 0.31)	0.77	0.09 (-0.19, 0.37)	0.52
MCV, fl	0.00 (-0.13, 0.14)	0.97	0.03 (-0.10, 0.17)	0.64	0.02 (-0.12, 0.16)	0.78
MCH, pg	0.00 (-0.01, 0.02)	0.99	0.00 (-0.01, 0.02)	0.83	0.00 (-0.01, 0.02)	0.78
MCHC, g/dl	0.01 (-0.00, 0.02)	0.28	0.01 (-0.01, 0.02)	0.34	0.00 (-0.01, 0.02)	0.36

RBC, RDW, MCV, MCH, MCHC indicate red blood cell, red cell distribution width, mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration, respectively. Association sizes (β), given with 95% confidence interval, express the change in the dependent variable for a 3-fold increase in the blood lead concentration. Adjusted models accounted for sex, age, follow-up duration, the time of day of blood sampling (nighttime *vs* daytime), and the baseline red blood cell biomarker being analysed. Fully adjusted models additionally accounted for baseline body mass index, change in body weight, and the baseline values of and changes during follow-up in smoking status, mean arterial pressure, antihypertensive medication (yes *vs* no), the total-to-HDL cholesterol ratio and γ-glutamyltransferase.

Table S7 | Association between changes in renal function and in blood lead in 223 workers not on antihypertensive drug treatment

Variable	Unadjusted		Adjusted		Fully adjusted	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Serum creatinine, $\times 10^{-2}$ mg/dl	-0.07 (-1.82, 1.69)	0.94	0.44 (-1.12, 2.00)	0.58	0.55 (-1.05, 2.16)	0.50
Serum cystatin C, $\times 10^{-2}$ mg/l	0.63 (-0.97, 2.22)	0.44	1.11 (-0.41, 2.64)	0.15	1.17 (-0.41, 2.76)	0.15
eGFRcrt, ml/min/1.73 m^2	-0.11 (-1.88, 1.66)	0.90	-0.64 (-2.20, 0.92)	0.42	-0.82 (-2.43, 0.80)	0.32
eGFRcys, ml/min/1.73 m^2	-0.82 (-2.71, 1.06)	0.39	-1.43 (-3.24, 0.38)	0.12	-1.51 (-3.39, 0.36)	0.11
eGFRcc, ml/min/1.73 m^2	-0.50 (-2.06, 1.06)	0.53	-1.14 (-2.53, 0.25)	0.11	-1.31 (-2.75, 0.13)	0.074
Serum osmolality, mOsm/kg	-0.10 (-0.79, 0.58)	0.77	-0.21 (-0.71, 0.30)	0.42	-0.21 (-0.73, 0.32)	0.43
Serum sodium, mmol/l	0.06 (-0.28, 0.40)	0.73	0.02 (-0.24, 0.29)	0.86	0.03 (-0.24, 0.29)	0.85
Blood glucose, mg/dl	-1.87 (-4.36, 0.63)	0.14	-1.18 (-3.11, 0.75)	0.23	-1.64 (-3.61, 0.32)	0.10
Insulin, %	-4.05 (-15.7, 9.27)	0.53	-5.72 (-16.3, 6.17)	0.33	-8.18 (-17.7, 2.49)	0.13
Blood urea nitrogen, mg/dl	-0.30 (-0.84, 0.24)	0.28	-0.32 (-0.78, 0.14)	0.17	-0.24 (-0.70, 0.22)	0.30
BUN-to-SCRT ratio	-0.20 (-0.73, 0.32)	0.45	-0.44 (-0.90, 0.02)	0.063	-0.39 (-0.86, 0.08)	0.10
Urinary specific gravity, $\times 10^{-2}$	-0.03 (-0.15, 0.09)	0.62	-0.05 (-0.14, 0.04)	0.25	-0.04 (-0.13, 0.05)	0.36
ACR, %	1.14 (-8.87, 12.3)	0.83	-2.06 (-9.88, 6.43)	0.62	-2.32 (-10.2, 6.27)	0.58

eGFRcrt, eGFRcys, and eGFRcc refer to the glomerular filtration rate estimated from serum creatinine, serum cystatin C or both (reference [9]). BUN-to-SCRT ratio is the ratio of blood urea nitrogen (mg/dl) to serum creatinine (mg/dl). Changes in serum insulin and the urinary albumin-to-creatinine ratio are expressed as percentage differences from baseline to follow-up. Association sizes (β), given with 95% confidence interval, express the change in the dependent variable for a 3-fold increase in the blood lead concentration. Adjusted models accounted for sex, age, the change of age from baseline to follow-up (equivalent to between-visit interval), the time of day of blood sampling (nighttime *vs* daytime), and the baseline renal function measure being analysed. Fully adjusted models additionally accounted for baseline body mass index, change in body weight, and the baseline values of and changes during follow-up in smoking status, mean arterial pressure, antihypertensive medication (yes *vs* no), the total-to-HDL cholesterol ratio and γ-glutamyltransferase.

Table S8 | Associations between renal function and blood lead at baseline and at last follow-up

Variable	Baseline		Last follow-up		*Pslope*
	β (95% CI)	*P* value	β (95% CI)	*P* value	
Serum creatinine, $\times 10^{-2}$ mg/dl	-1.15 (-3.80, 1.49)	0.39	0.38 (-2.81, 3.58)	0.81	0.47
Serum cystatin C, $\times 10^{-2}$ mg/l	0.26 (-1.43, 1.95)	0.76	2.96 (-0.06, 5.97)	0.056	0.13
eGFRcrt, ml/min/1.73 m^2	1.31 (-1.23, 3.85)	0.31	-0.80 (-3.78, 2.18)	0.60	0.29
eGFRcys, ml/min/1.73 m^2	-0.19 (-2.03, 1.65)	0.84	-3.36 (-6.65, -0.07)	0.047	0.099
eGFRcc, ml/min/1.73 m^2	0.63 (-1.43, 2.69)	0.55	-2.33 (-4.94, 0.29)	0.083	0.082
Serum osmolality, mOsm/kg	-0.42 (-1.06, 0.23)	0.21	0.23 (-0.69, 1.14)	0.62	0.26
Serum sodium, mmol/l	-0.23 (-0.53, 0.07)	0.14	0.21 (-0.22, 0.64)	0.35	0.10
Blood glucose, mg/dl	-0.44 (-3.10, 2.21)	0.74	-2.78 (-6.36, 0.79)	0.13	0.30
Insulin, %	3.25 (-2.64, 9.51)	0.29	-5.62 (-12.8, 2.17)	0.15	0.074
Blood urea nitrogen, mg/dl	0.19 (-0.40, 0.78)	0.53	-0.09 (-0.82, 0.64)	0.80	0.56
BUN-to-SCRT ratio	0.00 (-0.00, 0.01)	0.21	-0.00 (-0.01, 0.00)	0.50	0.18
Urine specific gravity$\times 10^{-2}$	-0.04 (-0.17, 0.09)	0.57	-0.01 (-0.14, 0.13)	0.89	0.77
ACR, %	-2.49 (-7.67, 2.97)	0.37	0.08 (-6.86, 7.55)	0.98	0.57

eGFRcrt, eGFRcys, and eGFRcc refer to the glomerular filtration rate estimated from serum creatinine, serum cystatin C or both (reference [9]). BUN-to-SCRT ratio is the ratio of blood urea nitrogen (mg/dl) to serum creatinine (mg/dl). Changes in serum insulin and the urinary albumin-to-creatinine ratio are expressed as percentage differences from baseline to follow-up. Association sizes (β), given with 95% confidence interval, express the change in the dependent variable for a 3-fold increase in the blood lead concentration. All models were adjusted for sex, age, the time of day of blood sampling (nighttime *vs* daytime), body mass index, smoking status, mean arterial pressure, antihypertensive medication (yes *vs* no), the total-to-HDL cholesterol ratio and γ-glutamyltransferase. *Pslope* derived by a z-statistic expresses the significance of the difference in the βs between baseline and last follow-up.

Table S9 | Association between changes in renal function and in blood lead stratified by the median baseline age

Variable	Baseline age <26.6 years (N = 127)		Baseline age ≥26.6 years (N = 124)		*Pint*
	β (95% CI)	*P* value	β (95% CI)	*P* value	
Serum creatinine, $\times 10^{-2}$ mg/dL	0.22 (-2.21, 2.66)	0.86	1.26 (-0.82, 3.34)	0.23	0.45
Serum cystatin C, $\times 10^{-2}$ mg/L	1.20 (-0.90, 3.29)	0.26	1.41 (-0.98, 3.79)	0.24	0.80
eGFRcrt, ml/min/1.73 m^2	-0.32 (-2.75, 2.10)	0.79	-1.15 (-3.14, 0.84)	0.25	0.49
eGFRcys, ml/min/1.73 m^2	-1.51 (-3.97, 0.95)	0.23	-1.90 (-4.66, 0.85)	0.17	0.76
eGFRcc, ml/min/1.73 m^2	-1.24 (-3.33, 0.84)	0.24	-1.43 (-3.33, 0.46)	0.14	0.58
Serum osmolality, mOsm/kg	0.36 (-0.35, 1.06)	0.32	-0.49 (-1.40, 0.42)	0.29	0.057
Serum sodium, mmol/l	0.39 (0.05 , 0.73)	0.026	-0.32 (-0.77, 0.14)	0.17	0.002
Blood glucose, mg/dl	-1.91 (-4.56, 0.74)	0.16	1.75 (-1.31, 4.80)	0.26	0.043
Serum insulin, %	-5.37 (-19.1, 10.6)	0.49	-6.30 (-20.8, 10.9)	0.45	0.66
Blood urea nitrogen, mg/dl	-0.45 (-1.03, 0.13)	0.12	0.04 (-0.64, 0.72)	0.90	0.36
BUN-to-SCRT ratio	-0.44 (-1.05, 0.16)	0.15	-0.34 (-1.03, 0.35)	0.33	0.85
Urine specific gravity, $\times 10^{-2}$	-0.11 (-0.23, -0.00)	0.045	0.11 (-0.03, 0.25)	0.12	0.019
ACR, %	1.33 (-8.88, 12.7)	0.81	-0.34 (-14.2, 15.7)	0.96	0.64

eGFRcrt, eGFRcys, and eGFRcc refer to the glomerular filtration rate estimated from serum creatinine, serum cystatin C or both (reference 9). BUN-to-SCRT ratio is the ratio of blood urea nitrogen (mg/dl) to serum creatinine (mg/dl). Changes in serum insulin and the urinary albumin-to-creatinine ratio are expressed as percentage differences from baseline to follow-up. Association sizes (β), given with 95% confidence interval, express the change in the dependent variable for a 3-fold increase in the blood lead concentration. All models were adjusted for sex, age, follow-up duration, the time of day of blood sampling (nighttime *vs* daytime), the baseline renal function measure being analysed, and baseline body mass index, change in body weight, and the baseline values of and changes during follow-up in smoking status, mean arterial pressure, antihypertensive medication (yes *vs* no), total-to-HDL cholesterol ratio and γ-glutamyltransferase. *Pint* expresses the significance of the between-group interaction.

Table S10 | Association between changes in renal function and in blood lead stratified by the median baseline blood lead

Variable	Baseline blood lead <4.32 µg/dl (N = 126)		Baseline blood lead ≥4.32 µg/dl (N = 125)		*Pint*
	β (95% CI)	*P* value	β (95% CI)	*P* value	
Serum creatinine, $\times 10^{-2}$ mg/dl	2.70 (0.38 , 5.01)	0.023	1.47 (-1.79, 4.73)	0.37	0.64
Serum cystatin C, $\times 10^{-2}$ mg/l	1.25 (-1.49, 3.98)	0.37	1.20 (-1.74, 4.14)	0.42	0.79
eGFRcrt, ml/min/1.73 m^2	-2.78 (-5.15, -0.41)	0.022	-1.49 (-4.51, 1.53)	0.33	0.75
eGFRcys, ml/min/1.73 m^2	-1.52 (-4.69, 1.65)	0.34	-1.24 (-4.60, 2.12)	0.47	0.73
eGFRcc, ml/min/1.73 m^2	-2.33 (-4.33, -0.32)	0.024	-2.05 (-4.95, 0.85)	0.16	0.93
Serum osmolality, mOsm/kg	-0.00 (-0.73, 0.72)	>0.99	0.40 (-0.69, 1.49)	0.47	0.91
Serum sodium, mmol/l	-0.02 (-0.41, 0.37)	0.91	0.23 (-0.26, 0.71)	0.36	0.91
Blood glucose, mg/dl	0.56 (-2.60, 3.72)	0.72	-3.74 (-7.71, 0.23)	0.065	0.96
Insulin, %	-3.83 (-18.5, 13.5)	0.64	-7.36 (-25.5, 15.2)	0.49	0.47
Blood urea nitrogen, mg/dl	0.16 (-0.48, 0.81)	0.62	0.39 (-0.46, 1.24)	0.36	0.49
BUN-to-SCRT ratio	-0.30 (-0.94, 0.35)	0.36	0.01 (-0.90, 0.93)	0.98	0.46
Urine specific gravity, $\times 10^{-2}$	0.02 (-0.11, 0.15)	0.77	0.02 (-0.15, 0.19)	0.79	0.94
ACR, %	-3.85 (-15.5, 9.41)	0.55	9.49 (-8.20, 30.6)	0.31	0.45

eGFRcrt, eGFRcys, and eGFRcc refer to the glomerular filtration rate estimated from serum creatinine, serum cystatin C or both (reference 9). BUN-to-SCRT ratio is the ratio of blood urea nitrogen (mg/dl) to serum creatinine (mg/dl). Changes in serum insulin and the urinary albumin-to-creatinine ratio are expressed as percentage differences from baseline to follow-up. Association sizes (β), given with 95% confidence interval, express the change in the dependent variable for a 3-fold increase in the blood lead concentration. All models were adjusted for sex, age, follow-up duration, the time of day of blood sampling (nighttime *vs* daytime), the baseline renal function measure being analysed, and baseline body mass index, change in body weight, and the baseline values of and changes during follow-up in smoking status, mean arterial pressure, antihypertensive medication (yes *vs* no), total-to-HDL cholesterol ratio and γ-glutamyltransferase. *Pint* expresses the significance of the between-group interaction.

Table S11 | Association between changes in renal function and in blood lead stratified by the median cumulative blood lead index

Variable	CBLI < 34.6 µg/dl × year (N = 123)		CBLI < 34.6 µg/dl × year (N = 128)		*Pint*
	β (95% CI)	*P* value	β (95% CI)	*P* value	
Serum creatinine, $\times 10^{-2}$ mg/dl	0.83 (-1.59, 3.24)	0.50	1.89 (-0.42, 4.21)	0.11	0.24
Serum cystatin C, $\times 10^{-2}$ mg/l	0.59 (-1.61, 2.79)	0.59	2.83 (0.53, 5.12)	0.016	0.063
eGFRcrt, ml/min/1.73 m^2	-0.72 (-3.23, 1.79)	0.57	-1.62 (-3.85, 0.61)	0.15	0.39
eGFRcys, ml/min/1.73 m^2	-0.93 (-3.51, 1.65)	0.48	-3.46 (-6.10, -0.82)	0.011	0.054
eGFRcc, ml/min/1.73 m^2	-0.93 (-3.03, 1.17)	0.38	-2.66 (-4.62, -0.69)	0.008	0.068
Serum osmolality, mOsm/kg	0.10 (-0.57, 0.77)	0.77	-0.04 (-0.90, 0.83)	0.94	0.34
Serum sodium, mmol/l	0.21 (-0.16, 0.58)	0.27	-0.04 (-0.44, 0.37)	0.86	0.12
Blood glucose, mg/dl	-1.06 (-4.28, 2.16)	0.52	0.14 (-3.32, 3.59)	0.94	0.41
Insulin, %	-11.6 (-24.3, 3.34)	0.12	4.45 (-11.8, 23.7)	0.61	0.16
Blood urea nitrogen, mg/dl	-0.22 (-0.85, 0.40)	0.48	0.13 (-0.58, 0.83)	0.72	0.42
BUN-to-SCRT ratio	-0.26 (-0.88, 0.36)	0.41	-0.36 (-1.08, 0.35)	0.31	0.95
Urine specific gravity, $\times 10^{-2}$	-0.07 (-0.19, 0.04)	0.21	0.02 (-0.11, 0.15)	0.79	0.58
ACR, %	2.99 (-8.37, 15.7)	0.62	1.95 (-12.4, 18.7)	0.80	0.59

CBLI is the cumulative blood lead index. eGFRcrt, eGFRcys, and eGFRcc refer to the glomerular filtration rate estimated from serum creatinine, serum cystatin C or both (reference 9). BUN-to-SCRT ratio is the ratio of blood urea nitrogen (mg/dl) to serum creatinine (mg/dl). Changes in serum insulin and the urinary albumin-to-creatinine ratio are expressed as percentage differences from baseline to follow-up. Association sizes (β), given with 95% confidence interval, express the change in the dependent variable for a 3-fold increase in the blood lead concentration. All models were adjusted for sex, age, follow-up duration, the time of day of blood sampling (nighttime *vs* daytime), the baseline renal function measure being analysed, and baseline body mass index, change in body weight, and the baseline values of and changes during follow-up in smoking status, mean arterial pressure, antihypertensive medication (yes *vs* no), the total-to-HDL cholesterol ratio and γ-glutamyltransferase. *Pint* expresses the significance of the between-group interaction.

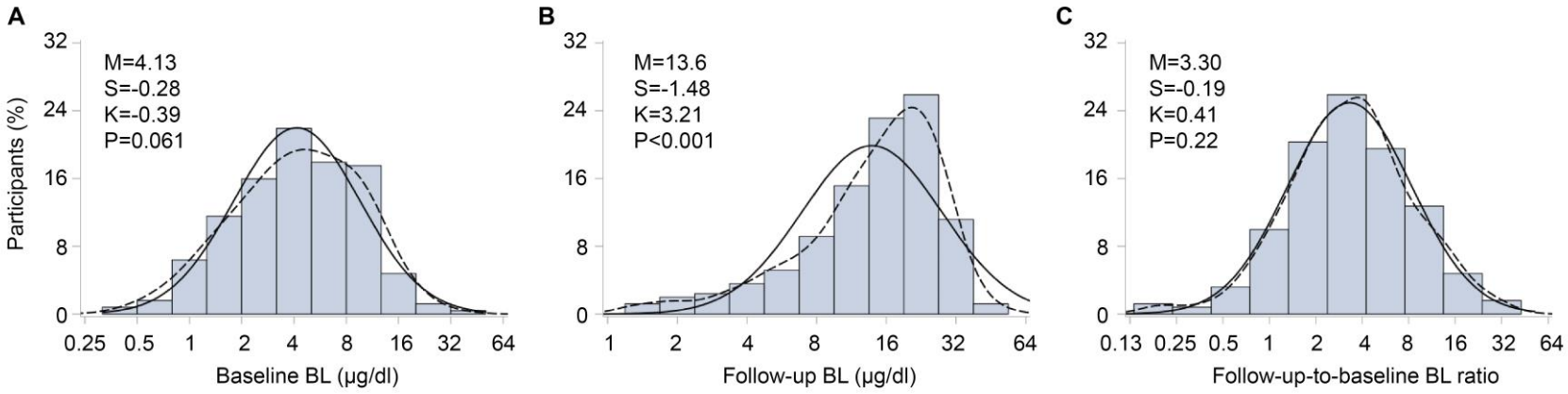

Figure S1

Distributions of blood lead at baseline (A) and last follow-up (B) and of the last-follow-up-to-baseline blood lead ratio (C). The solid and dotted lines represent the normal and kernel density distributions. *P* values are for departure of the actually observed distribution from normality according to the Shapiro-Wilk statistic. M indicates the geometric mean. Skewness (S) and kurtosis (K) were computed as the third and fourth moments about the mean divided by the cube of the standard deviation.

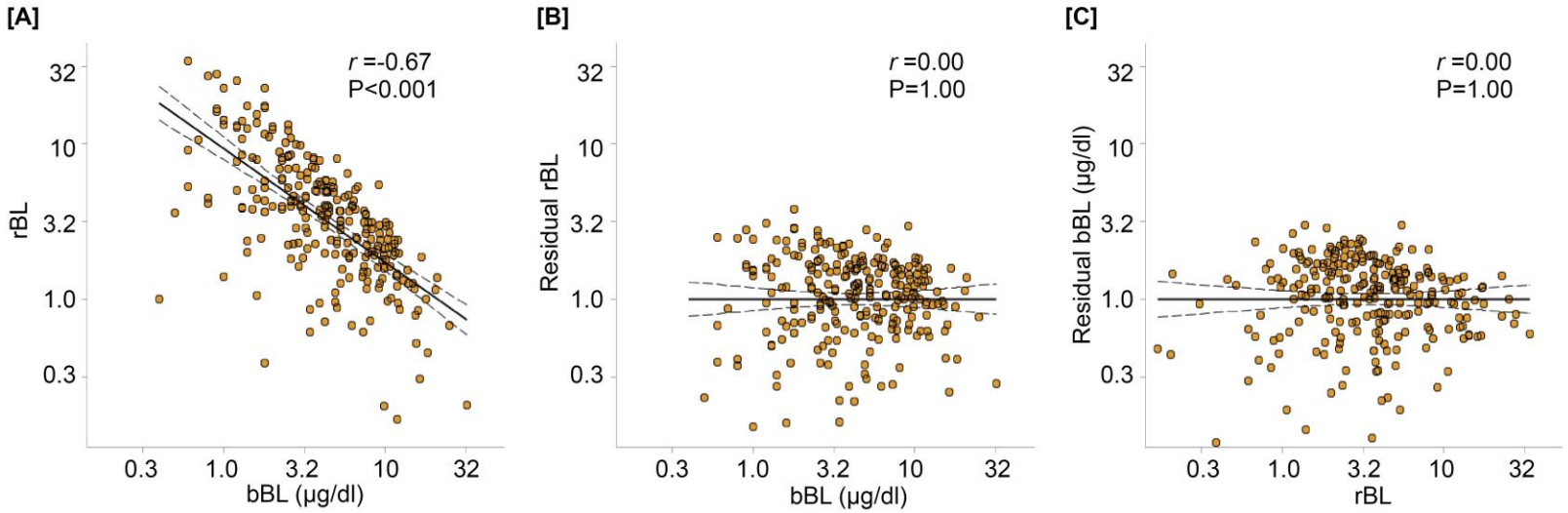

Figure S2

Linear associations between baseline blood lead (bBL) and the last-follow-up-to-baseline BL ratio (rBL; panel A), between bBL and the residual of rBL regressed on bBL (panel B), and rBL and between the residual of bBL regressed on rBL (panel C). The regression lines are given with 95% confidence interval for the prediction of the mean of the dependent variable at any level of the explanatory variable. The residuals remove any variance in the dependent variable explained by the explanatory variable, as evidenced by the null correlation coefficients (*r*) and the absence of any significance (*P*) in panels B and C.

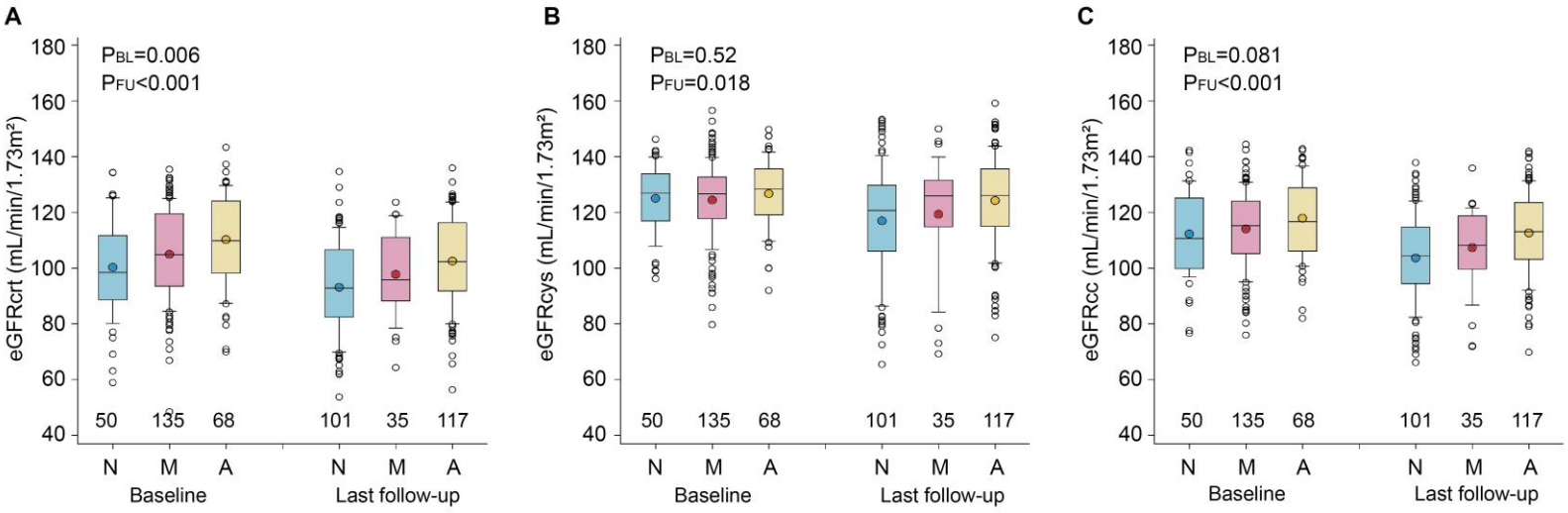

Figure S3

Boxplots showing the distributions of the glomerular filtration rate derived from serum creatinine (eGFRcrt; panel A), serum cystatin C (eGFRcys; panel B), or both serum creatinine and cystatin C (eGFRcc; panel C) by study phase (baseline and last follow-up) and by work shift (night [N], morning [M], and afternoon [A]). The central line, the upper and lower lines, and the upper and lower caps represent the median, interquartile range, and the 10th to 90th percentile interval. The arithmetic means and extreme measurements are represented by circles inside the box and outside the whiskers, respectively. The number of data points contributing to each whisker plot is given along the horizontal axis. *P* values denote the significance of the overall difference between the estimates of the glomerular filtration rate by time of day for baseline (P_{BL}) and follow-up (P_{FU}).

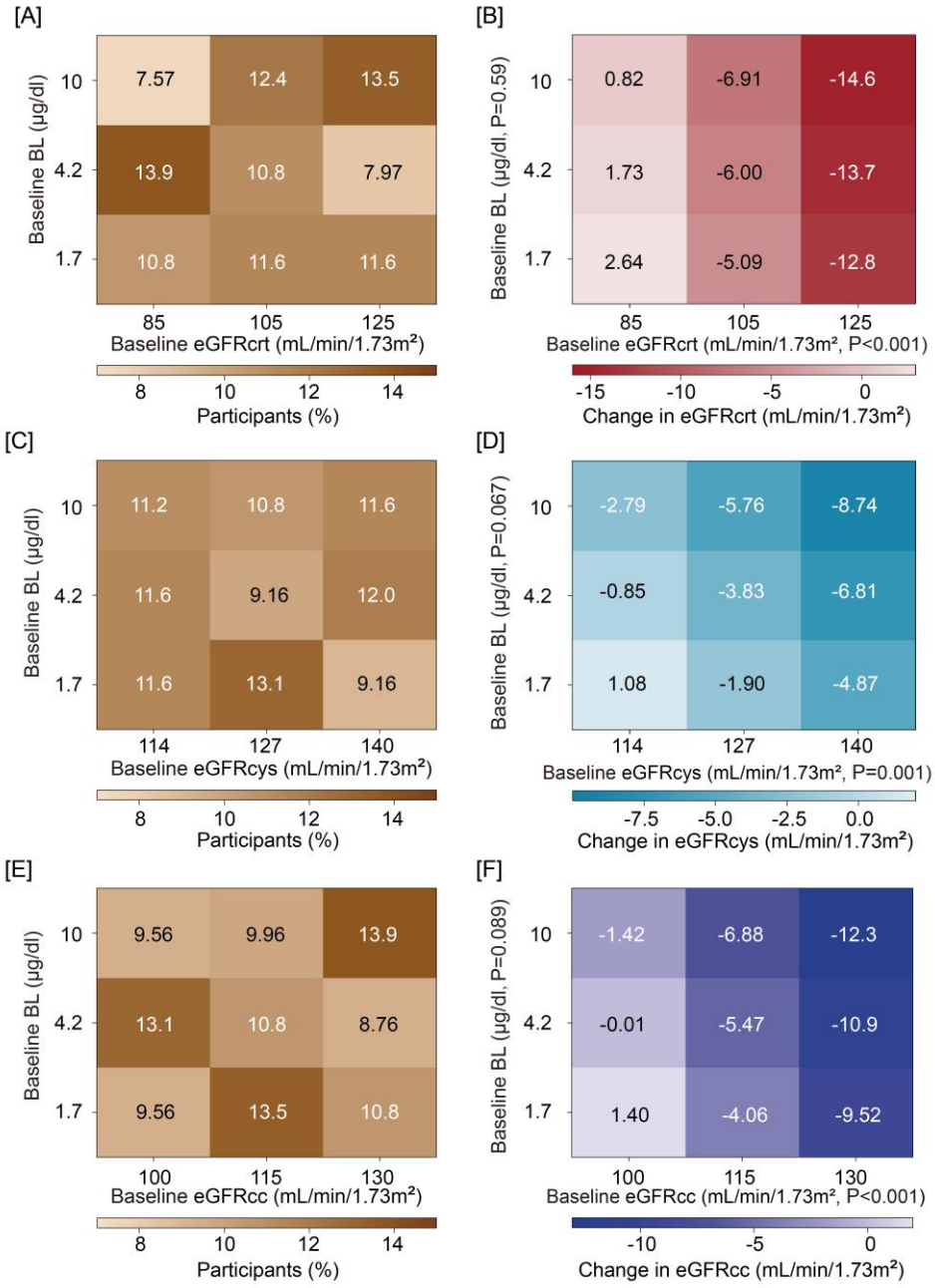

Figure S4

Heat maps relating the changes in glomerular filtration to their baseline values and the baseline blood lead (BL) concentration. Participants were cross-classified by thirds of the distributions of the baseline BL and the baseline glomerular filtration rate derived from serum creatinine (eGFRcrt; panels A and B), serum cystatin C (eGFRcys; panels C and D) or both (eGFRcc; panels E and F). The percentage of participants contributing to each cell of heat maps is given in panels A, C, and E. Associations sizes are point estimates corresponding with the thick marks and were derived from fully adjusted mixed models, which accounted for sex, age, follow-up duration, the time of day of blood sampling (daytime *vs* nighttime), body mass index, change in body weight, the follow-up-to-baseline BL ratio, and the baseline values of and changes during follow-up in smoking status, mean arterial pressure, antihypertensive medication (yes *vs* no), total-to-HDL cholesterol ratio, and γ-glutamyltransferase. The *P*-values of the interaction terms between baseline BL and the baseline eGFR were 0.50, 0.11 and 0.70 for eGFRcrt (B), eGFRcys (E) and eGFRcc (F), respectively.

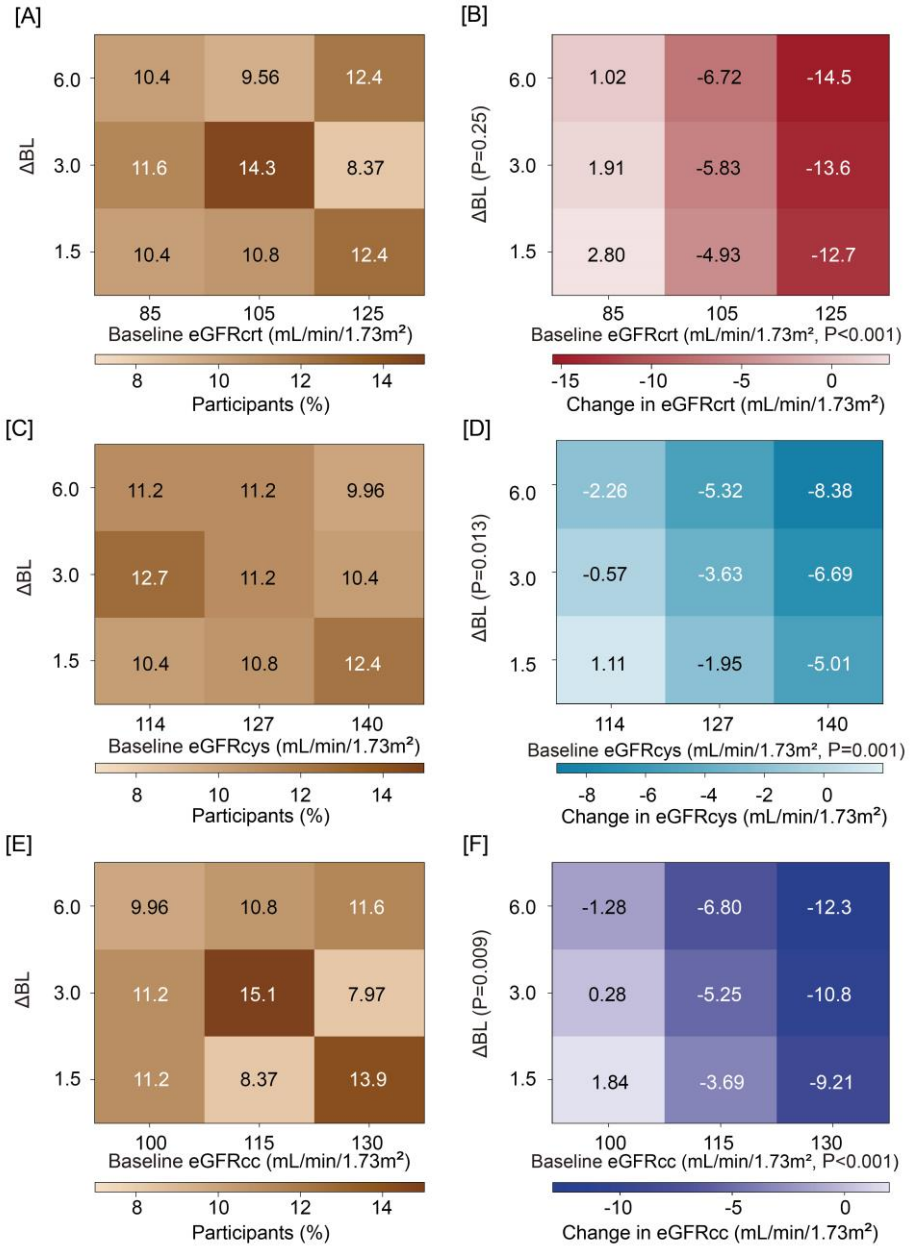

Figure S5

Heat maps relating the changes in glomerular filtration to their baseline values and the follow-up-to-baseline blood lead (BL) concentration ratio. Participants were cross-classified by thirds of the distributions of the follow-up-to-baseline BL ratio and the baseline glomerular filtration rate derived from serum creatinine (eGFRcrt; panels A and B), serum cystatin C (eGFRcys; panels C and D) or both (eGFRcc; panels E and F). The percentage of participants contributing to each cell of heat maps is given in panels A, C, and E. Associations sizes are point estimates corresponding with the thick marks and were derived from fully adjusted mixed models, which accounted for sex, age, follow-up duration, the time of day of blood sampling (daytime *vs* nighttime), body mass index, change in body weight, baseline BL, and the baseline values of and changes during follow-up in smoking status, mean arterial pressure, antihypertensive medication (yes *vs* no), the total-to-HDL cholesterol ratio, and γ-glutamyltransferase. The *P*-values of the interaction terms between the follow-up-to-baseline BL ratio and the baseline eGFR were 0.65, 0.33 and 0.85 for eGFRcrt (B), eGFRcys (E) and eGFRcc (F), respectively.