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Blood pressure and renal function responses in workers exposed to lead for up to six years

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Abstract

The Study for Promotion of Health in Recycling Lead (SPHERL) assessed the blood pressure (BP) and renal function (RF) responses for up to 6 years in the workers without previous occupational lead exposure. BP was the average of five consecutive readings and the estimated glomerular filtration rate was derived from serum creatinine (eGFRcrt) and cystatin C (eGFRcys). Blood lead (BL) was measured by inductively coupled plasma mass spectrometry (detection limit 0.5 μg/dL). The statistical methods included multivariable-adjusted mixed models and interval-censored Cox regression analysis. The 234 workers analyzed were on average 28.5 years old and included 91.9% men. The baseline BL concentration was 4.35 μg/dL and increased 3.17-fold over follow-up (median: 2.03 years; range: 0.92–6.45 years). The changes in BP and RF were not significantly correlated with the follow-up-to-baseline BL ratio ($p \geq .51$ and $p \geq .18$, respectively). The fully-adjusted changes in systolic/diastolic BP associated with a doubling of BL were −0.25/−0.12 mm Hg (CI: −0.94 to 0.44/−0.66 to 0.42 mm Hg). Accordingly, the incidence of stage-1 or -2 hypertension was not associated with the BL change ($p \geq .063$). Similarly, the changes in eGFRcrt and eGFRcys associated with a 3-fold BL increment were not significant, amounting to −0.70 mL/min/1.73 m^2 (CI: −1.70

to 0.30 mL/min/1.73 m^2) and −1.06 mL/min/1.73 m^2 (−2.16 to 0.03 mL/min/1.73 m^2). In conclusion, the BP and RF responses to an over 3-fold BL increment were small and not significant confirming the safety of modern lead-handing facilities operating under current safety rules.

KEYWORDS
blood pressure, hypertension, lead, occupational exposure, renal function

1 | INTRODUCTION

Lead is a widespread environmental toxicant. Although previous publications have demonstrated the significant associations of lead exposure with the risks of hypertension[1,2] or renal function (RF) decline,[3–6] these studies, either in environmental[2–5] or occupational[1,6] settings, were based on high-level lead exposure, had a cross-sectional design, or gave insufficient consideration to previous exposure or other confounders. The 2017 Global Burden of Disease (GBD) report[7] indicated that lead exposure, via increasing blood pressure (BP), might cause or aggravate a wide variety of cardiovascular diseases and renal dysfunction. However, the GBD investigators listed as potential limitations of their findings, residual confounding, the uncertainty as to the extent to which effect sizes were generalizable, the impossibility to account for temporal changes in the exposure to risk factors.

In the United States, the variation of lead in the environmental setting was assessed in consecutive cycles of the National Health and Nutrition Examination Survey (NHANES). The average blood lead (BL) concentration fell sharply from 13.1 μg/dL (1976–1980)[8] to 1.2—2.76 μg/dL (1988–1994),[8] and further to 1.64 μg/dL (1999–2002).[9,10] These BL levels (post-1988) were similar to the BL level of 2 μg in the pre-industrial human[7] and much lower than in occupational settings. However, there is currently no consensus whether low-level lead exposure raises BP or induces kidney dysfunction. The Study for Promotion of Health in Recycling Lead (SPHERL; NCT02243904)[11] is a real-world study assessing the health responses prior to and up to 6 years after starting lead exposure in the occupational setting. In the current manuscript, we aimed to investigate the predefined co-primary endpoints — longitudinal BP and RF — to lead exposure over up to three examination cycles.

2 | METHODS

2.1 | Study participants

SPHERL is a longitudinal study of newly hired workers without known previous occupational lead exposure employed at battery manufacturing and lead recycling plants in the United States.[11,12] The US Occupational Safety and Health Administration Standard (www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1025), including regular health check-ups, proper workplace ventilation, and the obligatory use of personal protective equipment, was implemented at all recruitment sites. SPHERL complies with the Helsinki declaration for investigations in humans. The Ethics Committee of the University Hospitals Leuven (Belgium) approved the study protocol (B322201421631).[11] Changes in BP and RF in response to the first occupational lead exposure were the predefined co-primary endpoints.[11]

Of 746 newly hired workers invited to participate in the study, 601 (80.6%) provided informed written consent. However, in the interval between consent and the planned baseline examination (median: 19 days; 5th—95th percentile interval: 9–59 days), 95 laborers left the companies or withdrew consent. From January 25, 2015 to September 19, 2017, 506 workers underwent the baseline examination, of whom 289 (57.1%) had at least one follow-up visit and 236 (46.6%) had two or more follow-up visits (Figure 1). The first, second and third follow-up visits were conducted from September 13, 2016 to March 28, 2019, from September 13, 2017 to October 4, 2019, and from September 2, 2021 to February 23, 2022, respectively. Of 289 participants with at least one follow-up visit, 55 were excluded because of missing information, leaving 234 workers for statistical analysis (Figure 1).

2.2 | Clinical and biochemical measurements

At the study sites, trained nurses applied current guidelines to measure office BP at the brachial artery. After the workers had rested for 5 min in the sitting position, the nurses obtained five consecutive BP readings to the nearest 2 mm Hg by auscultation of the Korotkoff sounds, using standard mercury sphygmomanometers. The five readings were averaged for analysis. Heart rate was counted over 15 s. BP was categorized according to the 2017 American College of Cardiology/American Heart Association guideline (Table S1).[13,14] Detailed description of BP measurements is given in the Data Supplement (pages 2–3).

The clinical variables and the analytical methods of laboratory tests, including the measurements of RF and BL, the quality control of these measurements, and the supporting references are given in the Data Supplement (pages 3–5). In short, 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]). The BL detection limit was 0.5 μg/dL. The estimated glomerular filtration rate was derived from

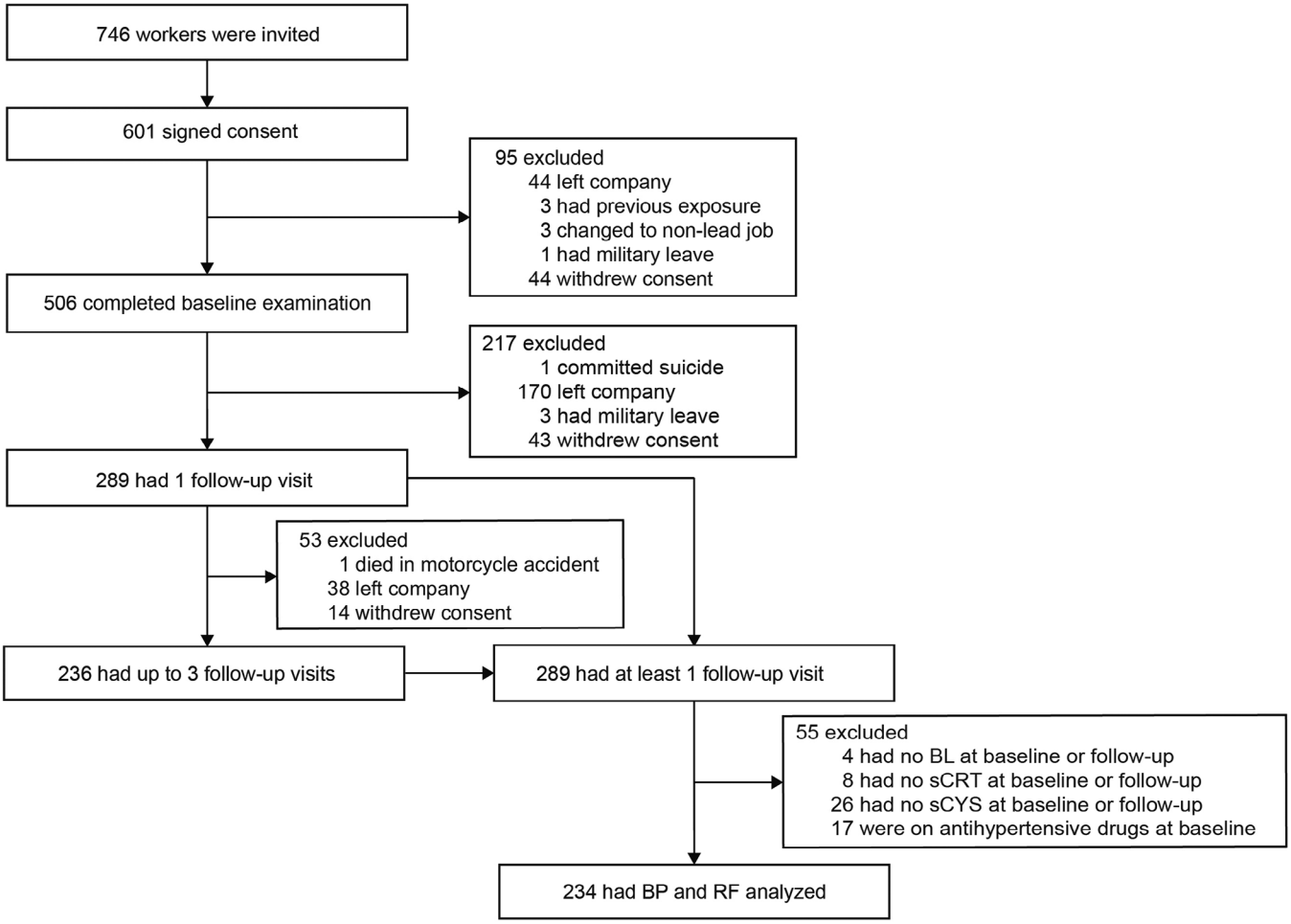

FIGURE 1 Flow chart. BL, blood lead; BP, blood pressure; RF, renal function; sCRT, serum creatinine; sCYS, serum cystatin C.

serum creatinine (eGFRcrt) and serum cystatin C (eGFRcys), using the Chronic Kidney Disease Epidemiology Collaboration equations.[15] To estimate the decline in glomerular filtration over the study period, age at each visit was introduced into the aforementioned equations. Serum osmolality was computed according to the formula: serum osmolality (mOsm/kg) = 2 × (serum Na+ [mmol/L]) + (blood glucose [mg/dL]/18) + (blood urea nitrogen [mg/dL]/2.8).[16] In addition, serum osmolality was measured by the freezing point depression technique in 37 workers to ascertain the accuracy of the formula against the true measurement of serum osmolality, using the Bland and Altman approach (Figure S1).

2.3 | Statistical analysis

For database management and statistical analysis, we used the SAS software, version 9.4, maintenance level 5 (SAS Institute Inc., Cary, NC). Departure from normality was evaluated by the Shapiro-Wilk statistic. To normalize the distributions, we applied a logarithmic transformation (base 10) to urinary albumin-to-creatinine ratio (ACR), γ-glutamyltransferase (index of alcohol consumption), and BL. We reported the central tendency and spread of continuously distributed variables as mean and standard deviation (SD) or as geometric mean and the interquartile range (IQR) or the 5th−95th percentile interval (PI) for logarithmically transformed variables. To compare means and proportions, we applied the t statistic or ANOVA for continuous variables, and the Fisher exact test for categorical variables, respectively.

In exploratory analyses, we assessed the BP and RF of workers across fourths of the distribution BL changes from baseline to the last follow-up. The changes in BP and RF responses to the change in BL were expressed for a doubling of the follow-up-to-baseline BL ratio. Estimates were derived from mixed models including the first and repeated follow-up visits, while accounting for clustering within participants using a random effect. The interval-censored proportional hazards regression was applied to estimate the association between incident hypertension and the BL change. The baseline hazard function was modeled using cubic splines with 3 knots. For the analysis of BP and incident hypertension, the covariables were ethnicity (white vs. others), sex, baseline age, baseline BP, the baseline value of body mass index and change in body weight during follow-up, and the baseline values of and the changes during follow-up in heart rate, smoking status,

TABLE 1 Baseline characteristics of 234 workers.

Characteristic	*N* (%)[a]	Characteristic	Mean (SD/IQR)[a]
Male	215 (91.9)	Age, years	28.5 (8.59)
Female	19 (8.12)	Body mass index, kg/m^2	28.6 (5.97)
White ethnicity	112 (47.9)	Systolic blood pressure, mm Hg	119.3 (10.0)
Hispanic ethnicity	104 (44.4)	Diastolic blood pressure, mm Hg	79.2 (8.72)
Black ethnicity	9 (3.85)	Heart rate, beats per minute	74.3 (12.1)
Other ethnicities	9 (3.85)	Serum creatinine, mg/dL[c]	0.96 (0.17)
Current smokers	57 (24.4)	Serum cystatin C, mg/L[c]	0.67 (0.10)
Alcohol intake	102 (43.6)	eGFRcrt, mL/min/1.73 m^2 [b]	106.4 (16.6)
Normotension	99 (42.3)	eGFRcys, mL/min/1.73 m^2 [b]	126.0 (12.6)
Elevated blood pressure	27 (11.5)	Serum osmolality, mOsm/kg	286.8 (3.78)
Hypertension stage ≥1	108 (46.2)	Urinary specific gravity	1.02 (0.01)
Hypertension stage ≥2	29 (12.4)	Total-to-HDL cholesterol ratio	3.88 (1.27)
Treated hypertension	0 (0.00)	ACR, mg/g	4.36 (2.83, 6.10)
Diabetes mellitus	7 (2.99)	γ-glutamyltransferase, U/L	22.1 (16.0,31.0)

Abbreviations: ACR, urinary albumin-to-creatinine ratio; HDL, high-density lipoprotein; IQR, interquartile range; *N* (%), number of participants (percent); SD, standard deviation.

[a]Values are number of participants (%), arithmetic mean (SD), or geometric mean (IQR). Blood pressure was the average of five readings. Normotension, elevated blood pressure and hypertension were categorized according to the 2017 ACC/AHA guideline, irrespective of treatment status (reference 13). Diabetes mellitus was a self-reported diagnosis, a fasting blood glucose of ≥126 mg/dL, or use of antidiabetic drugs.

[b]eGFRcrt and eGFRcys refer to the glomerular filtration rate estimated from serum creatinine and serum cystatin C (reference 15).

[c]To convert serum creatinine from mg/dL to micromol/L, multiply by 88.42; to convert cystatin C from mg/L to nmol/L, multiply by 74.9.

total-to-HDL serum cholesterol ratio, γ-glutamyltransferase and serum creatinine. For the analysis of RF, the covariables were sex, baseline age, baseline RF, follow-up duration, the time of day of blood sampling (nighttime vs. daytime), the baseline value of body mass index and change in body weight during follow-up, and the baseline values of and the changes during follow-up in smoking status, mean arterial pressure (diastolic BP plus one third of the difference between systolic and diastolic BP), the total-to-HDL cholesterol ratio and γ-glutamyltransferase, and changes in antihypertensive medication (yes vs. no) during follow-up.

3 | RESULTS

3.1 | Characteristics of workers

Table 1 lists the baseline characteristics of the 234 workers, of whom 215 (91.9%) were men. The cohort included 112 (47.9%) Whites, 112 (47.9%) Hispanics, 9 (3.85%) Blacks, and 9 (3.85%) workers with another self-reported ethnic background. At enrollment, age averaged 28.5 years, total and HDL cholesterol 169.9 and 46.3 mg/dL, and the corresponding total-to-HDL cholesterol ratio 3.9 (Table 1). The values of BP and RF at baseline and the last follow-up visit, and the corresponding changes are shown in Table S2. In the 37 duplicate measurements of serum osmolality (Figure S1), the bias determined according to the Bland and Altman approach was glutamyl transferase 1.86 mOsm/kg (95% CI: −0.06 to 3.78, $p = .057$).

3.2 | Blood lead

During the median follow-up time of 2.03 years (IQR: 1.96–2.16 years; range: 0.92–6.45 years), the geometric mean BL concentration increased from 4.35 μg/dL (IQR: 2.50–7.90 μg/dL; 5th–95th percentile interval: 0.90–15.2 μg/dL) at baseline, to 16.6 μg/dL (IQR: 10.5–22.2 μg/dL; 5th–95th percentile interval: 3.80–30.8 μg/dL) at the first follow-up visit, and to 15.3 μg/dL (IQR: 8.90–22.1 μg/dL; 5th–95th percentile interval: 3.20–31.4 μg/dL) at the last follow-up visit, respectively. The follow-up-to-baseline BL ratio averaged 3.17 (IQR: 1.88–5.46; 5th–95th percentile interval, 0.62–14.0).

3.3 | Blood pressure and incident hypertension

Baseline systolic/diastolic BP amounted to 119.3/79.2 mm Hg (Table 1). The corresponding mean arterial pressure was 92.6 mm Hg (SD: 8.5 mm Hg) and pulse pressure was 40.1 mm Hg (SD: 7.0 mm Hg). In exploratory analyses, there was no trend ($p \geq .51$) in the BP changes across increasing quartiles of the follow-up-to-baseline BL ratio (Table S3). In the unadjusted, adjusted and fully adjusted mixed models, accounting for the clustering within participants, the associations were not significant between the change in BP and the changes in BL ($p \geq .29$, Table 2). In the fully adjusted model (Table 2), the association sizes associated with a doubling of follow-up-to-baseline BL ratio were −0.25 mm Hg (CI: −0.94 to 0.44 mm Hg) for systolic BP and −0.12 mm Hg (CI, −0.66 to 0.42 mm Hg) for diastolic BP. Heat maps (Figure 2)

TABLE 2 Association between changes in blood pressure, incident hypertension and change in blood lead.

Outcome	Unadjusted		Adjusted		Fully adjusted	
Blood pressure[a]	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)[b]**	***p*-value**	**Estimate (95% CI)[c]**	***p*-value**
Systolic blood pressure, mm Hg	−0.11 (−0.95, 0.73)	.80	−0.39 (−1.07, 0.29)	.26	−0.25 (−0.94, 0.44)	.47
Diastolic blood pressure, mm Hg	0.32 (−0.44, 1.09)	.40	−0.13 (−0.66, 0.39)	.62	−0.12 (−0.66, 0.42)	.66
Mean arterial pressure, mm Hg	0.16 (−0.54, 0.85)	.66	−0.19 (−0.70, 0.33)	.47	−0.13 (−0.65, 0.39)	.63
Pulse pressure, mm Hg	−0.30 (−1.10, 0.50)	.46	−0.25 (−0.83, 0.34)	.41	−0.20 (−0.81, 0.41)	.52
Incident hypertension[d] (n/N[e])	**HR (95% CI)**	***p*-value**	**HR (95% CI)[g]**	***p*-value**	**HR (95% CI)[h]**	***p*-value**
Hypertension ≥ stage 1 (65/126)	1.15 (0.96, 1.38)	.14	1.15 (0.95, 1.39)	.13	1.21 (0.99, 1.48)	.063
Hypertension ≥ stage 2 (22/205)	0.94 (0.75, 1.18)	.58	0.95 (0.75, 1.19)	.65	1.03 (0.79, 1.34)	.84
Moving up categories[f] (97/234)	1.11 (0.97, 1.27)	.12	1.08 (0.95, 1.24)	.25	1.09 (0.94, 1.25)	.25

Abbreviations: 95% CI, 95% confidence interval, BP, blood pressure; HR, hazard ratio.

[a]For the analyses of blood pressure (BP), estimates express the difference in BP associated with a doubling of the follow-up-to-baseline blood lead ratio. Estimates were derived from mixed models accounting for clustering within participants using a random effect.

[b]Adjusted models accounted for sex and age, BP and body mass index at baseline.

[c]Fully adjusted models additionally accounted for ethnicity (white vs. other), change in body weight during follow-up, and the baseline values of and the changes during follow-up in heart rate, smoking status, total-to-HDL serum cholesterol ratio, γ-glutamyltransferase, and serum creatinine.

[d]Hypertension was categorized according to the to 2017 ACC/AHA guideline (references 13), irrespective of treatment status. Stage-1 and stage-2 hypertension were systolic or diastolic BP levels of 130–139/80–89 mm Hg and 140–159/90–99 mm Hg, respectively. If systolic and diastolic BP were in different categories, the highest category was applied. For the analysis of incident hypertension, Hazard ratios (HR), given with 95% confidence interval, HRs and 95% CI were obtained from proportional hazard models for interval censored data, using a cubic spline function to model the baseline hazard. HRs express the risk associated with a doubling of the follow-up-to-baseline blood lead level.

[e]n/N refers to the number of incident cases of hypertension and the total number of workers at risk. Workers at risk were those without stage-1 or stage-2 hypertension at baseline or all workers for moving up categories.

[f]Moving up categories indicates an increase in the blood pressure category by one or more steps during follow-up.

[g]Adjusted models accounted for sex, age, baseline body mass index and baseline mean arterial pressure (diastolic blood BP plus one third of the difference between systolic and diastolic BP).

[h]Fully adjusted models additionally accounted for ethnicity (white vs. other), change in body weight during follow-up, and the baseline value of and change during follow-up in heart rate, smoking status, total-to-HDL serum cholesterol ratio, γ-glutamyltransferase, and serum creatinine.

demonstrated that the changes in BP were mainly determined by baseline BP ($p < .0001$), while the change in BL did not reach significance in these analyses ($p \geq .47$).

Cross-classification of the baseline and follow-up BP (Table S4) demonstrated that of 99 workers, who were normotensive as baseline, 14 moved up to untreated elevated BP, 42 to untreated stage-1 hypertension, 7 to untreated stage-2 hypertension, no worker to untreated severe hypertension, and 1 to treated hypertension, whereas 35 workers stayed normotensive. Taken into account the baseline BP status, overall, 65/126 (51.6%) workers developed ≥stage-1 hypertension, 22/205 (10.0%) stage-2 hypertension, and 97/238 (40.8%) moved up across the BP classification. In the unadjusted, adjusted and fully adjusted analyses, the hazard ratios (HRs) for incident hypertension were not significant ($p \geq .063$, Table 2). For incident hypertension ≥ stage 1, the fully adjusted HR was 1.21 (CI: 0.99 to 1.48, Table 2). For moving up across the BP categories (Table 2), the fully adjusted HR was 1.09 (CI: 0.94 to 1.25).

3.4 | Renal function

At baseline, eGFRcrt averaged 106.4 mL/min/1.73 m^2 and eGFRcys 126.0 mL/min/1.73 m^2 (Table 1). In exploratory analyses, there was no trend ($p \geq .18$) in the RF changes across increasing quartiles of the follow-up-to-baseline BL ratio (Table S5). In addition, 12 (5.13%) workers had a self-reported history of nephrolithiasis at enrollment, but no new or recurrent incidence occurred during follow-up. There was no significant correlation between the changes in BP and changes in RF ($p \geq .71$). The age-dependent changes in eGFRcrt and eGFRcys were −1.77 and −1.21 mL/min/1.73 m^2, respectively.

In the unadjusted and adjusted mixed models, a doubling of BL was not significantly associated with the changes in RF ($p \geq .073$; Table 3). In the fully adjusted models, the association sizes associated with a doubling of follow-up-to-baseline BL ratio were −0.70 mL/min/1.73 m^2 (CI: −1.70 to 0.30 mL/min/1.73 m^2) for eGFRcrt and −1.06 mL/min/1.73 m^2 (CI: −2.16 to 0.03 mL/min/1.73 m^2) for eGFRcys (Table 3). Moreover, the changes in serum creatinine, serum cystatin C, serum osmolality, urinary specific gravity and ACR were not significantly associated with the changes in BL ($p \geq .081$; Table 3). Heat maps (Figure 3) indicated that the changes in RF were mainly determined by baseline eGFRcrt and eGFRcys ($p \leq .0011$), while the change in BL did not reach significance in these analyses ($p \geq .057$).

4 | DISCUSSION

In a real-world occupational setting, the over 3-fold BL increment was not significantly associated with increases in any BP component, higher

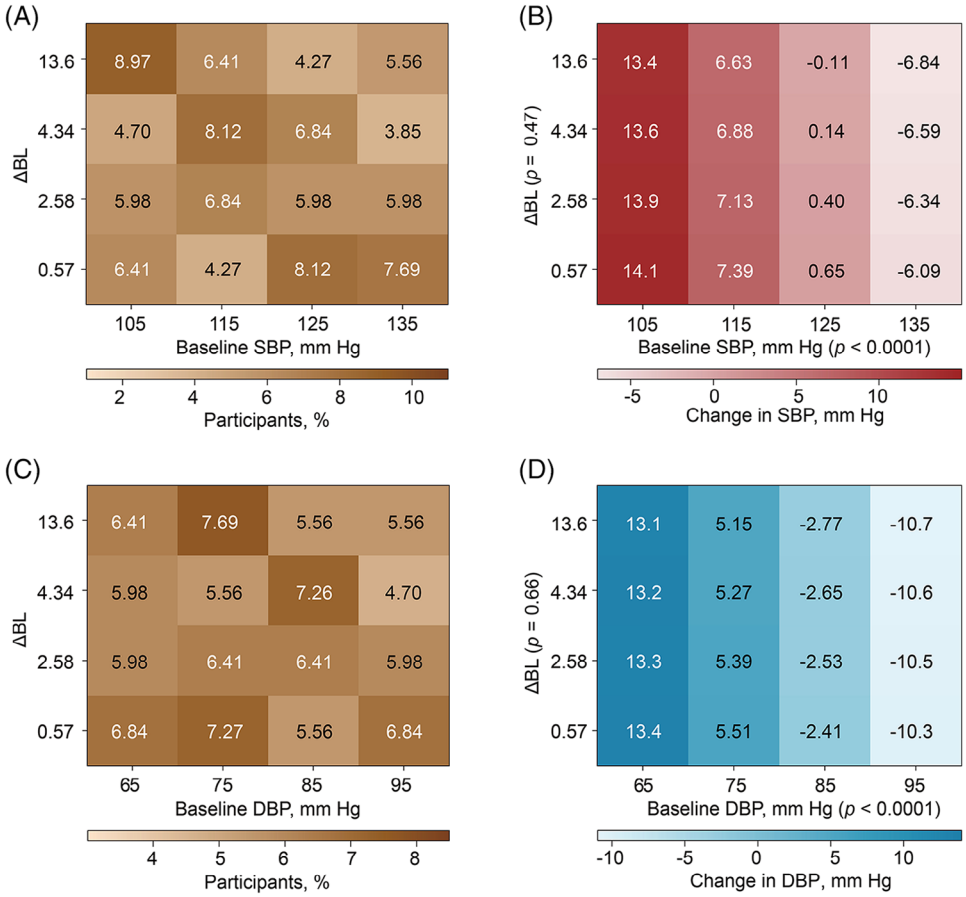

FIGURE 2 Heat maps relating the change in systolic and diastolic blood pressure to the blood pressure level at baseline and the change in blood lead from baseline to last follow-up. ΔBL, change in blood lead; SBP, systolic blood pressure; DBP, diastolic blood pressure. For SBP (B) and DBP (D), the associations were derived by mixed models (see Table 2). All models were fully adjusted. The percentage of participants (A and C) contributing to the cross-classification between the baseline blood pressure (horizontal axis) and the fold change in BL (vertical axis) are given for each analysis run.

TABLE 3 Association between changes in renal function and change in blood lead.

	Unadjusted		Adjusted[d]		Fully adjusted[e]	
Variable	Estimate (95% CI)[c]	*p*-value	Estimate (95% CI)[c]	*p*-value	Estimate (95% CI)[c]	*p*-value
Serum creatinine, $\times 10^{-2}$ mg/dL	−0.09 (−1.18, 1.01)	.88	0.47 (−0.55, 1.48)	0.37	0.56 (−0.48, 1.59)	.29
Serum cystatin C, $\times 10^{-2}$ mg/L	−0.37 (−1.33, 0.58)	.44	0.76 (−0.16, 1.68)	0.10	0.83 (−0.10, 1.77)	.081
eGFRcrt, mL/min/1.73 m^2 [a]	0.08 (−0.98, 1.13)	.88	−0.62 (−1.59, 0.36)	0.22	−0.70 (−1.70, 0.30)	.17
eGFRcys, mL/min/1.73 m^2 [a]	0.40 (−0.73, 1.53)	.48	−0.98 (−2.06, 0.09)	0.073	−1.06 (−2.16, 0.03)	.057
Serum osmolality, mOsm/kg	0.16 (−0.25, 0.56)	.44	−0.05 (−0.36, 0.26)	0.75	−0.06 (−0.38, 0.26)	.71
Urine specific gravity, $\times 10^{-2}$	−0.02 (−0.09, 0.06)	.68	−0.03 (−0.08, 0.03)	0.34	−0.01 (−0.06, 0.04)	.68
ACR, % b	−1.45 (−7.06, 4.49)	.62	−0.71 (−5.93, 4.80)	0.80	−0.81 (−6.05, 4.71)	.77

Abbreviations: 95% CI, 95% confidence interval; ACR, urinary albumin-to-creatinine ratio.

[a]eGFRcrt and eGFRcys refer to the glomerular filtration rate estimated from serum creatinine or serum cystatin C (reference 15).

[b]Change in urinary albumin-to-creatinine ratio are expressed as percentage differences from baseline to follow-up.

[c]Estimates express the difference in renal function associated with a doubling of the follow-up-to-baseline blood lead ratio. Estimates were derived from mixed models accounting for clustering within participants as random effect.

[d]Adjusted models accounted for sex, age, follow-up duration, the time of day of blood sampling (nighttime vs. daytime), and the baseline renal function measure being analyzed.

[e]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 (diastolic BP plus one third of the difference between systolic and diastolic BP, the total-to-HDL cholesterol ratio and γ-glutamyltransferase, and changes in antihypertensive medication (yes vs. no) during follow-up.

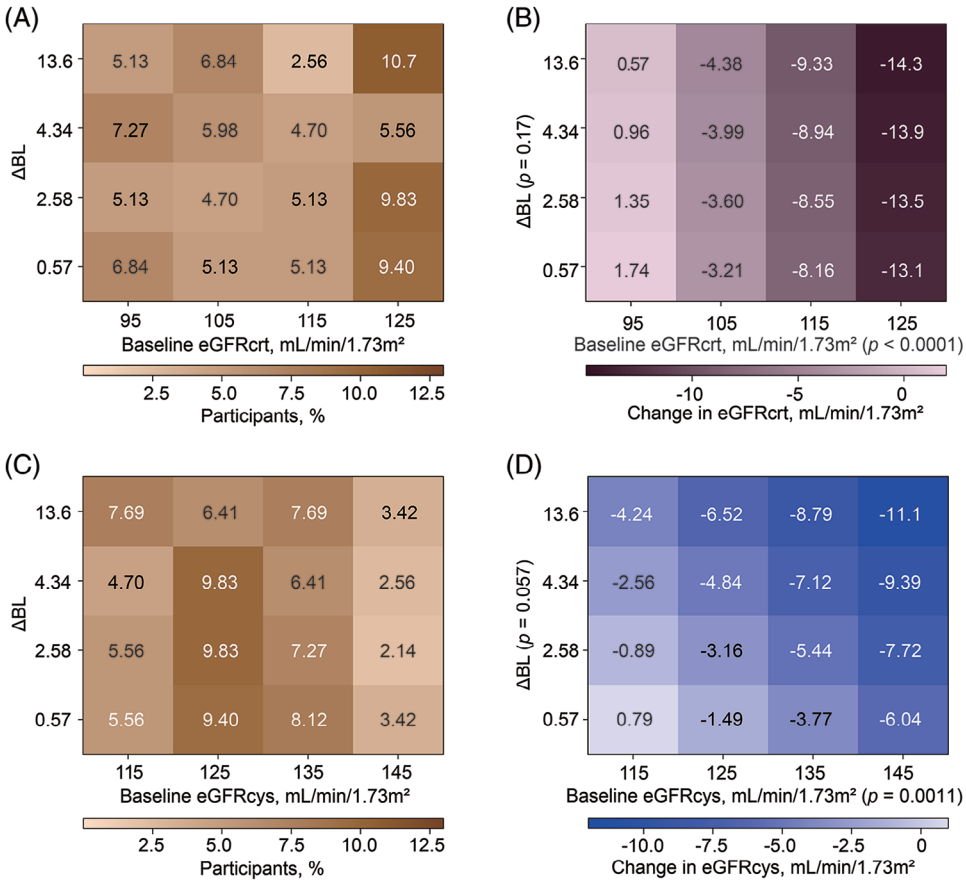

FIGURE 3 Heat maps relating the change in eGFRcrt and eGFRcys to the eGFR level at baseline and the change in blood lead from baseline to last follow-up. ΔBL, change in blood lead; eGFRcrt, the glomerular filtration rate estimated from serum creatinine; eGFRcys, the glomerular filtration rate estimated from serum cystatin C. For eGFRcrt (B) and eGFRcys (D), the associations were derived by mixed models (see Table 3). All models were fully adjusted. The percentage of participants (A and C) contributing to the cross-classification between the baseline blood pressure (horizontal axis) and the fold change in BL (vertical axis) are given for each analysis run.

risk of hypertension, or with a decline in a variety RF measurements in a cohort of workers without known previous occupational lead exposure. These findings confirmed the previously published cross-sectional analyses at baseline[12,17] and the longitudinal analyses at follow-up in the second cycle of the SPHERL project.[18,19] Compared with the previous publications,[18,19] the current study went through a longer follow-up period and indicated a stable BL levels after the first year, which could provide a more reliable outcome interpretation after starting the first occupational exposure. The HR and CI of incident hypertension ≥ stage 1 did not reach significant statistically, while this result could not exclude the risk of incident hypertension, as defined by the stricter criteria in 2017 American College of Cardiology/American Heart Association guideline (Table S1),[13,14] with certainty. In addition, the Bland and Altman approach indicated reasonable repeatability in the serum osmolarity measurements in[37] workers. The heat maps demonstrated that baseline BP (Figure 2) and baseline eGFRcrt and eGFRcys (Figure 3) were the principal determinants of their corresponding changes during follow-up, while the over 3-fold increment in BL did not significantly produce adverse health outcomes. Due to regression to mean, as revealed in all clinical measurements,[20] the workers with lower BP at baseline were more likely to have an increased BP level at follow-up or to move up across BP categories, while this tendency was inverse for the workers at the top tail of the baseline BP distribution (Figure 2). Similarly, the same regression to mean phenomenon affected the findings for eGFRcrt and eGFRcys (Figure 3). The eGFRcys, as derived from serum cystatin C, is a better biomarker reflecting glomerular filtration than eGFRcrt, for its higher reliability in the presence of confounding by ethnicity, sex, age, muscle mass and protein intake.[15] The expected age-related decline in eGFRcrt and eGFRcys (−1.77 and −1.21 mL/min/1.73 m^2, respectively), was of the similar magnitude compared with the corresponding fully adjusted changes in eGFRcrt and eGFRcys in relation to the baseline-to-follow-up BL ratio (Table 3).

In addition to regression to the mean, the present study highlights the importance to account in longitudinal studies for concealed albeit not unexpected confounders and to distinguish crudely observed changes in the glomerular filtration rate in the context of the biomarker of exposure of interest, BL in the current study. Both serum creatinine and serum cystatin C, from which glomerular filtration is derived, show a diurnal rhythm with little influence of meals or meat ingestion on serum cystatin C level, whereas these confounders increase serum creatinine level.[21] Along similar lines, during sleep, urine flow

decreases and the tubular reabsorption of water increases.[22,23] The newly hired workers recruited into SPHERL transited not only from environmental to occupational exposure but also from a sedentary to a physically demanding lifestyle. On the basis of the published tables,[24] the jobs offered to the workers required an energy expenditure of 6 to > 8 metabolic equivalents defined as the amount of oxygen consumed while resting in the sitting position. Physical labor induces acute renal changes in healthy adults.[25] In young adults, exercise reduces renal plasma flow and glomerular filtration with smaller effects on eGFRcys than on eGFRcrt.[26]

In the current analysis, the changes in BP and in glomerular filtration were not significantly correlated. In contrast, a recent NHANES study (1999–2014)[27] with 20,073 participants (49.01% men, mean age, 47.27 years, mean BL, 1.81 μg/dL), demonstrated a positive association of BP with BL and an inverse association of eGFR with both BL and BP. However, this cross-sectional analysis did not allow excluding the alternative hypothesis that lead accumulation is a consequence instead of a cause of kidney dysfunction. Among 7341 male Korean lead exposed workers (mean age, 31.1 years; mean BL, 5.3 μg/dL), the odds ratio relating the risk of hypertension to BL in the highest quartile of BL distribution (6.87–10.0 μg/dL) was 1.54 (95% CI, 1.26–1.89).1 However, this study did not account for the previous occupational lead exposure and could not demonstrate a continuous association between BP and BL over the whole BL range.[1] A previous study by Mujaj and coworkers reported an inverse association between ACR and BL.[12] The present study also showed an inverse association, although it was not statistically significant (Table 3). Creatinine is removed from the circulating blood by glomerular filtration but also by proximal tubular secretion. Little or no tubular reabsorption of creatinine occurs. Small proteins that pass the glomerular sieve undergo tubular reabsorption. The aforementioned publication[12] could not clarify whether the inverse association between ACR and BL was induced by higher tubular reabsorption of small proteins or higher proximal tubular excretion of creatinine. Along similar lines, several studies reported an inverse association between eGFR and BL in response to environmental[4,5,28–31] or occupational6 exposure. However, as 70% of lead is excreted via kidney,[32,33] whether higher BL induces renal impairment or vice versa cannot be distinguished.

Lead is a cumulative toxicant, 90%–95% of which is stored in bone, from where it is recirculated with a half-life of 20–25 years.[34,35] BL, which for 99% is carried by red blood cells, reflects recent exposure over the past 1–2 months and the amount of lead released and recirculated from bone stores.[34] Bone lead correlates with BL[35,36] and explains around 20% of the variance in BL, depending on seasonality[35] and hormonal and other endogenous and environmental stimuli influencing the balance between bone formation and resorption.[36] Therefore, BL in older individuals increasingly represent the pre-existing body burden[34,35] originating from the historical environmental lead exposure. In the United States, leaded paint was effectively prohibited in 1976 and leaded gasoline was completely phased out in 1995.[37] The SPHERL finding are not vulnerable to this phenomenon, given that young age of most of its participants and the exclusion of workers with previous occupational lead exposure.

The strong points of SPHERL study are the longitudinal study design in young workers without known previous occupational exposure and the rigorous quality control of BL concentrations with a detection limit as low as 0.5 μg/dL. An important concept highlighted by the SPHERL experience is that in longitudinal studies in an occupational setting not accounting for confounders, such as aging, the diurnal variation in body functions, shift work, or the physiological changes normally associated with physically strenuous work might lead to falsely attributing noxious effects to the pollutant under study. On the other hand, the current study must also be interpreted within the context of its limitations. First, the attrition rate among 506 workers originally was 42.9%, predominately because of occupational mobility. Therefore, more than 500 participants were enrolled to meet the sample size for addressing BP and RF as the co-primary endpoints. Second, the healthy worker effect[38] might potentially account for the non-significance of the current findings, given the mean age of 28.5 years in this occupational cohort. Third, although the ethnic distribution of the workers was representative for the population at the recruitment sites, women were under-represented. Only 11.6% of study participants were female, which precluded analyses stratified by sex. The current observations should not be unthoughtfully generalized and are therefore not applicable to older individuals or patients with comorbidities, such as diabetes, which increases the vulnerability of RF. Fourth, taking five consecutive measurements is in keeping with all previous epidemiological and other research conducted by our group. Moreover, if a drop of the BP level occurs from the first to the fifth, this decreases the risk of white-coat hypertension and falsely classifying a worker as being hypertensive.[39–41] Finally, the co-exposure of cadmium was not assessed, which is commonly present in lead recycling plants and has adverse effects on renal tubular and glomerular function.

5 | CONCLUSIONS

A real-world experiment involving workers without know previous lead exposure did not demonstrate significant associations of BP, the risk of hypertension or RF measurements with an over 3-fold BL increment. Thus, using a state-of-the art longitudinal cohort design, SPHERL confirmed that in modern lead-handing facilities operating under current rules imposed by OSHA, workers over an employment period of 2 years, in some extending to up to 6 years, were well protected with minimal risk for hypertension or renal dysfunction.

AUTHOR CONTRIBUTIONS

Jan A. Staessen designed the SPHERL study and secured funding. Yu-Ling Yu, De-Wei An, and Wen-Yi Yang contributed to the construction and management of the database. Yu-Ling Yu and Jan A. Staessen performed the statistical analysis and wrote the first draft of the manuscript, on which Peter Verhamme, Karel Allegaert, and Tim S. Nawrot provided feedback. All authors contributed to the interpretation of the results and performed a critical revision of the manuscript and all approved the final version before submission. The corresponding author had full access of all the data in the study and

had responsibility for guaranteeing the integrity of the data and the decision to submit the manuscript for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

In consultation with the Ethics Committee that approved the study protocol, SPHERL data cannot be made publicly available. Reasons are that the informed consent signed by the workers did not cover data sharing and that an anonymized and deidentified data set still contains elements, which could potentially lead to the identification of the study participants. Only Jan A. Staessen (the PI and corresponding author) and Yu-Ling Yu had full access to the SPHERL database. They will provide additional results according to a scientifically justified statistical analysis plan proposed by other investigators in a request addressed to Jan A. Staessen.

CLINICAL TRIAL REGISTRATION

Study for Promotion of Health in Recycling Lead (SPHERL) was registered on ClinicalTrials.gov (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02243904).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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