

## Two-Year Responses of Office and Ambulatory Blood Pressure to First Occupational Lead Exposure

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**Abstract**—Lead exposure causing hypertension is the mechanism commonly assumed to set off premature death and cardiovascular complications. However, at current exposure levels in the developed world, the link between hypertension and lead remains unproven. In the Study for Promotion of Health in Recycling Lead (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02243904), we recorded the 2-year responses of office blood pressure (average of 5 consecutive readings) and 24-hour ambulatory blood pressure to first occupational lead exposure in workers newly employed at lead recycling plants. Blood lead (BL) was measured by inductively coupled plasma mass spectrometry (detection limit 0.5 µg/dL). Hypertension was defined according to the 2017 American College of Cardiology/American Heart Association guideline. Statistical methods included multivariable-adjusted mixed models with participants modeled as a random effect and interval-censored Cox regression. Office blood pressure was measured in 267 participants (11.6% women, mean age at enrollment, 28.6 years) and ambulatory blood pressure in 137 at 2 follow-up visits. Geometric means were 4.09 µg/dL for baseline BL and 3.30 for the last-follow-up-to-baseline BL ratio. Fully adjusted changes in systolic/diastolic blood pressure associated with a doubling of the BL ratio were 0.36/0.28 mmHg (95% CI, −0.55 to 1.27/−0.48 to 1.04 mmHg) for office blood pressure and −0.18/0.11 mmHg (−2.09 to 1.74/−1.05 to 1.27 mmHg) for 24-hour ambulatory blood pressure. The adjusted hazard ratios of moving up across hypertension categories for a doubling in BL were 1.13 (0.93–1.38) and 0.84 (0.57–1.22) for office blood pressure and ambulatory blood pressure, respectively. In conclusion, the 2-year blood pressure responses and incident hypertension were not associated with the BL increase on first occupational exposure.

**Graphic Abstract**—A [graphic abstract](#) is available for this article. (*Hypertension*. 2020;76:1299-1307. DOI: 10.1161/HYPERTENSIONAHA.120.15590.) • [Data Supplement](#)

**Key Words:** ambulatory blood pressure monitoring ■ environmental exposure ■ hypertension ■ lead ■ occupational exposure

Lead is an ubiquitous environmental toxicant, which at high exposure levels causes hypertension and renal failure.<sup>1</sup> However, in a meta-analysis of summary statistics extracted from 31 studies and involving 58 518 participants,<sup>2</sup> doubling of blood lead was only associated with a marginally higher blood pressure, on average 1.0 mmHg systolic (95% CI, 0.5–1.4 mmHg) and 0.6 mmHg diastolic (CI, 0.4–0.8 mmHg). All studies combined in this meta-analysis had been conducted before 2001.<sup>2</sup> The National Health Examination Survey (NHANES) demonstrated that mean blood lead levels among American adults dropped from 13.1 µg/dL in NHANES II (1976–1980)<sup>3</sup>

to 2.76 µg/dL in NHANES III (1988–1994),<sup>3</sup> and further to 1.64 µg/dL in NHANES IV (1999–2002).<sup>4,5</sup> In the light of the falling environmental lead exposure,<sup>3–5</sup> agencies, such as the National Toxicology Program<sup>6</sup> and the Environmental Protection Agency<sup>7,8</sup> reviewed the literature in weight-of-the-evidence analyses<sup>9</sup> and proposed that blood lead levels of 5 µg/dL or lower might be associated with adverse health effects.<sup>6–9</sup> Along similar lines, in 2010, the American College of Occupational and Environmental Medicine requested that the US Occupational and Health Administration align itself with the scientific evidence, referring in particular to hypertension.<sup>10</sup>

Received May 22, 2020; first decision June 10, 2020; revision accepted July 16, 2020.

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This article was sent to Theodore A. Kotchen, Guest Editor, for review by expert referees, editorial decision, and final disposition.

**The Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.120.15590>.**

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*Hypertension* is available at <https://www.ahajournals.org/journal/hyp>

DOI: 10.1161/HYPERTENSIONAHA.120.15590

In the SPHERL (Study for Promotion of Health in Recycling Lead (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02243904),<sup>11,12</sup> we assessed the 2-year blood pressure response to lead exposure in newly hired workers not occupationally exposed before. In line with current hypertension guidelines,<sup>13,14</sup> office blood pressure measurement was backed up by ambulatory monitoring.

## Methods

The SPHERL data and the SAS programs written for the present analysis will not be made available to other researchers, because participant-level data sharing was not covered by the informed consent and because this option is not in compliance with the General Data Protection Act (EU Directive 2016/680). However, any scientifically motivated request, submitted to the study coordinator (J.A. Staessen), to run additional analyses on the data set used in the current article, will be honored if only summary statistics are requested.

## Study Participants

SPHERL (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02243904) complied with the Helsinki declaration for investigations in human subjects.<sup>15</sup> All participants signed an informed consent form. The Ethics Committee of the University Hospitals Leuven (Belgium) approved the study (No. B322201421631), of which the protocol has been published.<sup>11</sup> In short, SPHERL is a prospective follow-up study of workers without known previous occupational lead exposure, who were newly hired at lead recycling and battery manufacturing plants in the United States.<sup>11</sup> Changes in the office and 24-hour ambulatory blood pressure in response to starting occupational lead exposure was the primary study end point.

Of 746 workers invited to be enrolled, 601 (80.6%) consented. However, in the interval between consent and the planned baseline examination (median, 19 days; fifth–95th percentile interval [fifth–95th PI], 9–59 days), 95 laborers left the work place or withdrew. From January 25, 2015 until September 19, 2017, 506 workers underwent the baseline examination, of whom 289 (57.1%) had one and 236 (46.6%) had 2 follow-up visits (Figure 1). Participants disqualified for analysis of office blood pressure (Figure 1), if blood lead had not been measured at baseline (n=3) or follow-up (n=1) or if they were on antihypertensive drugs at baseline (n=18). A further 130 workers were excluded from analysis of their ambulatory blood pressure, because baseline (n=5) or follow-up (n=11) ambulatory recordings were missing or because baseline (n=59) or follow-up (n=55) recordings included fewer than the required 8 daytime or 4 night-time readings.<sup>16</sup> Thus, the number of workers statistically analyzed totaled 267 for office blood pressure and 137 for the ambulatory blood pressure.

## Clinical and Biochemical Measurements

At the study sites, trained nurses 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 5 consecutive blood pressure readings to the nearest 2 mmHg by auscultation of the Korotkoff sounds, using standard mercury sphygmomanometers. For analysis, the 5 readings were averaged. Heart rate was counted over 15 seconds. The ambulatory blood pressure was recorded on the same arm as the office blood pressure with similarly sized cuffs, using validated<sup>17</sup> oscillometric Mobil-O-Graph 24-hour PWA monitors (ie, M. GmbH, Stolberg, Germany). The monitors were programmed to obtain readings at 15-minute intervals during waking hours and every 30 minutes during sleep. On monitoring days, the workers kept a diary, in which they recorded the beginning and end of sleep. Intraindividual awake and asleep blood pressures were calculated as the arithmetic mean of all awake and asleep readings, respectively. Mean 24-hour blood pressure was the average of the awake and asleep blood pressures weighed for the duration of the awake and asleep periods. The dipping ratio was calculated by dividing the asleep by the awake blood pressure. Office and ambulatory blood pressure were categorized according to the 2017 American

College of Cardiology/American Heart Association guideline (Table S1 in the [Data Supplement](#)).<sup>13,18</sup>

Venous blood samples, obtained after 8 hours of fasting, were immediately spun and divided into aliquots. All biochemical tests were performed by laboratories certified by the Clinical Laboratory Improvement Amendments of 1988. Blood lead was determined by inductively coupled plasma mass spectrometry at a single laboratory certified for blood lead analysis in compliance with the provisions of the Occupational and Health Administration Lead Standard, 29CFR 1910.1025 (Occupational Safety and Health Administration). This laboratory participated in the US CDC Blood Lead Proficiency Testing Program. Before analysis, specimens were digested in nitric acid and spiked with an iridium internal standard. The limit of detection was 0.5 µg/dL. The deviation from known lead standards analyzed along with the samples in each test run was <10%. The biochemical measurements included serum creatinine, total and HDL (high-density lipoprotein) serum cholesterol, serum  $\gamma$ -glutamyltransferase (index of alcohol intake), and fasting blood glucose. The appendix (Methods and references 1–11 in the [Data Supplement](#)) provides details of the methodology and quality control of the blood pressure and biochemical measurements.

## 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. Skewness and kurtosis were computed as the third and fourth moments about the mean divided by the cube of the SD. To approximate the normal distribution, blood lead and  $\gamma$ -glutamyltransferase were logarithmically transformed (basis 10). We reported the central tendency and spread of continuously distributed variables as mean and SD or as geometric mean and interquartile range (IQR) for logarithmically transformed variables. To compare means and proportions, we applied *t* statistics or ANOVA, and the Fisher exact test, respectively. For pairwise comparison of proportions, we applied the McNemar test.

In exploratory analyses, we assessed the blood pressure and characteristics of workers across fourths of the blood lead distribution at baseline. The blood pressure responses to the changes in the blood lead concentration were expressed for a doubling of the follow-up-to-baseline blood lead ratio. Estimates were derived from mixed models including the first and repeat follow-up visits, while accounting for within-subject correlations as random effect. We used interval-censored proportional hazards regression to estimate the association between incident hypertension and the blood lead change. The baseline hazard function was modeled using cubic splines with 3 knots. The covariables considered were ethnicity (White versus others), sex, baseline age and blood lead, 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, total-to-HDL serum cholesterol ratio,  $\gamma$ -glutamyltransferase, and serum creatinine.

## Results

### Characteristics of Workers

Of 267 participants in the office blood pressure cohort, 31 were female (11.6%), 125 (46.8%) were White, 122 (45.7%) were Hispanic, and 20 (7.5%) had other self-reported ethnicities; among the 137 participants in the ambulatory blood pressure cohort, corresponding numbers were 14 (10.2%), 71 (51.8%), 61 (44.5%), and 5 (3.6%), respectively. In the office blood pressure cohort, at enrollment, age averaged 28.6 years, body mass index 28.6 kg/m<sup>2</sup>, serum creatinine 83.8 µmol/L, total and HDL serum cholesterol 4.4 and 1.2 mmol/L, the total-to-HDL serum cholesterol ratio 3.8, and serum  $\gamma$ -glutamyltransferase 21.5 U/L (Table S2). The baseline characteristics of the workers in the ambulatory blood pressure cohort were similar (Table S2).

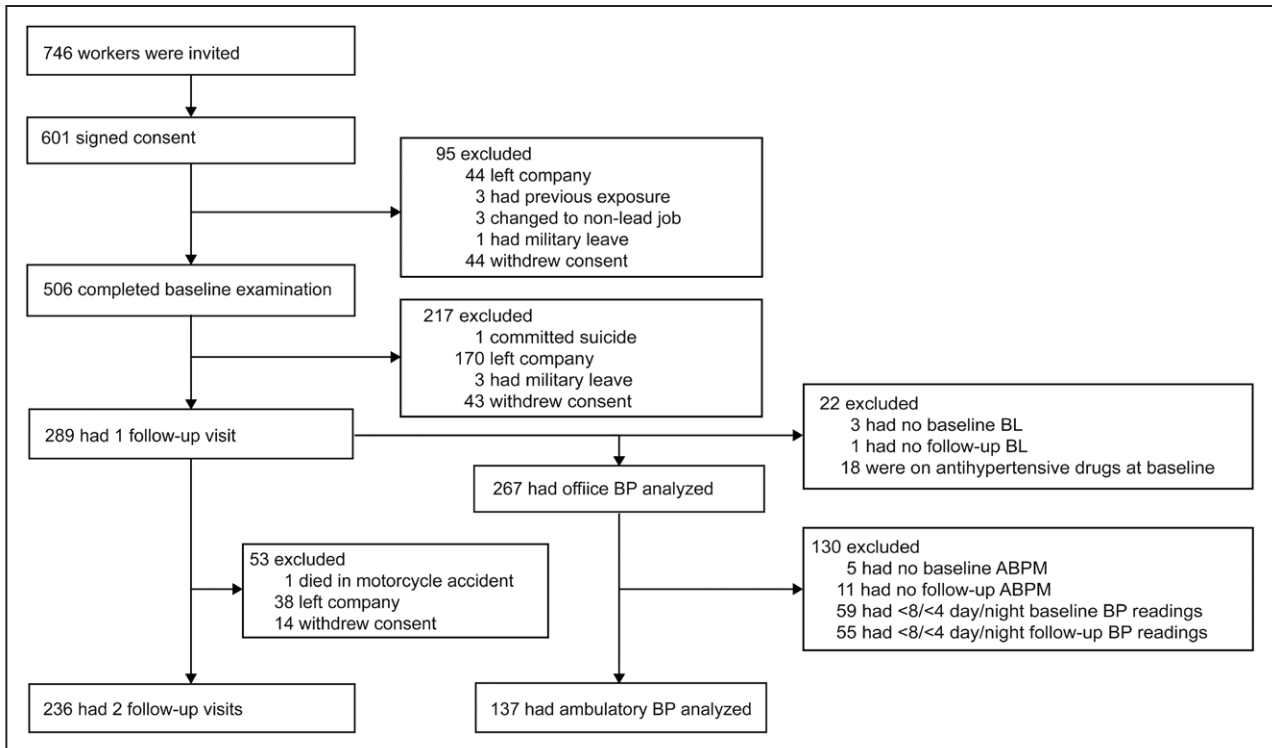


Figure 1. Flow chart. ABPM indicates ambulatory blood pressure monitoring; BL, blood lead level; and BP, blood pressure.

The office blood pressure readings obtained in 267 workers did not show number or terminal digit preference (Table S3). The median number of ambulatory blood pressure readings obtained over 24 hours in 137 participants was 33 at baseline (IQR, 29–40; fifth–95th PI, 22–52) and 23 at the last available follow-up (IQR, 18–29; fifth–95th PI, 14–41). The corresponding numbers for the awake and asleep blood pressures were 23 and 9 at baseline (IQR, 15–29 and 7–16; fifth–95th PI, 10–40 and 4–22), and 15 and 7 at last follow-up (IQR, 11–21 and 5–9; fifth–95th PI, 14–41 and 4–14).

**Blood Lead Concentration**

In the office blood pressure cohort, the geometric mean blood lead concentration was 4.09 µg/dL (fifth–95th PI, 0.90–15.2 µg/dL) at baseline and 13.5 µg/dL (fifth–95th PI, 3.10–30.8 µg/dL) at the last follow-up visit. In the ambulatory blood pressure cohort, the corresponding lead levels were 4.00 µg/dL (fifth–95th PI, 0.90–13.0 µg/dL) and 14.6 µg/dL (fifth–95th PI, 4.25–30.2 µg/dL). Thus, last-follow-up-to-baseline blood lead ratio averaged 3.30 (fifth–95th PI, 0.88–15.6) and 3.66 (fifth–95th PI, 0.94–16.2) in the office and ambulatory blood pressure groups, respectively (Figure S1).

**Analysis of the Office Blood Pressure Cohort**

In unadjusted analyses (Table 1), the office systolic/diastolic blood pressure increased by 3.4/1.4 mmHg (CI, 2.3–4.6/0.3–2.5 mmHg;  $P \leq 0.013$ ) from 119.7/79.4 mmHg at baseline to 123.1/80.8 mmHg at the last available follow-up. However, across fourths of the distribution of the changes in blood lead with correction for the baseline blood pressure applied (Table S4), greater increases in blood lead were not associated more rise in blood pressure ( $P_{\text{linear trend}} \geq 0.85$ ). In mixed models,

accounting for the clustering within participants, there was no association between the changes in blood pressure and in blood lead, if otherwise unadjusted or adjusted for sex and baseline age, blood pressure, and body mass index (Table 2). In fully adjusted models, the association sizes associated with a doubling of the follow-up-to-baseline blood lead ratio were 0.36 mmHg (CI, –0.55 to 1.27 mmHg) systolic and 0.28 mmHg (CI, –0.48 to 1.04 mmHg) diastolic (Table 2).

Cross-classification of the blood pressure categories demonstrated that 70 patients, normotensive at baseline, became hypertensive during follow-up (Table S5). Ninety-six workers developed new-onset stage-1 or higher office hypertension, 38 developed new-onset stage-2, severe or treated office hypertension, and 134 moved up across the blood pressure categories (Table 3). In unadjusted and adjusted analyses, none of the hazard ratios reached significance ( $P \geq 0.082$ ). For moving up across the office blood pressure categories, the fully adjusted hazard ratio was 1.13 (CI, 0.93–1.38).

**Analysis of the Ambulatory Blood Pressure Cohort**

In unadjusted analyses (Table 1), the 24-hour systolic blood pressure did not change, averaging 123.8 mmHg at baseline and 123.4 mmHg at follow-up (change, –0.4 mmHg; CI, –2.0 to 1.2 mmHg), whereas the 24-hour diastolic blood pressure increased by 1.0 mmHg (CI, 0.0–2.0 mmHg;  $P = 0.046$ ). Furthermore, across fourths of the distribution of the changes in blood lead with correction for the baseline level applied (Table S4), greater increases in blood lead were not associated more blood pressure rise ( $P_{\text{linear trend}} \geq 0.51$ ). In mixed models, there was no association between the changes in the 24-hour blood pressure and in blood lead in unadjusted, adjusted and fully adjusted models (Table 2). In fully adjusted models, the association sizes

Table 1. Baseline and Follow-Up Blood Pressures in the Office and Ambulatory Blood Pressure Cohorts

BP Index*	Baseline	Last Follow-Up	Δ (95% CI)†	P Value‡
Office BP cohort (n=267)				
Office systolic BP, mm Hg	119.7 (10.3)	123.1 (9.4)	3.4 (2.3 to 4.6)	<0.0001
Office diastolic BP, mm Hg	79.4 (8.8)	80.8 (7.3)	1.4 (0.3 to 2.5)	0.013
Ambulatory BP cohort (n=137)				
Office systolic BP, mm Hg	118.5 (9.2)	122.0 (10.1)	3.5 (1.9 to 5.1)	<0.0001
Office diastolic BP, mm Hg	78.9 (8.0)	80.2 (7.9)	1.4 (−0.2 to 2.9)	0.083
24-h systolic BP, mm Hg	123.8 (10.2)	123.4 (10.4)	−0.4 (−2.0 to 1.2)	0.63
24-h diastolic BP, mm Hg	73.0 (7.7)	74.0 (7.1)	1.0 (0.0 to 2.0)	0.046
Awake systolic BP, mm Hg	127.8 (11.0)	126.6 (10.5)	−1.2 (−2.9 to 0.5)	0.15
Awake diastolic BP, mm Hg	77.2 (7.9)	77.5 (7.5)	0.4 (−0.8 to 1.5)	0.53
Asleep systolic BP, mm Hg	115.0 (11.9)	116.5 (12.9)	1.5 (−0.9 to 3.8)	0.23
Asleep diastolic BP, mm Hg	63.6 (8.9)	66.2 (8.7)	2.6 (1.0 to 4.2)	0.0016
Dipping ratio systolic BP	0.90 (0.083)	0.92 (0.078)	0.02 (0.00 to 0.04)	0.050
Dipping ratio diastolic BP	0.83 (0.087)	0.86 (0.10)	0.03 (0.01 to 0.05)	0.0073

BP indicates blood pressure.

\*Values are means (SD) of blood pressure or changes in BP.

†Δ (95% CI) refers to the change from baseline to follow-up.

‡The P values denote the significance of the changes from baseline and to the last available follow-up.

associated with a doubling of the follow-up-to-baseline blood lead ratio were  $-0.18$  mmHg (CI,  $-2.09$  to  $1.74$  mmHg) systolic and  $0.11$  mmHg (CI,  $-1.05$  to  $1.27$  mmHg) diastolic for the 24-hour blood pressure (Table 2). Findings for the awake and asleep ambulatory blood pressure and for the dipping ratio were all nonsignificant in unadjusted and adjusted models (Table 2).

Cross-classification of the 24-hour blood pressure categories demonstrated that 6 patients, normotensive at baseline, became hypertensive on 24-hour ambulatory monitoring during follow-up (Table S6). Twenty-six workers developed new-onset stage-1 or higher 24-hour ambulatory hypertension, 20 developed new-onset stage-2, severe or treated 24-hour ambulatory hypertension, and 51 moved up across the blood pressure categories (Table 3). In unadjusted and adjusted analyses, none of the hazard ratios reached significance ( $P \geq 0.073$ ). For moving up across the 24-hour ambulatory blood pressure categories, the fully adjusted hazard ratio was  $0.84$  (CI,  $0.57$ – $1.22$ ).

## Heat Maps

Heat maps are 3-dimensional plots, in which one variable is plotted along the horizontal axis, one variable is plotted along the vertical axis, and a third variable is color-coded. Heat maps (Figure 2) showed that the baseline blood pressure was the main determinant of the systolic (Figure 2A and 2B) and diastolic (Figure 2C and 2D) blood pressure at the last available follow-up and of the probability of moving up across hypertension categories (Figure 2E and 2F). Fold change in the blood lead concentration did not reach significance ( $0.49 \leq P \leq 0.88$ ) in any of these analyses.

## Discussion

In a real-world experiment, among workers without known previous occupational exposure and taking up new jobs in lead

recycling and battery manufacturing plants, an over 3-fold increase in the blood lead concentration over the 2-year follow-up was not associated with a change in systolic or diastolic blood pressure or with a higher risk of developing new-onset hypertension. These results are in agreement with the previously published cross-sectional analysis of the SPHERL baseline data.<sup>12</sup> The heat maps demonstrated, as is true for all clinical measurements,<sup>19</sup> that the baseline blood pressure was the main determinant of blood pressure at follow-up (Figure 2). Due to regression to the mean workers with low blood pressure at enrollment were more likely to experience an increase in their office and ambulatory blood pressure or to move up across the American College of Cardiology/American Heart Association hypertension categories,<sup>13,18</sup> whereas the opposite was the case for workers in the top tail of the baseline blood pressure distribution. However, as shown in Table S7, there was no systematic shift in the blood pressure distributions from baseline to last follow-up. The association of mortality and cardiovascular complications with blood pressure as explanatory variable is strongest for the 24-hour and night-time blood pressure compared with any other blood pressure component,<sup>20</sup> supporting the guideline-based recommendation<sup>13,14</sup> to apply ambulatory monitoring as the state-of-the-art method in the assessment of blood pressure and the management of hypertension. On the contrary, when blood pressure is the response variable, associations with its determinants, such as age and body mass index, are weaker for the ambulatory than for office pressure,<sup>21</sup> a phenomenon now confirmed in the current longitudinal study (Figure 2A versus 2B and Figure 2C versus 2D). We applied the 2017 American College of Cardiology/American Heart Association thresholds for the categorization of blood pressure,<sup>13,18</sup> which explains the very high incidence of new-onset hypertension or of moving up across hypertension classes.



**Table 2. Associations Between Changes in Blood Pressure and in Blood Lead**

BP measurement	Unadjusted		Adjusted*		Fully Adjusted†	
	Estimate‡ (95% CI)	P Value	Estimate‡ (95% CI)	P Value	Estimate‡ (95% CI)	P Value
Office BP cohort (n=267)						
Office systolic BP, mmHg	0.28 (−0.55 to 1.10)	0.51	−0.10 (−0.75 to 0.56)	0.77	0.36 (−0.55 to 1.27)	0.43
Office diastolic BP, mmHg	0.15 (−0.62 to 0.91)	0.70	−0.27 (−0.81 to 0.28)	0.34	0.28 (−0.48 to 1.04)	0.47
Ambulatory BP cohort (n=137)						
Office systolic BP, mmHg	0.64 (−0.55 to 1.84)	0.29	0.03 (−0.99 to 1.05)	0.96	1.68 (0.06 to 3.30)	0.042
Office diastolic BP, mmHg	0.11 (−1.02 to 1.23)	0.85	−0.28 (−1.15 to 0.58)	0.51	1.05 (−0.43 to 2.54)	0.16
24-h systolic BP, mmHg	−0.16 (−1.40 to 1.07)	0.79	0.12 (−0.96 to 1.21)	0.82	−0.18 (−2.09 to 1.74)	0.85
24-h diastolic BP, mmHg	−0.22 (−1.02 to 0.58)	0.58	−0.13 (−0.79 to 0.54)	0.71	0.11 (−1.05 to 1.27)	0.85
Awake systolic BP, mmHg	−0.31 (−1.62 to 1.00)	0.64	−0.02 (−1.13 to 1.09)	0.98	−0.57 (−2.52 to 1.38)	0.56
Awake diastolic BP, mmHg	−0.09 (−0.97 to 0.78)	0.83	−0.05 (−0.79 to 0.70)	0.90	0.23 (−1.08 to 1.53)	0.73
Asleep systolic BP, mmHg	−0.09 (−1.80 to 1.63)	0.92	0.41 (−1.05 to 1.87)	0.58	1.01 (−1.57 to 3.59)	0.44
Asleep diastolic BP, mmHg	−0.29 (−1.44 to −0.87)	0.62	−0.18 (−1.13 to 0.78)	0.71	0.07 (−1.58 to 1.71)	0.93
Dipping ratio systolic BP	0.00 (−0.01 to 0.02)	0.74	0.00 (−0.01 to 0.01)	0.40	0.01 (−0.00 to 0.03)	0.12
Dipping ratio diastolic BP	−0.00 (−0.02 to 0.01)	0.74	−0.00 (−0.01 to 0.01)	0.82	0.01 (−0.02 to 0.02)	0.96

BP indicates blood pressure; and HDL, high-density lipoprotein.

\*Adjusted models accounted for sex and age, blood pressure, and body mass index at baseline.

†Fully adjusted models additionally accounted ethnicity (White versus other), change in body weight during follow-up, the baseline value of blood lead, and the baseline values of and the changes during follow-up in heart rate, smoking status, total-to-HDL serum cholesterol ratio,  $\gamma$ -glutamyltransferase, and serum creatinine.

‡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 including both the 1-year and 2-year changes in blood pressure and blood lead and accounting for clustering within participants using a random effect.

Various factors might explain why we failed to demonstrate any pressor response to new-onset occupational lead exposure over the 2 years of follow-up. Previous studies in workers suggest that the toxic effects of lead on the cardiovascular system occur at much higher blood lead levels than in the population, possibly as a consequence of the healthy worker effect.<sup>22</sup> The 2-year exposure of predominantly young and healthy adults might have been too short to result in a blood pressure rise. Within individuals office and ambulatory blood pressure are poorly reproducible even over short time intervals, so that a true blood pressure change might have been masked, because of reproducibility issues inherent to the blood pressure variability.<sup>23</sup> However, our current observations are in keeping with our previous research. In a meta-analysis of summary statistics extracted from 31 studies involving 58 518 participants, all published before February 2001,<sup>2</sup> doubling of blood lead was associated with a marginally higher blood pressure. The summative estimates averaged 1.0 mmHg (CI, 0.5–1.4 mmHg) systolic and 0.6 mmHg (CI, 0.4–0.8 mmHg) diastolic. In a prospective population study of 728 individuals (50.7% women; age range, 20–82 years), blood pressure was measured conventionally at baseline (1985–1989) and at follow-up (1991–1995), and by 24-hour ambulatory monitoring at follow-up.<sup>24</sup> Over a median follow-up of 5.2 years (range, 3.5–8.4 years), the geometric mean blood lead concentration dropped by 32% from the baseline level of 8.7  $\mu\text{g}/\text{dL}$  (range, 1.7–72.5  $\mu\text{g}/\text{dL}$ ). The small changes in the systolic/diastolic blood pressure on conventional measurement (−1.5/+1.7 mmHg) were unrelated to the blood lead concentration at baseline or to the blood lead changes over follow-up. Similarly, the 24-hour

ambulatory blood pressure was not associated with blood lead at baseline or follow-up.<sup>24</sup> An analysis of NHANES IV data (2003–2010) demonstrated weak and inconsistent associations of blood pressure with blood lead.<sup>5</sup> These observations based on close to present-day environmental lead exposure levels in the United States practically eliminated high blood pressure as the mechanism driving the association between cardiovascular or coronary mortality and blood lead in the United States.<sup>5</sup>

As reviewed elsewhere,<sup>25</sup> the concept that hypertension explains the association of total and cardiovascular mortality with lead exposure rests to a large extent on 3 NHANES III reports<sup>26–28</sup> and the 2012 Global Burden of Disease review.<sup>29</sup> The NHANES III participants had been recruited from 1988 until 1994. In particular, the 2018 report on the long-term association between mortality and blood lead over a median follow-up of 19.3 years<sup>28</sup> has little relevance for public health policies in the second decade of the 21st century. The justification for this assessment includes the nonrepresentativeness of NHANES III blood lead levels for contemporary exposure<sup>3–5</sup>; the excessively low threshold for which the population attributable risk fraction of mortality in relation to blood lead was computed (blood lead concentration below 1.0  $\mu\text{g}/\text{dL}$ )<sup>28</sup>; the absence of a firmly proven causal pathway linking mortality to lead at present-day environmental exposure levels<sup>30</sup>; the neglect to consider competing risks and residual confounding<sup>25</sup>; and the drastic reduction over the past 20 years in the case-fatality rates associated with coronary, cerebrovascular and other vascular accidents by application of modern pharmacological and invasive therapies. Furthermore, the baseline blood lead concentrations in NHANES III (1988–1994), with higher

Table 3. Hazard Ratios for Incident Hypertension in Relation to Blood Lead Changes in the Office and Ambulatory Blood Pressure Cohorts

Cohort	n/N*	Unadjusted		Adjusted†		Fully Adjusted‡	
		HR§ (95% CI)	P Value	HR§ (95% CI)	P Value	HR§ (95% CI)	P Value
Office BP cohort (n=267)							
Hypertension≥stage 1	96/139	1.17 (0.98–1.39)	0.082	1.15 (0.96–1.38)	0.12	1.18 (0.90–1.54)	0.24
Hypertension≥stage 2	38/231	0.89 (0.70–1.12)	0.31	0.87 (0.69–1.10)	0.25	1.01 (0.71–1.43)	0.94
Moving up categories	134/267	1.11 (0.98–1.27)	0.11	1.08 (0.95–1.23)	0.24	1.13 (0.93–1.38)	0.22
Ambulatory BP cohort (n=137)							
Office hypertension							
Hypertension≥stage 1	44/74	1.03 (0.80–1.32)	0.83	1.04 (0.81–1.34)	0.76	0.93 (0.59–1.47)	0.76
Hypertension≥stage 2	11/121	0.79 (0.49–1.28)	0.34	0.83 (0.51–1.35)	0.45	2.02 (0.42–9.62)	0.38
Moving up categories	55/137	0.99 (0.81–1.22)	0.93	0.96 (0.78–1.18)	0.70	1.16 (0.77–1.74)	0.47
24-h ambulatory hypertension							
Hypertension≥stage 1	26/69	1.09 (0.82–1.45)	0.54	1.10 (0.82–1.47)	0.53	1.12 (0.59–2.11)	0.74
Hypertension≥stage 2	20/93	1.37 (0.94–1.94)	0.073	1.25 (0.89–1.77)	0.20	1.20 (0.51–2.83)	0.67
Moving up categories	51/137	0.98 (0.79–1.21)	0.84	0.98 (0.79–1.22)	0.86	0.84 (0.57–1.22)	0.35

ACC indicates American College of Cardiology; AHA, American Heart Association; BP, blood pressure; HDL, high-density lipoprotein; and HR, hazard ratio.

\*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 at risk of moving up categories. Moving up categories indicates an increase in the blood pressure category by one or more steps during follow-up.

†Adjusted models accounted for sex, age, baseline body mass index, and baseline mean blood pressure, that is, diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure.

‡Fully adjusted models additionally accounted for ethnicity (White versus other), change in body weight during follow-up, the baseline value of blood lead, and the baseline value of and change during follow-up in heart rate, smoking status, total-to-HDL serum cholesterol ratio,  $\gamma$ -glutamyltransferase, and serum creatinine.

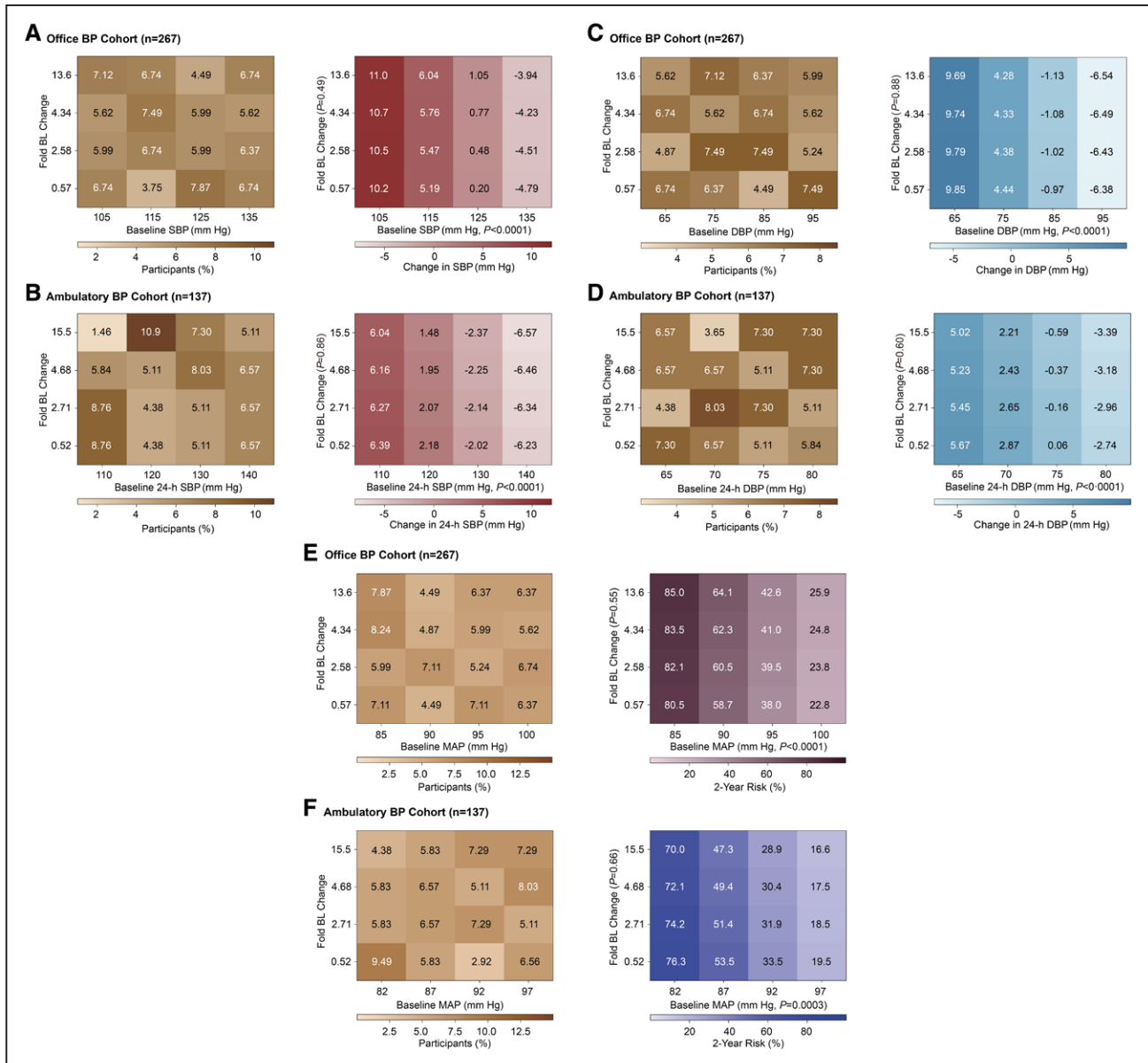
§HR, given with 95% CI, were obtained from proportional hazard models for interval-censored data, using a cubic spline function to model the baseline hazard. HRs express the risk associated with a doubling of the follow-up-to-baseline blood lead level.

||Stage-1, stage-2, and severe office hypertension were systolic or diastolic levels of 130–139/80–89, 140–159/90–99, and  $\geq 160/\geq 100$  mm Hg, respectively. The corresponding thresholds for 24-h ambulatory hypertension were 125–129/75–79, 130–144/80–89, and  $\geq 145/\geq 90$  mm Hg, respectively. Hypertension was categorized according to the 2017 ACC/AHA guideline (Whelton et al<sup>13</sup> and Cheng et al<sup>18</sup>), irrespective of treatment status. If systolic and diastolic blood pressure were in different categories, the highest category was applied.

age, increasingly represented the preexisting body burden<sup>31,32</sup> originating from the historical environmental lead contamination. In the United States, lead-containing paint was effectively banned in 1976, and leaded gasoline was completely phased out in 1995.<sup>33</sup> Furthermore, the Global Burden of Disease investigators assumed that lead exposure, via its pressor effect, was a direct cause of a panoply of illnesses,<sup>29</sup> including: right heart disease; ischemic heart disease; ischemic, hemorrhagic and other nonischemic stroke; hypertensive heart disease; aortic aneurysm; the aggregate of cardiomyopathy, myocarditis and endocarditis; the aggregate of atrial fibrillation and flutter; pulmonary vascular disease; other cardiovascular disease; and chronic kidney disease.<sup>34</sup> We did not observe any incident cases of these illnesses among the SPHERL participants. The Global Burden of Disease investigators listed among possible limitations of their results: residual confounding; uncertainty as to the extent to which effect sizes were worldwide generalizable; and the impossibility to account for temporal changes in the exposure to risk factors.<sup>29</sup>

Strong points of our study are the use of ambulatory blood pressure monitoring and the stringent quality control of the blood lead concentration with detection limit as low as 0.5  $\mu\text{g}/\text{dL}$  (Method in the [Data Supplement](#)). However, our study also has limitations. First, the attrition rate among the 506 workers, who had undergone a baseline examination but defaulted from

follow-up, amounted to 217 (42.9%). According to the protocol paper,<sup>11</sup> the anticipated attrition rate was 50%, and 500 workers had to be enrolled. We met these numbers. The baseline characteristics of workers with or without follow-up were grossly similar (Table S8), so that it is unlikely that cohort attrition significantly biased the study results. Second, the median follow-up of 2.0 years (fifth–95th percentile interval, 1.5–2.3 years) might have been too short for pressor effects associated with lead exposure to become evident. For this reason, as anticipated,<sup>11</sup> the cohort will be kept in follow-up for an additional 2 years. Third, we met our prespecified sample size for office blood pressure, but not for the 24-hour ambulatory blood pressure. With the 2-sided significance set at 5% and power at 90%, approximately 260 participants had to be followed up for 2 years. The workers enrolled in SPHERL were mostly engaged in physically demanding jobs and in shift work. The discomfort caused by the cuff inflations during strenuous work and sleep<sup>35,36</sup> explained why many workers declined ambulatory monitoring or had recordings with an insufficient number of readings either at baseline or at follow-up<sup>16</sup> and had, therefore, to be removed from analysis (Figure 1). Fourth, 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. Finally, the dipping ratio has little prognostic significance once the 24-hour



**Figure 2.** Heat maps relating the change in office and ambulatory blood pressure (BP) and the risk of moving up across hypertension categories to the blood pressure level at baseline and the fold change in blood lead (BL) from baseline to last follow-up. For systolic BP (SBP; **A** and **B**) and diastolic BP (DBP; **C** and **D**), the associations were derived by mixed models (see Table 2) and for the risk of moving up across hypertension categories (**E** and **F**) by interval-censored proportional hazards regression (see Table 3). All models were fully adjusted. The percentage of participants contributing to the cross-classification between the baseline blood pressure (horizontal axis) and the fold change in BL are given for each analysis run. For moving up across the hypertension categories, MAP was plotted along the horizontal axis, that is, diastolic blood pressure plus one-third of pulse pressure, because the ACC/AHA hypertension criteria rest on both systolic and diastolic blood pressure thresholds. MAP indicates mean arterial pressure.

or night-time blood pressure level are known.<sup>20</sup> In addition, the participants in the present study were shift worker, and the day of ambulatory blood pressure monitoring was not standardized with regards to the start of a shift cycle (early and late day and night shifts).<sup>37</sup>

### Perspectives

We failed to demonstrate any association of change in blood pressure or the risk of new-onset hypertension in workers exposed to an over 3-fold increase in their blood lead concentration. Lead exposure represents an occupational and environmental health hazard that should be addressed worldwide. However, if there is no causal link between hypertension and

lead exposure, as our findings suggest, current recommendations, as voiced by the Environmental Protection Agency<sup>7-9</sup> or the American College of Occupational and Environmental Medicine<sup>10</sup> might consume resources that could be spent more effectively in the prevention of cardiovascular disease and premature mortality. This reflection might inform policy planners designing lead exposure thresholds for the general population and for occupational settings.

### Acknowledgments

We acknowledge the nursing staff employed at the study sites in the United States and the expert clerical assistance of Vera De Leebeek and Renilde Wolfs.

## Sources of Funding

The International Lead Association ([www.ila-lead.org](http://www.ila-lead.org)) provided an unrestricted grant to the Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, partially supporting database management and statistical analysis. NPA Alliance for the Promotion of Preventive Medicine received a nonbinding grant from OMRON Healthcare Co Ltd, Kyoto, Japan.

## Disclosures

None.

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## Novelty and Significance

### What Is New?

- Lead exposure causing hypertension is the mechanism commonly assumed to lead to fatal and nonfatal cardiovascular disease. However, at current exposure levels, the link between hypertension and lead remains unproven. We recorded the 2-year responses of office and ambulatory blood pressure to first occupational lead exposure in workers newly employed at lead recycling plants.

### What Is Relevant?

- Over follow-up, blood lead increased to 3.30 times above the baseline level of 4.09  $\mu\text{g}/\text{dL}$ .
- For a doubling of the baseline-to-follow-up blood lead ratio, the multi-variable-adjusted association sizes were 0.36/0.28 mmHg for systolic/diastolic office blood pressure ( $P \geq 0.43$ ) and 0.18/0.11 mmHg the 24-hour ambulatory blood pressure ( $P \geq 0.44$ ).

- The adjusted hazard ratios for moving up across hypertension categories were 1.13 and 0.84 for office and ambulatory blood pressure, respectively ( $P \geq 0.22$ ).

### Summary

The 2-year blood pressure responses and incident hypertension were not associated with the blood lead increase on first occupational exposure. Lead exposure represents an occupational and environmental health hazard that should be addressed worldwide. However, if there is no causal link between hypertension and lead exposure, current recommendations for reducing lead exposure thresholds might have to be revised.