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Research Article

Association of office and ambulatory blood pressure with blood lead in workers before occupational exposure

Wen-Yi Yang, MD[a], Ljupcho Efremov, MD[a], Blerim Mujaj, MD, PhD[a], Zhen-Yu Zhang, MD[a], Fang-Fei Wei, MD[a], Qi-Fang Huang, MD, PhD[a], Lutgarde Thijs, MSc[a], Thomas Vanassche, MD, PhD[b], Tim S. Nawrot, PhD[c], and Jan A. Staessen, MD, PhD[a,d,*]

[a]*Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium;*

[b]*Department of Cardiology, University Hospitals Leuven, Leuven, Belgium;*

[c]*Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium; and*

[d]*Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands*

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Abstract

In view of decreasing lead exposure and guidelines endorsing ambulatory above office blood pressure (BP) measurement, we reassessed association of BP with blood lead (BL) in 236 newly employed men (mean age, 28.6 years) without previous lead exposure not treated for hypertension. Office BP was the mean of five auscultatory readings at one visit. Twenty-four-hour BP was recorded at 15- and 30-minute intervals during wakefulness and sleep. BL was determined by inductively coupled plasma mass spectrometry. Systolic/diastolic office BP averaged 120.0/80.7 mm Hg, and the 24-hour, awake, and asleep BP 125.5/73.6, 129.3/77.9, and 117.6/65.0 mm Hg, respectively. The geometric mean of blood lead was 4.5 μg/dL (interquartile range, 2.60–9.15 μg/dL). In multivariable-adjusted analyses, effect sizes associated with BL doubling were 0.79/0.87 mm Hg ($P = .11/.043$) for office BP and 0.29/−0.25, 0.60/−0.10, and −0.40/−0.43 mm Hg for 24-hour, awake, and asleep BP ($P \geq .33$). Neither office nor 24-hour ambulatory hypertension was related to BL ($P \geq .14$). A clinically relevant white coat effect (WCE; office minus awake BP, ≥20/≥10 mm Hg) was attributable to exceeding the systolic or diastolic threshold in 1 and 45 workers, respectively. With BL doubling, the systolic/diastolic WCE increased by 0.20/0.97 mm Hg ($P = .57/.046$). Accounting for the presence of a diastolic WCE, reduced the association size of office diastolic BP with BL to 0.39 mm Hg (95% confidence interval, −0.20 to 1.33; $P = .15$). In conclusion, a cross-sectional analysis of newly hired workers before lead exposure identified the WCE as confounder of the association between office BP and BL and did not reveal any association between ambulatory BP and BL. J Am Soc Hypertens 2018;12(1):14–24.

Keywords: Hypertension; lead; occupational medicine; white coat hypertension.

W.-Y.Y. and L.E. contributed equally to this article.

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*Corresponding author: Jan A. Staessen, MD, PhD, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Campus int Rafaël, Kapucijnenvoer 35, Box 7001, BE-3000 Leuven, Belgium. Tel: +32-16-34-7104 (office), +32-47-632-4928 (mobile); Fax: +32-16-34-7106 (office).

E-mails: jan.staessen@med.kuleuven.be, ja.staessen@maastrichtuniversity.nl

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Introduction

Whereas high-level lead exposure leads to hypertension, there is no consensus as to whether low-level lead exposure raises blood pressure (BP) and by this mechanism contributes to cardiovascular complications.[1,2] Lead studies traditionally relied on office BP measurement. Using this approach entails inaccuracy originating in patients, for instance as a consequence of arousal,[3] in the BP measuring device, or in the overall application of the technique.[4] In the auscultatory approach, the observer is the principal source of bias.[4] Ambulatory monitoring substantially refines the precision of BP measurement because of the greater number of readings, the absence of digit preference and observer bias, and the minimization of the white coat effect (WCE).[3,5] Guidelines in North America[6,7] and Europe[5,8] unanimously recommend ambulatory monitoring as the method of choice to record BP.

In the light of falling environmental lead exposure,[9–11] agencies such as the National Toxicology Program[12] and the Environmental Protection Agency[13,14] reviewed the literature in weight-of-the-evidence analyses[15] and suggested that blood lead levels as low as 5 μg/dL might be associated with adverse health effects.[12–15] Along similar lines, in 2010, the American College of Occupational and Environmental Medicine requested that the US Occupational and Health Administration (OSHA) align itself with the scientific evidence, referring in particular to hypertension and cardiovascular disease.[16] However, 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.[17] Using the baseline data of the ongoing Study for Promotion of Health in Recycling Lead (SPHERL[18]; NCT02243904), we assessed the association between BP and blood lead, using both office and ambulatory BP measurement, in newly hired workers before occupational lead exposure.

Methods

Study Participants

SPHERL complies with the Helsinki declaration for investigations in human subjects.[19] All participants provided written informed consent. The Ethics Committee of the University Hospitals Leuven (Belgium) approved the study protocol published elsewhere.[18] In short, the nursing staff at a lead–acid battery manufacturing and recycling plant in the United States enrolled (2015–2017) new hires for detailed health evaluations before blood lead elevations associated with occupational exposure. By May 1, 2017, 336 of 490 invited men (68.6%) consented to participate. Of those, we excluded 100 workers, who declined ambulatory BP monitoring (n = 24) or who had fewer than 7 or 3 ambulatory readings during wakefulness and sleep (n = 56), patients on antihypertensive drug treatment (n = 13) and workers with blood lead measurement not yet available at the time of writing of this article (n = 7). The number of workers statistically analyzed, therefore, totaled 236.

Office BP Measurement

Office BP was measured according to current guidelines[20–22] with application of a stringent quality control program.[23,24] At the enrolment visit, nurses measured the workers' upper arm circumference. Standard cuffs had a 12 × 24 cm inflatable portion, but if upper arm girth exceeded 31 cm, larger cuffs with 15 × 35 cm bladders were used. BP measurements were obtained on the nondominant arm, unless at recruitment, the systolic or diastolic BP differences between both arms were 10 mm Hg or more. In this case, the cuffs for office and ambulatory BP measurement were applied to the arm giving the highest BP reading. After the workers had rested for 5 minutes in the sitting position, nurses obtained five consecutive BP readings to the nearest 2 mm Hg, using a standard mercury sphygmomanometers. The five readings were averaged for analysis. Heart rate was counted over 15 seconds. Terminal digit preference and number preference were the criteria applied for quality control of the office BP. Terminal digit preference refers to the observer rounding off the BP reading to a digit of her or his choosing, most often five or zero.[23,24] Number preference refers to the number of identical BP readings made by an observer within participants.[24]

At the enrollment visit, nurses administered standardized questionnaires providing information on each worker's medical history, smoking and drinking habits, use of medications, and previous occupational exposure. Body mass index was weight in kilograms divided by squared height in meters. The waist-to-hip ratio was waist circumference divided by hip circumference.

Ambulatory BP Monitoring

The ambulatory BP was recorded using validated[25] oscillometric Mobil-O-Graph 24-hour PWA monitors (I.E.M. GmbH, Stolberg, Germany), which 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. If the ambulatory recordings were longer than 1 day, only the first 24 hours were analyzed. The same SAS macro processed all recordings. Intra-individual means of the BP readings over 24 hours and during the awake and asleep periods were weighted by the time interval between successive readings.[26]

Having both office and 24-hour BP allows categorizing individuals.[27] Office hypertension is an office BP of at least 140 mm Hg systolic or 90 mm Hg diastolic. The corresponding thresholds for ambulatory hypertension are 130 mm Hg systolic and 80 mm Hg diastolic for the 24-hour BP and 135 mm Hg and 85 mm Hg and 120 mm Hg and 70 mm Hg for the awake and asleep BP, respectively.[27] Truly normotensive people and hypertensive patients have a consistently normal or elevated BP on office and awake ambulatory measurement.[27] White coat hypertension is a high office BP in the presence of a normal awake BP. Its counterpart, masked hypertension, is characterized by a normal office BP, but an elevated awake BP.[27] If systolic and diastolic BP resulted in discordant categories, we used the highest BP to classify individuals. We computed the WCE by subtracting the awake from the office BP and considered it clinically relevant if the office BP was at least 20 mm Hg systolic or 10 mm Hg diastolic higher than the awake BP.[5]

Biochemical Measurements

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 laboratory certified for blood lead analysis in compliance with the provisions of the OSHA Lead Standard, 29CFR 1910.1025 (Occupational Safety and Health Administration). This laboratory participates 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 ran along with the samples in each test run was $<$10%. Measurements on serum included total and high-density lipoprotein (HDL) cholesterol, cystatin C, and γ-glutamyltransferase (index of alcohol intake). The estimated glomerular filtration rate (eGFR) was derived from serum cystatin C, using the equation proposed by the Chronic Kidney Disease-Epidemiology Collaboration.[28]

Database Management and Statistical Analysis

For database management and statistical analysis, we used SAS software version 9.4 (Cary, NC, USA). The Studies Coordinating Centre (Leuven, Belgium) developed electronic case report forms as interactive PDF forms, which the study nurses completed at the study side. XML files exported from the PDFs were uploaded to a secured server in Leuven. After quality control and addition of the codes for symptoms, diseases, and concurrent medications, the XML files were directly imported into the SAS database, using the SAS XML Mapper, version 9.4.

Departure from normality was evaluated by Shapiro-Wilk's statistic. Skewness and kurtosis were computed as the third and fourth moments about the mean divided by the cube of the standard deviation (SD). To approximate the normal distribution, blood lead and γ-glutamyltransferase were logarithmically transformed. 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. In exploratory analyses, we assessed the characteristics and the BP of workers across fourths of the blood lead distribution. Next, we applied multivariable-adjusted linear and logistic regression to relate BP indexes as continuous or categorical outcomes with the blood lead concentration while adjusting for physiologically relevant covariables: first, for age and body mass index, and in a second step, additionally for heart rate, waist-to-hip ratio, current smoking, γ-glutamyltransferase, total-to-HDL cholesterol ratio, and eGFR. Significance was a two-tailed α-level of $\leq$.05.

Results

Characteristics of Participants

The 236 workers included 108 Hispanics (45.8%), 113 Whites (47.9%), and 15 (6.3%) of Black (n = 7), Asian (n = 1), or mixed (n = 7) descent. The prevalence of smoking and self-reported alcohol intake was 28.4% (n = 67) and 47.0% (n = 111), respectively. Among all men, mean values ($\pm$SD) were 28.6 $\pm$ 9.4 years (5th–95th percentile interval, 19.3–48.7 years) for age, 28.2 $\pm$ 5.5 kg/m^2 for body mass index, 4.39 $\pm$ 0.89 mmol/L and 1.20 $\pm$ 0.30 mmol/L for total and HDL cholesterol, and 129.9 $\pm$ 13.6 mL/min/1.73 m^2 for eGFR. None of the workers had a history of cardiovascular disease and 2 (0.9%) had diabetes mellitus.

The blood lead concentration ranged from 0.60 to 32.0 μg/dL (Figure 1). The geometric mean blood lead level was 4.50 μg/dL (IQR, 2.60–9.15). Ethnicity, lifestyle habits and anthropometric characteristics, eGFR, and serum γ-glutamyltransferase did not differ ($P \geq .28$) across fourths of the blood lead distribution (Table 1). Total cholesterol and the total-to-HDL cholesterol ratio decreased with increasing blood lead (Table 1). Among 23 workers (9.8%), who reported previous occupational exposure, the geometric mean blood lead level was 3.88 μg/dL (IQR, 1.8–8.2; range, 0.9–12.3).

Office BP

Within individual participants, there were no missing office BP readings in each series of five measurements. Of 2360 systolic plus diastolic BP readings, 581 (24.6%) terminated on 0, 493 (20.9%) on 2, 381 (16.1%) on 4, 360 (15.3%) on 6, and 545 (23.1%) on 8. None of the

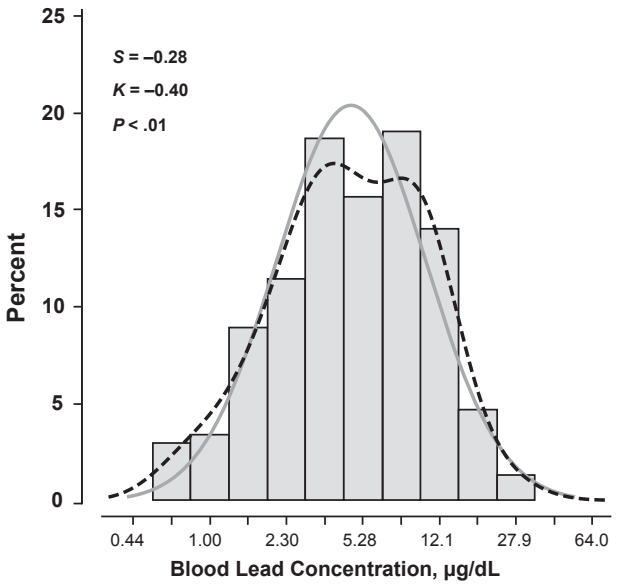

Figure 1. The logarithmically transformed distribution of blood lead. *S* and *K* are the coefficients of skewness and kurtosis. The *P* value is for departure of the actually observed distribution (dashed line) from normality (full line) according to the Shapiro-Wilk statistic.

office readings ended on an odd number. The five consecutive BP readings obtained in individual workers were identical in only one (0.42%) for systolic pressure and in none for diastolic pressure. In all participants, office BP averaged 120.0 ± 9.6 mm Hg systolic and 80.7 ± 8.2 mm Hg diastolic. The corresponding systolic and diastolic levels in 113 Whites, 108 Hispanics, and 15 workers of other ethnicities were 121.1 ± 9.2 and 81.3 ± 7.9 mm Hg, 118.8 ± 9.9 and 79.9 ± 8.4 mm Hg, and 120.0 ± 9.9 and 81.4 ± 9.6 mm Hg, respectively, with no significant differences between ethnicities ($P \geq .21$). In exploratory analyses, office systolic and diastolic pressure did not show any trend ($P \geq .15$) across the fourths of the blood lead concentration (Table 2). In regression analysis (Table 3), office systolic and diastolic pressure tended to increase with blood lead. These associations were consistent in unadjusted and adjusted analyses and were not dependent on the degree of adjustment. The effect sizes for a doubling of blood lead were around 0.8 mm Hg systolic and 0.9 mm Hg diastolic but reached significance ($P \leq .045$) for diastolic pressure only. After exclusion of 47 workers with a blood lead concentration ≥10 µg/dL, the association size with diastolic pressure remained similar but lost significance (0.85 mm Hg; 95% confidence interval, −0.25 to 1.96, $P = .13$).

Table 1
Characteristics of workers by fourths of the blood lead distribution

Characteristic	Blood Lead Limits, mg/dL				*P*
	<2.7	2.7–4.6	4.6–9.2	≥9.2	
No. of participants in category	61	58	58	59	
No. of participants (%)					
Ethnicity					
Hispanic	29 (47.5)	27 (46.5)	22 (37.9)	30 (50.8)	.97
Non-Hispanic White	28 (45.9)	24 (41.4)	36 (62.1)*	25 (42.4)*	.73
Other	4 (6.6)	7 (12.1)	0 (0)	4 (6.8)	.43
Smokers	15 (24.6)	18 (31.0)	19 (32.8)	15 (25.4)	.86
Drinking alcohol	28 (45.9)	32 (55.2)	27 (46.6)	24 (40.7)	.41
Mean (±SD) of characteristic					
Anthropometrics					
Age, y	26.9 ± 6.6	31.0 ± 10.4	28.2 ± 9.7	28.3 ± 10.3	.75
Body mass index, kg/m^2	27.9 ± 5.4	29.0 ± 6.3	28.5 ± 5.0	27.5 ± 5.3	.60
Waist-to-hip ratio	0.96 ± 0.08	0.98 ± 0.09	0.97 ± 0.08	0.97 ± 0.08	.63
Heart rate, bpm	72.4 ± 9.9	74.9 ± 12.7	73.8 ± 10.4	73.2 ± 12.5	.83
Biochemical data					
Total cholesterol, mmol/L	4.47 ± 0.80	4.54 ± 0.94	4.44 ± 0.97	4.12 ± 0.79	.027
HDL cholesterol, mmol/L	1.18 ± 0.27	1.17 ± 0.28	1.18 ± 0.30	1.29 ± 0.35	.060
Total/HDL cholesterol ratio	3.96 ± 1.13	4.1 ± 1.21	3.97 ± 1.34	3.39 ± 1.06	.0084
eGFR, mL/min/1.73 m^2	132.0 ± 11.5	127.9 ± 14.5	128.8 ± 13.6	130.9 ± 14.7	.73
γ-GT, units/L	22 (16–30)	24 (17–31)	21 (14–27)	20 (13–29)	.30

γ-GT, γ-glutamyltransferase measured as index of alcohol intake; eGFR, glomerular filtration rate estimated from serum cystatin C using the Chronic Kidney Disease Epidemiology Collaboration equation; HDL, high-density lipoprotein; SD, standard deviation.

For γ-glutamyltransferase, values are geometric mean (interquartile range).

P values are for linear trend.

Significance of the difference with the adjacent lower fourth: *$P \leq .05$.

Table 2
Blood pressure by fourths of the blood lead distribution

Blood Pressure Index	Blood Lead Limits, mg/dL				*P*
	<2.7	2.7–4.6	4.6–9.2	≥9.2	
No. of participants in category	61	58	58	59	
Office pressure, mm Hg					
Systolic	117.9 ± 8.9	120.0 ± 10.7	122.4 ± 9.9	119.7 ± 8.5	.15
Diastolic	78.6 ± 7.8	81.0 ± 10.1	81.9 ± 7	81.3 ± 7.6	.56
Ambulatory pressure, mm Hg					
24-h systolic	125.0 ± 9.6	125.3 ± 11.8	126.1 ± 10.9	125.5 ± 10.2	.71
24-h diastolic	73.5 ± 7.0	73.5 ± 7.9	74.5 ± 8.8	73.1 ± 8.0	.97
Awake systolic	128.6 ± 10.4	128.6 ± 12.5	130.8 ± 12.0	129.4 ± 11.3	.48
Awake diastolic	77.6 ± 7.4	77.3 ± 8.7	79.4 ± 8.9	77.2 ± 8.6	.85
Asleep systolic	117.5 ± 11.5	118.8 ± 14.7	117.4 ± 12.1	116.8 ± 12.5	.63
Asleep diastolic	64.9 ± 8.4	65.7 ± 9.3	65.1 ± 10.7	64.5 ± 9.8	.77
White coat effect, mm Hg					
Systolic, mm Hg	−10.7 ± 9.9	−8.6 ± 10.4	−8.4 ± 11.4	−9.7 ± 11.6	.59
Diastolic, mm Hg	1.0 ± 7.1	3.7 ± 8.9	2.4 ± 8.9	4.1 ± 8.7	.094
Prevalence, %	7 (11.5)	10 (17.2)	14 (24.1)	14 (23.7)	.056
No. with hypertension (%)					
Office	7 (11.5)	12 (20.7)	8 (13.8)	7 (11.9)	.79
24-h	17 (27.9)	18 (31.0)	26 (44.8)	20 (33.9)	.25
Awake	17 (27.9)	19 (32.8)	23 (40.0)	24 (40.7)	.10
Asleep	26 (42.6)	28 (48.3)	26 (44.8)	22 (37.3)	.51
Cross-classification					
True normotension	42 (68.9)	37 (63.8)	33 (56.9)	34 (57.6)	.15
White coat hypertension	2 (3.3)	2 (3.4)	2 (3.4)	1 (1.7)	.63
Masked hypertension	12 (19.7)	9 (15.5)	17 (29.3)	18 (30.5)	.064
Sustained hypertension	5 (8.2)	10 (17.2)	6 (10.3)	6 (10.2)	.98

Blood pressure thresholds are ≥140/≥90 mm Hg for office hypertension and ≥130/≥80 mm Hg, ≥135/≥85 mm Hg, or ≥120/≥70 mm Hg for ambulatory hypertension over 24 h or during wakefulness or sleep. Prevalence of the white coat effect refers to an awake minus office blood pressure difference of ≥20 mm Hg systolic or ≥10 mm Hg diastolic. True normotensive and sustained hypertensive workers have a consistently normal or elevated blood pressure on office and ambulatory measurement during wakefulness. White coat hypertension is a high office blood pressure with normal awake ambulatory blood pressure. Masked hypertension is a normal office blood pressure combined with an elevated awake ambulatory blood pressure.

P values are for linear trend. None of the differences between adjacent columns reached significance.

The overall prevalence of office hypertension was 14.4% (n = 34) because of the systolic threshold in 3 (1.3%) participants, the diastolic threshold in 22 (9.3%), or both thresholds in 9 (3.8%). In unadjusted and adjusted analyses (Table 4), the risk of office hypertension was unrelated to the blood lead concentration ($P \geq .51$).

Ambulatory BP

The number of BP readings obtained by ambulatory monitoring ranged from 12 to 80 (median, 34; 5th–95th percentile interval, 17–51) over 24 hours, from 7 to 60 (median, 20; 5th–95th percentile interval, 9–39) during wakefulness and from 3 to 35 (median, 10; 5th–95th percentile interval, 3–24) during sleep. In all workers, the 24-hour BP averaged 125.5 ± 10.6 mm Hg systolic and 73.6 ± 7.9 mm Hg diastolic. The corresponding averages were 129.3 ± 11.5 mm Hg and 77.9 ± 8.4 mm Hg for BP during wakefulness and 117.6 ± 12.8 mm Hg and 65.0 ± 9.5 mm Hg for BP during sleep. The ambulatory BP levels did not differ between ethnicities ($P \geq .089$). Exploratory analyses did not reveal any trend ($P \geq .33$) in 24-hour, awake, or asleep ambulatory BP across fourths of the blood lead distribution (Table 2). Similarly, irrespective of adjustment (Table 3 and Figure 2), the 24-hour, awake, and asleep BPs were not related to the blood lead concentration ($P \geq .31$). In unadjusted and adjusted analyses (Table 4), the risk of having ambulatory hypertension over the whole day or during sleep was not associated with blood lead ($P \geq .14$). However, having hypertension during wakefulness tended to increase with higher blood lead in unadjusted ($P = .11$) and adjusted ($P \geq .069$) models with an odds ratio for a doubling of blood lead of approximately 1.25.

Cross-Classification of Office and Ambulatory BP

In all participants, the WCE averaged −9.4 ± 10.8 mm Hg systolic ($P < .0001$) and 2.8 ± 8.5 mm Hg diastolic ($P < .0001$). There were no disparities in the systolic and

Table 3
Association of blood pressure with blood lead

Blood Pressure	Unadjusted Model		Adjusted Model		Fully Adjusted Model	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Office						
Systolic	0.82 (−0.23 to 1.87)	.12	0.78 (−0.19 to 1.74)	.11	0.79 (−0.17 to 1.76)	.11
Diastolic	0.92 (0.02 to 1.82)	.045	0.90 (0.06 to 1.74)	.036	0.87 (0.03 to 1.72)	.043
Ambulatory						
24-h systolic	0.15 (−1.01 to 1.32)	.80	0.24 (−0.85 to 1.34)	.66	0.29 (−0.82 to 1.41)	.60
24-h diastolic	−0.20 (−1.07 to 0.66)	.64	−0.26 (−0.97 to 0.46)	.48	−0.25 (−0.97 to 0.48)	.50
Awake systolic	0.48 (−0.78 to 1.75)	.45	0.60 (−0.59 to 1.79)	.32	0.60 (−0.61 to 1.81)	.33
Awake diastolic	−0.05 (−0.98 to 0.87)	.91	−0.08 (−0.86 to 0.71)	.84	−0.10 (−0.90 to 0.70)	.81
Asleep systolic	−0.57 (−1.96 to 0.82)	.42	−0.51 (−1.86 to 0.84)	.46	−0.40 (−1.77 to 0.97)	.57
Asleep diastolic	−0.37 (−1.41 to 0.67)	.49	−0.47 (−1.38 to 0.45)	.31	−0.43 (−1.35 to 0.50)	.37
White coat effect						
Systolic	0.34 (−0.85 to 1.53)	.57	0.18 (−0.97 to 1.33)	.76	0.20 (−0.96 to 1.35)	.57
Diastolic	0.97 (0.05 to 1.90)	.039	0.98 (0.06 to 1.90)	.037	0.97 (0.05 to 1.90)	.046

CI, confidence interval.

Partially adjusted models account for age and body mass index and fully adjusted models include as additional covariables heart rate, hip-to-waist circumference ratio, smoking, total-to-high-density lipoprotein cholesterol ratio, γ-glutamyltransferase, and estimated glomerular filtration rate. Estimates express the difference in blood pressure in mm Hg associated with a doubling of the blood lead concentration.

diastolic WCE ($P \geq .56$) between Whites (-9.7 ± 10.8 and 2.1 ± 7.5 mm Hg), Hispanics (-9.0 ± 10.7 and 3.4 ± 9.7 mm Hg), or other ethnicities (-9.4 ± 12.5 and 3.3 ± 6.1 mm Hg).

Overall, the prevalence of a clinically meaningful WCE of at least 20 mm Hg systolic or 10 mm Hg diastolic was 45 (19.1%), which was due to reaching the diastolic threshold in 44 and both the systolic (≥20 mmHg) and diastolic (≥10 mm Hg) thresholds in 1. In unadjusted ($P = .039$) and adjusted ($P \leq .043$) analyses, the odds of having a clinically relevant WCE increased by approximately 30% for a doubling of the blood lead concentration. Accounting for the presence of a diastolic WCE as categorical variable (0, 1) removed the significance of the association of office diastolic BP with blood lead (Figure 3). In fully adjusted models, the effect size of the association of office diastolic BP with blood lead was 0.39 mm Hg (95% confidence interval, −0.20 to 1.33; $P = .15$).

Discussion

The current OSHA lead standard was adopted in the late 1970s at a time when the geometric mean blood lead concentration in the US population was 12.8 μg/dL.[16] However, in successive rounds of the National Health Examination Survey (NHANES), mean blood lead levels among US adults decreased from 13.1 μg/dL in NHANES II (1976–1980)[9,10] to 1.64 μg/dL in NHANES IV (1999–2002).[11] Another issue that warrants reassessment of the association between BP and blood lead is the introduction of 24-hour

Table 4
Risk of hypertension in relation to blood lead

Hypertension	Unadjusted Model		Adjusted Model		Fully Adjusted Model	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Office hypertension	0.96 (0.70–1.31)	.79	0.89 (0.63–1.26)	.51	0.89 (0.62–1.28)	.52
24-h hypertension	1.17 (0.92–1.48)	.19	1.20 (0.93–1.55)	.15	1.21 (0.94–1.57)	.14
Awake hypertension	1.21 (0.96–1.53)	.11	1.27 (0.98–1.63)	.069	1.26 (0.98–1.64)	.073
Asleep hypertension	0.90 (0.72–1.12)	.35	0.89 (0.71–1.12)	.32	0.92 (0.73–1.16)	.46
White coat effect	1.37 (1.02–1.83)	.039	1.36 (1.01–1.82)	.041	1.36 (1.01–1.82)	.043

CI, confidence interval.

Blood pressure thresholds are ≥140/≥90 mm Hg for office hypertension and ≥130/≥80 mm Hg, ≥135/≥85 mm Hg, or ≥120/≥70 mm Hg for ambulatory hypertension over 24 h or during wakefulness or sleep. The white coat effect refers to an awake minus office blood pressure difference of ≥20 mm Hg systolic or ≥10 mm Hg diastolic. Partially adjusted models account for age and body mass index and fully adjusted models include as additional covariables heart rate, hip-to-waist circumference ratio, smoking, total-to-high-density lipoprotein cholesterol ratio, γ-glutamyltransferase, and estimated glomerular filtration rate. Estimates are odds ratios (95% CI) associated with a doubling of the blood lead concentration.

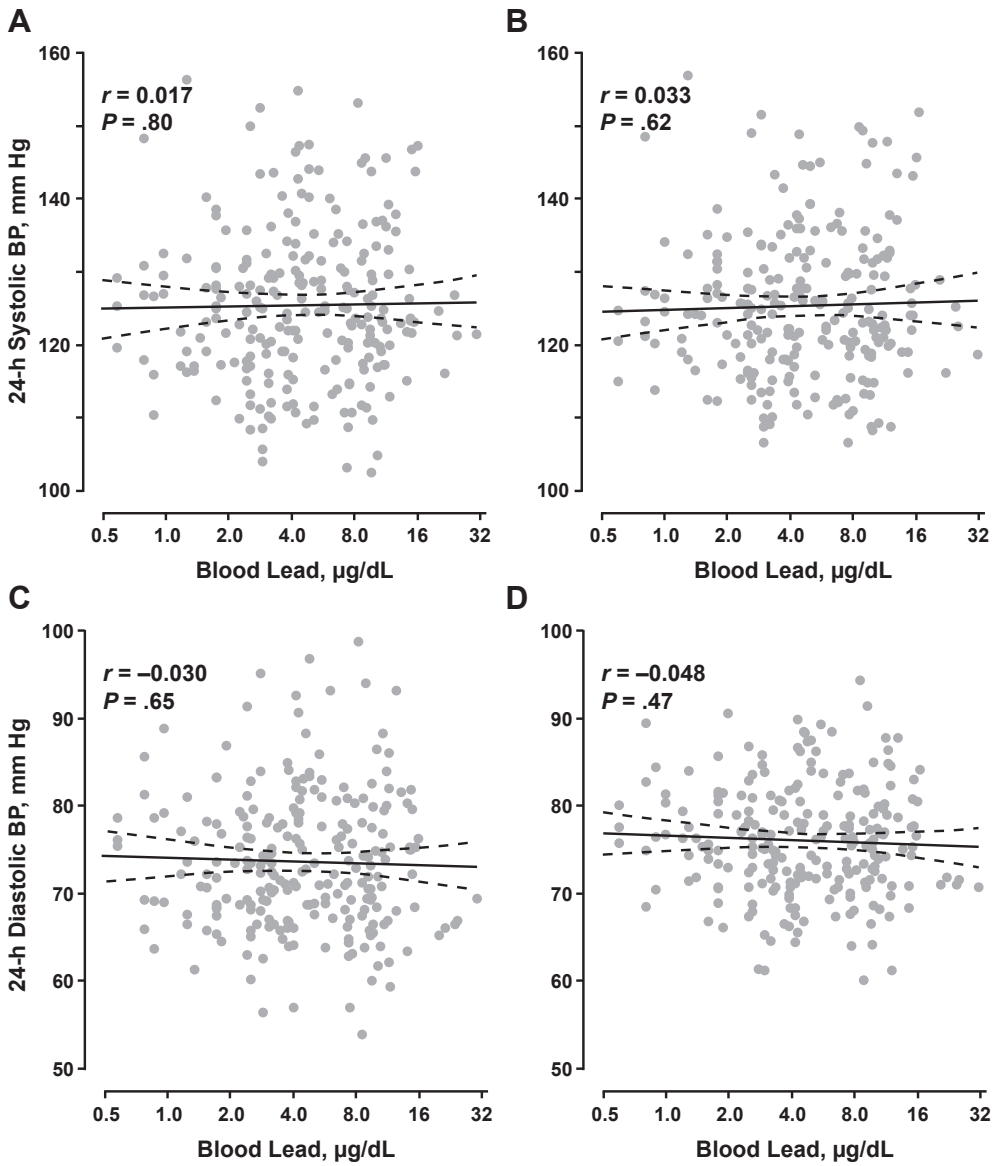

Figure 2. Plot of the association of ambulatory 24-h systolic (A and B) and diastolic (C and D) blood pressure (BP) with blood lead unadjusted (A and C) or with multivariable adjustment (B and D). *r* and *P* indicate the single (A and C) or partial (B and D) correlation coefficients and associated statistical significance. The regression line is depicted with 95% confidence interval.

ambulatory monitoring as the technology of choice to measure BP.[5–8] In the present study, we assessed the association of BP with blood lead in 236 newly hired workers before occupational lead exposure, at a geometric mean lead concentration of 4.5 μg/dL. The key findings were (1) on office measurement, BP tended to be higher with elevated blood lead concentration with effect sizes for a doubling of the exposure of around 0.8 mm Hg systolic ($P \geq .11$) and 0.9 mm Hg diastolic ($P \leq .045$); (2) the 24-hour, awake, and asleep systolic and diastolic BPs in unadjusted and multivariable-adjusted analyses were unrelated to the blood lead concentration; (3) the risk of office or ambulatory hypertension was not correlated with blood lead; (4) and the WCE explained the significant association of office diastolic BP with blood lead.

With regard to the association of BP with lead exposure, a meta-analysis of 58,518 subjects, recruited from the general population in 119 surveys and from occupationally exposed workers in 12 studies, documented for a doubling of blood lead a 1.0 mm Hg increase in systolic BP and a 0.6 mm Hg increase in diastolic BP.[1] All 131 studies with the exception of one[29] exclusively applied conventional in-office BP measurement. Some large studies, which supported a positive relation between office BP and blood lead, based their conclusions on a single BP reading and would therefore grossly fail current quality criteria.[30,31] In a

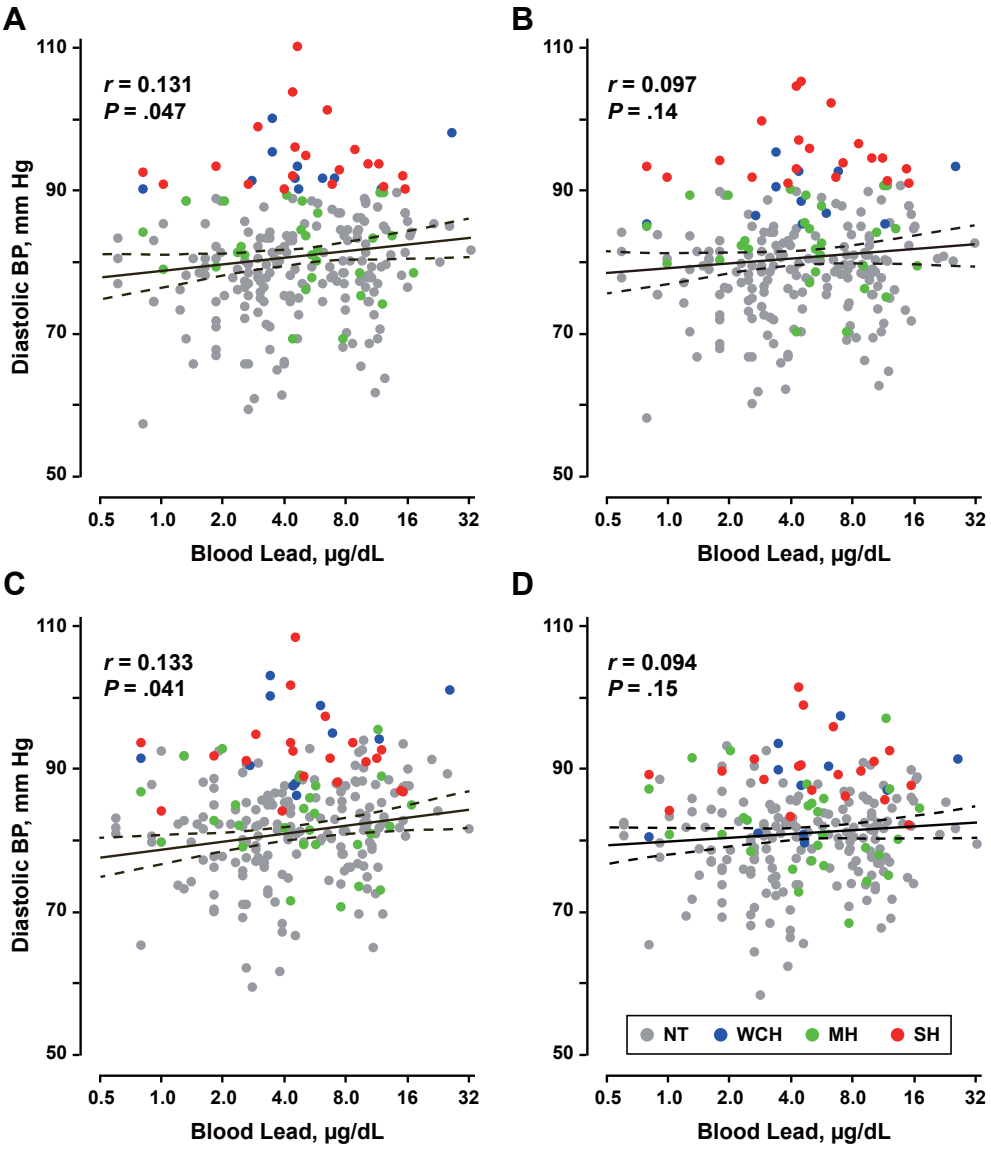

Figure 3. Plot of the association of office diastolic blood pressure (BP) with blood lead unadjusted (A) or with multivariable adjustment (C). Accounting for the presence of a clinically relevant diastolic white coat effect (office minus awake diastolic BP $\geq$ 10 mm Hg; panels B and D) removed the significance of the association of office diastolic BP with blood lead. *r* and *P* indicate the single (A) or partial (B–D) correlation coefficients and associated statistical significance. The regression line is depicted with 95% confidence interval. NT, WCH, MH, and SH indicate workers with true normotension or with white coat, masked, or sustained hypertension cross-classified based on office and awake ambulatory diastolic pressure.

Flemish longitudinal study,[29] BP was the average of five auscultatory readings obtained at the participants' homes. At baseline (1985–1989), it averaged 130 mm Hg systolic and 77 mm Hg diastolic, and the geometric mean blood lead concentration was 8.7 µg/dL. Over 5.2 years of follow-up, blood lead dropped by 2.9 µg/dL (32%), systolic pressure decreased by 1.5 mm Hg, diastolic pressure increased by 1.7 mm Hg, and 47 participants became hypertensive. However, changes in BP and blood lead were unrelated and baseline blood lead did not predict incidence of hypertension (odds ratio for doubling of baseline lead, 1.2; confidence interval, 0.7–2.0). The 24-hour BP measured in 684 participants at follow-up (1991–1994) averaged 119 mm Hg systolic and 71 mm Hg diastolic and was unrelated to blood lead at baseline or follow-up.[29]

Using as keywords "blood pressure" and "blood lead," we conducted a PubMed search (July 21, 2017) to ascertain whether recent studies relating BP to blood lead had adopted the more accurate methodologies currently available for BP measurement. Our search identified 108 potentially relevant articles published since the conduct of our 2002 meta-analysis.[1] We excluded 78 articles as being irrelevant

based on title and/or abstract and carefully checked the 30 remaining articles for the methodology of BP measurement. All 30 articles with the exception of one[32] used conventional office BP readings. In the Canadian Health Measures Survey,[7] six BpTRU readings were taken in each participant (n = 4550; age range, 70–79 years) with the last five averaged to determine systolic and diastolic BP. The BpTRU (BpTRU Medical Devices Ltd., Coquitlam, British Columbia) is an automated and validated[33] electronic monitor. Blood lead averaged 1.64 μg/dL. Systolic BP in the bottom 5th blood lead percentile averaged 111.9 and 122.8 mm Hg in the top 95th percentile. Multivariable-adjusted associations of systolic and diastolic BPs with blood lead were only significant in the 40–54 years age range, whereas for diastolic BP, the association was driven by men.[32] As in the present study and several other studies,[2,29] there was no association between the risk of hypertension and blood lead.[32]

The argumentation linking cardiovascular complications to lead exposure builds on the premise that the rise in BP in response to exposure is the mediator.[30,31] However, as reviewed elsewhere,[2,34] no single study documented the full track from exposure over BP to adverse cardiovascular outcomes. In Pirkle's landmark study,[31] elevated blood lead was associated with a higher cardiovascular risk score, but was actually not evaluated as predictor of cardiovascular complications. A comprehensive meta-analysis concluded that there was sufficient evidence to infer a causal relation of hypertension with lead exposure,[2] but the same experts proposed that although suggestive, there is not enough solid evidence for a causal relation of lead exposure with clinical cardiovascular outcomes.[2] Reports on adverse cardiovascular outcomes in relation to blood lead originated from large population studies, but were not obvious in workers.[2] The explanations commonly put forward for the apparent contradiction between epidemiologic and occupational studies are higher statistical power in large population studies relative to smaller occupational cohorts and selection bias, often referred to as the healthy worker effect.[17,35] Stroke is the complication of hypertension most closely linked to BP.[36] However, 75% of strokes occur at levels of the office BP that are within the normotensive range.[36] The Global Burden of Stroke Study 1990–2013 involved 188 countries.[34] Unhealthy lifestyle, clusters of unhealthy metabolic factors, and environmental pollutants such as lead were the first, second, and third largest contributors to stroke-related disability-adjusted life-years lost. Globally, in low-income combined with middle-income countries and in high-income countries, lead exposure was estimated to contribute 6.4%, 7.8%, and 1.4% to the stroke burden.[34] However, the study consortium highlighted that as in many other studies they had been unable to account for major risk factors, including atrial fibrillation, substance abuse, and predisposition to stroke associated with other disease, for example, valvular heart disease.[34]

Sympathetic arousal in response to the medical environment and the observer measuring the BP causes the WCE, characterized by an increase in heart rate, cardiac output, and peripheral arterial resistance.[3,37] In young people with elastic central arteries and performant baroreflexes, such as our workers, the systolic WCE is adequately buffered. The diastolic BP and its WCE predominantly reflect acute vasoconstriction mediating an increase in peripheral resistance.[38] Indeed, association of vascular reaction to stimuli[39] and BP variability[40] with lead exposure were observed in experimental or population studies.[39,40] However, in a placebo-controlled double-blind randomized clinical trial, BP variability did not predict cardiovascular complications.[41]

Strong points of the present study are the assessment of BP by guideline-recommended methods and the implementation of a stringent quality control program for measurement of BP and blood lead. However, the study must also be interpreted in the light of some limitations. First, we analyzed ambulatory BP recordings with at least seven awake and three asleep readings. However, limiting the analyses to ambulatory recordings with at least 10 awake and five asleep readings, a criterion applied by international consortia,[42–44] eliminated only 38 workers from the analysis and did not change our results. Second, we excluded 100 participants from the current analyses because of quality of ambulatory BP measurements, antihypertensive treatment, or missing blood lead measurement. However, compared with the study population, those excluded had similar characteristics, including blood lead (4.11 vs. 4.16 μg/dL; $P = .27$) and office BP (120.0/80.7 vs. 120.9/80.1 mm Hg; $P = .42/.61$). Third, over the whole day, the median number of ambulatory readings was only 34 because participants, most of whom were engaged in physically strenuous labor, had the option to cancel readings interfering with their work. Finally, the current cross-sectional analysis includes only baseline SPHERL data obtained before occupational lead exposure. Workers will be kept in follow-up and will provide a unique opportunity to correlate changes in BP and blood lead over a median of 2 years, during which blood lead levels are expected to rise 4- to 5-fold.

In conclusion, we were unable to demonstrate any association between blood lead as marker of exposure and the ambulatory BP, which is currently the guideline-endorsed[5–8] state-of-the-art method to assess BP. Moreover, our study suggests that at least part of the association of the conventionally measured office BP with blood lead might be attributable to the inaccuracy of office measurement and the WCE.[3,4] The American College of Occupational and Environmental Medicine requested that OSHA align itself with the recent scientific evidence on the toxic effects of low-level lead exposure, referring in particular to

hypertension and cardiovascular disease.[16] However, there is no conclusive proof of a causal association between a higher risk of cardiovascular complications and blood lead at current levels of exposure.[2] While the guideline-endorsed ambulatory approach to BP measurement is firmly established in clinical and epidemiologic research, the time has come for occupational medicine to embrace this technology to characterize the first hub in the pathway, that is, the link between blood pressure and lead exposure.

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