HHS Public Access
Author manuscript
J Occup Environ Med. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:
J Occup Environ Med. 2015 April ; 57(4): 355–360. doi:10.1097/JOM.0000000000000427.

The Relationship between Occupational Metal Exposure and Arterial Compliance

Jason Y.Y. Wong, Sc.D[1,2], **Shona C. Fang, Sc.D**[3,4], **Rachel Grashow, Ph.D**[4], **Tianteng Fan, Sc.D**[4,6], and **David C. Christiani, MD MPH**[4,5]

[1]Stanford University School of Medicine 300 Pasteur Dr. Stanford, CA. 94304. USA.

[2]Veterans' Affairs Palo Alto Health Care System 3801 Miranda Ave. Palo Alto, CA. 94304. USA.

[3]New England Research Institute 480 Pleasant Street, Watertown, MA. 02472 USA

[4]Harvard School of Public Health, Dept. of Environmental Health 665 Huntington Ave. Boston, MA. 02115. USA

[5]Department of Medicine, Harvard Medical School - Massachusetts General Hospital 55 Fruit St. Boston, MA. 02114. USA

[6]Adheris Health 1 Van De Graaff Drive. Burlington, MA. 01803. USA.

Abstract

Background—The objective of this study was to evaluate the relationship between cumulative occupational exposure to various metals and arterial compliance in welders.

Methods—The observational follow-up study consisted of 25 subjects. Levels of nickel (Ni), lead (Pb), cadmium (Cd), manganese (Mn), and arsenic (As) from toenails were assessed using mass spectrometry. Arterial compliance as reflected by augmentation index (AIx) was measured using SphygmoCor Px Pulse Wave Analysis System. Linear regression models were used to assess the associations.

Results—For every 1 unit increase in log-transformed toenail Ni, there was a statistically significant 5.68 (95%CI: 1.38, 9.98, p=0.01) unit increase in AIx. No significant associations were found between AIx and Pb, Cd, Mn, and As.

Conclusions—Cumulative Ni exposure is associated with increased arterial stiffness in welders and may increase risk of adverse cardiovascular outcomes.

Keywords

Augmentation Index; Metals; Nickel; Arterial Compliance; Cardiovascular; Welding Fumes

Corresponding / Lead Author: Jason Y.Y. Wong jyywong@stanford.edu Phone: 617-407-7650.
Senior Author: David C. Christiani (dchris@hsph.harvard.edu)

The authors declare no conflicts of interest.

Introduction

Metal-rich airborne particles are the primary components of welding fumes responsible for toxicity (1). Heavy metal agglomerates of fine particulate matter are formed when electrodes and base metals are heated, vaporized, and subsequently react with moisture in the air during the welding process. Depending on the composition of the base metals and electrodes, these metals may include lead (Pb), cadmium (Cd), manganese (Mn), iron (Fe), and arsenic (As). The pulmonary and systemic health effects of welding fume exposure are well-documented in previous studies (2). However, there is growing occupational health concern regarding adverse cardiovascular effects in highly exposed professions (2). Indeed, previous studies reported increased risk of myocardial infarction, cardiovascular events, and death from ischemic heart disease among welders (3, 4). Although, the underlying mechanisms of each metal component on the cardiovascular system have yet to be fully understood, altered vascular function may be involved (5).

Nickel (Ni) is another metal component of welding fumes that contributes to its toxicity (6). Ni levels have been found to be associated with adverse cardiovascular outcomes including the number of carotid arteries with plaques in geriatric populations (7). Ni is widely used in electrical components and in a variety of applications including metallurgical processes. Although Ni is most readily absorbed in its soluble form, inhalation exposure in occupational settings is a primary route for Ni-induced toxicity (8). Inhalation exposure to various Ni compounds has been shown to cause toxic effects in the respiratory tract and on the immune system (9). The toxicity of Ni may be associated with its interference with the physiological processes of calcium, manganese, zinc, and magnesium, which can lead to varied physiological effects. (10). Furthermore, Ni is known to bind to specific proteins and amino acids in the blood serum, induce oxidative stress, and form adducts in DNA (11-13). The kidneys and lungs are the primary sites of Ni accumulation (14). However, Ni may also accumulate spleen, liver, heart and testes (8). Previous studies have also shown that Ni accumulates in toenails and its levels in this material may possibly be reflective of long-term cumulative exposure (15).

Arterial compliance is the extent to which arteries distend and constrict following systole. Structural changes in arteries such as to the distribution of collagen, elastin, and smooth muscle, are inevitable with progressing age and lead to reduced arterial compliance (16). However, environmental exposures may also accelerate degeneration of arterial compliance (17). Diminished arterial compliance has been investigated as both a cause and a consequence of vascular disease (18). Arterial stiffness in the aorta has been found to be associated with increased risk of adverse cardiovascular outcomes, in addition to morbidity and mortality in older populations (19). Furthermore, arterial compliance is reduced in patients with hypertension, with accelerated structural changes of the arterial wall (20). Previous studies have examined acute changes in arterial compliance as reflected by central augmentation index (AIx) in relation to occupational exposure to fine particulate matter (PM2.5) (21). However, no known epidemiological study has examined the association between cumulative metal levels and arterial compliance over a longer induction period.

The objective of this study was to evaluate cumulative levels of metals from toenail samples, in relation to measures of arterial compliance. The hypothesis was that increased cumulative exposure to metals is associated with increased arterial stiffness due to oxidative damage to the endothelial lining of arteries and/or altered biochemical signal transduction. In particular, given that Ni is an inorganic calcium antagonist (22) and also induces oxidative stress, it may affect the heart and vasculature through various mechanisms. Release of intracellular calcium from the sarcoplasmic reticulum (SR) is required for cardiac muscle contraction (23). Therefore, changes in signaling due to antagonistic competition that prevents effective elevation of cytosolic calcium would likely impair contractility; as the contraction of heart muscle is directly determined by the level of calcium elevation during systole (23).

Furthering the knowledge of how metal components in the environment affects cardiovascular risk factors would reinforce the basis for stricter permissible exposure limits and may be beneficial in improving the health and safety of exposed populations.

Materials and Methods

Study Design

The Harvard Boilermakers Study is a prospective open-cohort comprised of a series of periodic short-term panel studies. The source population consists of members of the International Brotherhood of Boilermakers Union, Local 29 in Quincy, MA. There are approximately 400 active union members, 190 of which have been prospectively followed since 1999. Their primary occupational activity is assembling and welding boilers that provide high-pressure steam to drive electrical turbines in power plants.

The current investigation was an observational follow-up study. The inclusion criteria were: being male, unionized apprentices or journeymen, over 18 years of age at the time of recruitment, having toenail metal measurements at baseline, and having data for AIx during the subsequent follow-up. The study population was composed of 25 subjects with complete exposure and outcome data. Informed consent was obtained from each participant and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Office of Human Research Administration (OHRA) of the Harvard Longwood Medical Area.

Exposure data on toenail metal levels were only collected during the first sample collection period (baseline) between January 29th 2010 and June 17th 2011. Outcome data on AIx were collected during the second sample collection period between June 17th 2011 and October 2nd 2012. Therefore, the exposure measurements temporally precede the outcome measurements. The average time from the exposure data collection to the outcome assessment was 207 ± 166SD days. Furthermore, previous studies in the Boilermakers' Study found that the various metals were marginally correlated to welding hours 7-9 months prior to toenail collection (24). Therefore, toenail metal levels were considered to be reflective of cumulative exposure during that timeframe.

Exposure Assessment: Toenail Metal Levels

Toenail samples were collected at baseline to assess internal accumulation of Ni, Pb, Cd, Mn, and As. Subjects with sufficient toenail growth clipped all 10 toenails at the study site. Subjects who provided toenails 21 or more days after questionnaire information collection by mail were excluded. Toenail concentrations of metals were assessed at the Harvard School of Public Health Trace Metals Laboratory using a dynamic reaction cell-inductively coupled plasma mass spectrometer (DRC-ICP-MS, Elan 6100, Perkin Elmer, Norwalk, CT). Toenail clippings from all ten toes were combined for each subject and analyzed as previously described (25). Five replicate reactions were performed for each subject. The net average concentration for each metal was calculated by subtracting detectable laboratory blank concentrations within each batch.

Outcome Assessment: Central Augmentation Index

Measurements for AIx were performed in a temperature-controlled room with a SphygmoCor Px Pulse Wave Analysis System Model SCOR-Px (Atcor Medical Pty Ltd., Sydney, Australia) as per manufacturer's protocol and as previously described (21). In brief, data were directly collected onto computers installed with the system software (Version 7.1) by two trained study technicians. Calibration of peripheral pressure recordings was performed with the average of three brachial systolic and diastolic blood pressure readings obtained with an automated blood pressure machine before each augmentation index measurement. Subjects were seated with both feet planted on the ground and with the dominant arm extended onto a flat surface, ensuring that the bend at the elbow was at heart level. After five minutes of rest, a high-fidelity micronanometer was used to flatten the radial artery with gentle pressure. Ten seconds of sequential pulse pressure waveforms were recorded during each reading. The waveforms were transformed into a corresponding central aortic waveform via a validated transfer function. The systolic part of the central aortic waveform is characterized by a first peak caused by left ventricular ejection and a second peak caused by wave reflection. The difference between the peaks reflects the degree to which the central aortic pressure is augmented by wave reflection. AIx is defined as the augmented pressure (AP) divided by the pulse pressure (PP), multiplied by 100. Larger values of the index indicate increased wave reflection, thus increased arterial stiffness. AIx adjusted to a heart rate of 75 bpm was used as the outcome in the regression models. This metric is also known as the central augmentation pressure/pulse height ratio at heart rate 75 (C_AGPH_HR75). The quality control of the pressure waveforms is based on the homogeneity and height of the recorded waves. Three AIx measurements were taken for each subject and only those with operator indices ≥ 85 were considered acceptable. Not all the subjects had three acceptable AIx measurements; therefore, subjects with more than one acceptable measurement had their extra replicates dropped at random which should be unbiased. A random drop was used in this situation because a valid mean and standard deviation can only be obtained with at least three replicates. The median within-subject coefficient of variation (%CV) for heart rate adjusted AIx in 35 boilermakers who had repeated-measures was 14.9% IQR (7.4%-27.2%). This %CV was comparable to those found in previous studies (26).

Covariate Assessment

Self-reported questionnaires were used to collect demographic data such as birthdate, race, current smoking status, past smoking status, and work history. Number of years as a boilermaker was used as a proxy for long-term particulate matter exposure from welding fumes (27). Height and weight were measured by research personnel at the study site to derive body mass index.

Data Analysis

Pearson and Spearman correlation coefficients were used to evaluate linear and monotonic correlations between the metals, respectively. Natural log-transformation was performed on right-skewed continuous variables to obtain normally distributed data. Multiple linear regression models were used to assess the relationship between toenail metal levels at baseline and AIx from the subsequent data collection. Separate independent models were used for each metal component to assess their associations with AIx. The models controlled for potential confounders including log-transformed number of years as a boilermaker (continuous), current smoking intensity (cigarettes per day), log-transformed BMI (continuous), age at baseline (continuous), and self-reported race (white vs. others). AIx was adjusted to a heart rate of 75 bpm. Due to increased family-wise error rate from multiple testing, p-values below a Bonferroni-corrected α-threshold of 0.01 were considered statistically significant. Although Bonferroni correction assumes independence between tests, correlation between the metals would make the adjustment “conservative” in that it still protects well against false-positives, but there would be decreased power to detect true-positives. Statistical analyses were implemented in SAS v9.3.

Results

Baseline characteristics

There were a total of 25 participants in the current study, 8 (32%) of whom were current smokers and 17 (68%) were past smokers (Table 1). The study population was predominantly self-reported white (80%). The average age at baseline was 43 ± 13SD years, while the average BMI was 27.7 ± 4.7SD kg/m^2. However, the relatively high average BMI in this particular population was not entirely reflective of adiposity. The average toenail Ni levels were 8.1 ± 24.5SD μg/g, while the average heart rate adjusted AIx was 17.7 ± 11.7SD %.

Correlation between toenail metals

There was a statistically significant linear correlation between log-transformed Cd levels and Pb, Mn, and Ni (Table 2). Moreover, there was a statistically significant monotonic relationship between Cd, Pb, and Mn; but not between Cd and Ni.

The association between toenail metal levels and arterial stiffness

There was a positive linear association between toenail Ni levels, and arterial stiffness as reflected by AIx (Table 3). For every 1 unit increase in log-transformed toenail Ni, there was a statistically significant 5.68 (95%CI: 1.38, 9.98, p=0.01) unit increase in AIx adjusted to a heart rate of 75 bpm, controlling for specified confounders, and after Bonferroni correction. (Table 3). However, AIx was not found to be associated with toenail levels of Pb, Cd, Mn, and As.

Discussion

To our knowledge, this is one of the first epidemiological investigations into the association between metal components of fine particulate matter and arterial compliance. Findings from this study suggest that increased cumulative levels of Ni was positively correlated with AIx. There have been a limited number of studies which have examined the mechanisms by which Ni affects the arterial vasculature. Most of these studies were conducted in mice, rats, and other animal models. Studies involving inhalation exposures to resuspended emission source particles that are enriched in transition metals such as Ni have reported effects on cardiovascular function (28). Suspected mechanisms of action on vasculature include induction of oxidative stress, upregulation of particular gene expression, and modulating calcium ion channels (29). One study found that Ni exposure induces endothelial dysfunction through oxidative stress-dependent inhibition of eNOS dimerization (30). Furthermore, the release of Ni ions from intravascular stents has been reported to result in elevated oxidative stress in human umbilical vein endothelial cells (31). On a molecular level, Ni has been shown to up-regulate NFκB which results in increased expression of intracellular, vascular, and endothelial adhesion molecules ICAM-1, VCAM-1, and E-selectin (32). Therefore, Ni exposure may be involved in leukocyte recruitment which results in vascular inflammation and dysfunction. Another study showed that inhalation of Ni nanoparticles resulted in functionally impaired endothelial progenitor cells and reduced number in the bone marrow, which may lead to enhanced progression of atherosclerosis (33).

Nickel has also been shown to have effects on the functionality of the heart. Arterial compliance is calculated by the augmented pressure divided by pulse pressure, whereas pulse pressure is the difference between systolic (SP) and diastolic (DP) pressure. Ni deprivation was found to induce changes in SP in mouse models due to its critical role in regulating physiological function through the cyclic-GMP signaling pathway (34). Furthermore, the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study found that increased Ni was associated with left ventricular hypertrophy and relative wall thickness, which may decrease SP (35). However, studies in young Chinese population found positive associations between Ni and other particulate matter constituents with SP (36). There may be a U-shaped relationship between Ni levels and SP, in that high and low levels of Ni are associated with higher SP, whereas moderate levels of Ni are associated with lower SP.

The main strength of the study was the AIx outcome assessment. Previous studies showed that augmentation index is an accurate, sensitive, and responsive measure of arterial compliance, particularly in younger populations (37). Accurate AIx assessment would reduce random outcome mismeasurement /misclassification and would reduce variance in regression modeling. Additionally, assessment of metal levels from toenails is an accurate and easy method to assess internalized cumulative exposure in epidemiological studies.

Assessment of internalized metals exposure forgoes the complications of measuring environmental exposure from multiple sources and individual factors affecting biological uptake of exposure. Additionally, since measurement of toenail metal levels and AIx were independent, it was unlikely there was any differential misclassification of the exposure or outcome. Furthermore, the metal exposure assessment temporally precedes the outcome assessment which strengthens the possibility of a causal relationship between Ni and arterial compliance. Lastly, toenail samples are arguably less prone to contamination compared to fingernails and hair samples, as they tend to be covered throughout the work day.

The most significant limitation of this study was its small sample size which may reduce the power of the study to discern subtle effects. However, limited sample size is an issue affecting many occupational epidemiology studies, often due to small source populations from which to draw subjects. Given the seasonal work schedule of the boilermakers and only having 190 members of the union followed since 1999, the size of the current study is a respectable proportion of the whole. The study population was restricted to subjects with complete exposure and outcome data. The Boilermakers cohort is composed of multiple periodic short-term panel studies, in which the current study population was derived. Each of these short-term panels had separate, independent recruitment phases. In the current study, having complete exposure data at baseline and outcome data during the follow-up was primarily attributed to the seasonal nature of the occupation, in addition to personal work schedules. It was unlikely due to factors attributed to both the exposure and outcome which may lead to selection bias (conditioning on a collider). As with all epidemiological studies, there may be unmeasured confounders which may bias the direction of the estimates depending on the strength and direction of their association with the exposure and outcome. However, most of the pertinent confounders related to both metals levels and arterial compliance based on previous literature, feasibility, and subject matter knowledge were controlled for. Furthermore, this study does not address acute changes in AIx which has been shown to be induced by short-term exposure to environmental exposures (21). Rather, this study evaluates if long-term internal accumulation of particular welding fume components, are associated with AIx under the assumption of an induction time of approximately 1 - 2 years.

With respect to the statistical analysis, the multiple linear regression models controlled for a number of potential confounders required to reduce bias. However, with only a limited number of samples, it is possible that the models were over-fitted, thus increasing the variance of the estimates. Despite the possibility of increased variance, statistically significant results were still observed for the relationship between Ni and AIx correcting for multiple testing with Bonferroni adjustment. Assuming no other unmeasured confounding, sampling bias, and information bias, increased sample size would likely narrow the variance of the estimates and increase the significance. However, we cannot exclude the possibility that the significant results in the models were chance findings due to limited sample size.

Occupational fine particulate matter from welding fumes is composed of various metal components. Therefore, with concurrent environmental exposure, levels of these metals in toenails may be correlated. Correlation of exposures is a pressing issue in environmental, nutritional, and genetic epidemiology, since the observed association may not be due to the component of interest, but rather its correlation with other "driver" and "passenger" components. However, only a marginal correlation was found between Ni and Cd, whereas Cd was not found to be associated with AIx. Furthermore, Ni was not found to be correlated with the other metal components, which lends further support that Ni may be a driving component with respect to increased arterial stiffness, independent of other metals.

In summary, increased levels of toenail Ni were found to be associated with increased arterial stiffness as reflected by augmentation index. Conversely, Pb, Mn, Cd, and As were not found to be associated with augmentation index. Findings from this study suggest that Ni maybe an important component of occupational fine particulate matter which exerts adverse effects on the cardiovascular system. However, caution should be taken when interpreting the findings given the limited sample size. Future studies should employ a substantially larger study population in order to achieve statistical power to discern subtle effects. Furthermore, greater emphasis should be placed on eliciting the mechanism of action by which Ni and other metal impart effects on different aspects of the cardiovascular system in human populations. Gaining insight into such mechanisms will likely involve large longitudinal repeated-measure studies involving extensive mediation analysis of oxidative stress, inflammatory biomarkers, cardiovascular markers, cGMP expression, nitric oxide levels and activity of various signaling receptors.

Acknowledgments

This project was made possible by funding from the National Institute of Environmental Health Sciences (NIEHS) grants R01ES009860 and P50ES00002, in addition to a grant from the American Heart Association (AHA).

References

1. Chang C, Demokritou P, Shafer M, Christiani D. Physicochemical and toxicological characteristics of welding fume derived particles generated from real time welding processes. Environmental science Processes & impacts. 2013; 15(1):214–24. [PubMed: 24592438]
2. Antonini JM, Lewis AB, Roberts JR, Whaley DA. Pulmonary effects of welding fumes: review of worker and experimental animal studies. American journal of industrial medicine. 2003; 43(4):350–60. [PubMed: 12645092]
3. Fang SC, Cavallari JM, Eisen EA, Chen JC, Mittleman MA, Christiani DC. Vascular function, inflammation, and variations in cardiac autonomic responses to particulate matter among welders. American journal of epidemiology. 2009; 169(7):848–56. [PubMed: 19153215]
4. Steenland K. Ten-year update on mortality among mild-steel welders. Scandinavian journal of work, environment & health. 2002; 28(3):163–7.
5. Niu J, Liberda EN, Qu S, Guo X, Li X, Zhang J, et al. The role of metal components in the cardiovascular effects of PM2.5. PloS one. 2013; 8(12):e83782. [PubMed: 24386277]
6. Nemery B. Metal toxicity and the respiratory tract. The European respiratory journal. 1990; 3(2): 202–19. [PubMed: 2178966]
7. Lind PM, Olsen L, Lind L. Circulating levels of metals are related to carotid atherosclerosis in elderly. The Science of the total environment. 2012; 416:80–8. [PubMed: 22178028]
8. Zhao J, Shi X, Castranova V, Ding M. Occupational toxicology of nickel and nickel compounds. Journal of environmental pathology, toxicology and oncology : official organ of the International Society for Environmental Toxicology and Cancer. 2009; 28(3):177–208.
9. Schaumloffel D. Nickel species: analysis and toxic effects. Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements. 2012; 26(1):1–6.

10. Coogan TP, Latta DM, Snow ET, Costa M. Toxicity and carcinogenicity of nickel compounds. Critical reviews in toxicology. 1989; 19(4):341–84. [PubMed: 2663022]
11. Zoroddu MA, Peana M, Medici S, Casella L, Monzani E, Costa M. Nickel binding to histone H4. Dalton transactions. 2010; 39(3):787–93. [PubMed: 20066223]
12. Das KK, Buchner V. Effect of nickel exposure on peripheral tissues: role of oxidative stress in toxicity and possible protection by ascorbic acid. Reviews on environmental health. 2007; 22(2): 157–73. [PubMed: 17894205]
13. Chang J, Watson WP, Randerath E, Randerath K. Bulky DNA-adduct formation induced by Ni(II) in vitro and in vivo as assayed by 32P-postlabeling. Mutation research. 1993; 291(2):147–59. [PubMed: 7680419]
14. Das KK, Das SN, Dhundasi SA. Nickel, its adverse health effects & oxidative stress. The Indian journal of medical research. 2008; 128(4):412–25. [PubMed: 19106437]
15. Grashow R, Zhang J, Fang SC, Weisskopf MG, Christiani DC, Kile ML, et al. Inverse association between toenail arsenic and body mass index in a population of welders. Environmental research. 2014; 131:131–3. [PubMed: 24721130]
16. Glasser SP, Arnett DK, McVeigh GE, Finkelstein SM, Bank AK, Morgan DJ, et al. The importance of arterial compliance in cardiovascular drug therapy. Journal of clinical pharmacology. 1998; 38(3):202–12. [PubMed: 9549658]
17. O'Neill MS, Diez-Roux AV, Auchincloss AH, Shen M, Lima JA, Polak JF, et al. Long-term exposure to airborne particles and arterial stiffness: the Multi-Ethnic Study of Atherosclerosis (MESA). Environmental health perspectives. 2011; 119(6):844–51. [PubMed: 21245016]
18. Herrington DM, Kesler K, Reiber J, Davis W, Brown WV, Helms R, et al. Arterial compliance adds to conventional risk factors for prediction of angiographic coronary artery disease. American heart journal. 2003; 146(4):662–7. [PubMed: 14564320]
19. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. JAMA : the journal of the American Medical Association. 1999; 281(7):634–9.
20. Marchais SJ, Guerin AP, Pannier B, Delavaud G, London GM. Arterial compliance and blood pressure. Drugs. 1993; 46(Suppl 2):82–7. [PubMed: 7512488]
21. Fang SC, Eisen EA, Cavallari JM, Mittleman MA, Christiani DC. Acute changes in vascular function among welders exposed to metal-rich particulate matter. Epidemiology. 2008; 19(2):217–25. [PubMed: 18300696]
22. Nossen JO, Rustan AC, Drevon CA. Calcium-antagonists inhibit secretion of very-low-density lipoprotein from cultured rat hepatocytes. The Biochemical journal. 1987; 247(2):433–9. [PubMed: 3122726]
23. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA : the journal of the American Medical Association. 2003; 290(21):2805–16.
24. Grashow R, Zhang J, Fang SC, Weisskopf MG, Christiani DC, Cavallari JM. Toenail metal concentration as a biomarker of occupational welding fume exposure. Journal of occupational and environmental hygiene. 2014; 11(6):397–405. [PubMed: 24372360]
25. Mordukhovich I, Wright RO, Hu H, Amarasiriwardena C, Baccarelli A, Litonjua A, et al. Associations of toenail arsenic, cadmium, mercury, manganese, and lead with blood pressure in the normative aging study. Environmental health perspectives. 2012; 120(1):98–104. [PubMed: 21878420]
26. Dhindsa M, Barnes JN, DeVan AE, Sugawara J, Tanaka H. Comparison of augmentation index derived from multiple devices. Artery Research. 2011; 5(3):112–4.
27. Ozdemir O, Numanoglu N, Gonullu U, Savas I, Alper D, Gurses H. Chronic effects of welding exposure on pulmonary function tests and respiratory symptoms. Occupational and environmental medicine. 1995; 52(12):800–3. [PubMed: 8563842]
28. Lippmann M, Ito K, Hwang JS, Maciejczyk P, Chen LC. Cardiovascular effects of nickel in ambient air. Environmental health perspectives. 2006; 114(11):1662–9. [PubMed: 17107850]

29. Li M, Zhang M, Huang L, Zhou J, Zhuang H, Taylor JT, et al. T-type Ca2+ channels are involved in high glucose-induced rat neonatal cardiomyocyte proliferation. Pediatric research. 2005; 57(4): 550–6. [PubMed: 15695594]

30. Ying Z, Xu X, Chen M, Liu D, Zhong M, Chen LC, et al. A synergistic vascular effect of airborne particulate matter and nickel in a mouse model. Toxicological sciences : an official journal of the Society of Toxicology. 2013; 135(1):72–80. [PubMed: 23788629]

31. Plant SD, Grant DM, Leach L. Behaviour of human endothelial cells on surface modified NiTi alloy. Biomaterials. 2005; 26(26):5359–67. [PubMed: 15814134]

32. Denkhaus E, Salnikow K. Nickel essentiality, toxicity, and carcinogenicity. Critical reviews in oncology/hematology. 2002; 42(1):35–56. [PubMed: 11923067]

33. Liberda EN, Cuevas AK, Gillespie PA, Grunig G, Qu Q, Chen LC. Exposure to inhaled nickel nanoparticles causes a reduction in number and function of bone marrow endothelial progenitor cells. Inhalation toxicology. 2010; 22(Suppl 2):95–9. [PubMed: 20936915]

34. Nielsen FH. A mild magnesium deprivation affects calcium excretion but not bone strength and shape, including changes induced by nickel deprivation, in the rat. Biological trace element research. 2006; 110(2):133–50. [PubMed: 16757842]

35. Lind PM, Olsen L, Lind L. Elevated circulating levels of copper and nickel are found in elderly subjects with left ventricular hypertrophy. Ecotoxicology and environmental safety. 2012; 86:66–72. [PubMed: 23079738]

36. Wu S, Deng F, Huang J, Wang H, Shima M, Wang X, et al. Blood pressure changes and chemical constituents of particulate air pollution: results from the healthy volunteer natural relocation (HVNR) study. Environmental health perspectives. 2013; 121(1):66–72. [PubMed: 23086577]

37. McEniery CM, Yasmin, Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, et al. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. Hypertension. 2005; 46(1):221–6. [PubMed: 15867140]

Table 1

Characteristics of the Boilermakers Study Population at Baseline Data Collection

Variable		**Total n=25 Frequency**	**(%)**
Current Smoking Status			
	Non-smoker	17	68
	Smoker	8	32
Past Smoking Status			
	Never	8	32
	Ever	17	68
Self-Reported Race			
	White	20	80
	African-American	3	12
	Hispanic	2	8

		Mean	**Std. Dev.**	**Median**	**IQR (25th - 75th perc.)**	
Age		43	13	43	35	54
Number of Years Working as a Boilermaker		12	10	10	3	13
Body Mass Index (BMI), kg/m^2		27.7	4.7	26.6	25.2	29.4
Central Augmentation Index (cAIx)		129	24	130	113	145
cAIx Adjusted to a Heart Rate of 75 bpm		17.7	11.7	21.0	7.0	27.0
Daily Cigarette Smoking Intensity (cigs/day)		6	9	0	0	15
Resting Heart Rate (beats/min)		70	14	71	59	78
Toenail Metal Levels (μg/g)						
	Ni	8.14	24.47	2.28	1.39	3.84
	Pb	0.87	1.76	0.34	0.21	0.62
	Cd	0.03	0.03	0.02	0.01	0.04
	Mn	3.72	10.35	1.00	0.55	2.00
	As	0.22	0.21	0.17	0.12	0.27

Table 2

Pearson and Spearman Correlations between Toenail Metal Levels at Baseline Data Collection

i. Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0

	Ni	Pb	Cd	Mn	As
Ni	1	0.33	0.43	0.19	0.26
		0.10	0.03*	0.36	0.21
Pb		1	0.47	0.28	0.27
			0.02*	0.17	0.20
Cd			1	0.52	0.25
				0.01*	0.23
Mn				1	0.27
					0.19
As					1

ii. Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0

	Ni	**Pb**	**Cd**	**Mn**	**As**
Ni	1	0.29	0.17	0.34	0.29
		0.16	0.43	0.10	0.16
Pb		1	0.50	0.42	0.39
			0.01*	0.04*	0.06
Cd			1	0.58	0.31
				<0.01*	0.13
Mn				1	0.32
					0.12
As					1

‡Toenail metal levels were log-transformed to obtain normal distributions

*p-values ≤ 0.05 were considered statistically significant

Table 3

The Association between Toenail Metal Levels and Arterial Compliance in the Boilermakers' Study

	I. Crude Unadjusted Models				*II. Covariate Adjusted Models*			
Main Effects	**Effect Estimate**	**95%CI Lower**	**95%CI Upper**	**p-value**	**Effect Estimate**	**95%CI Lower**	**95%CI Upper**	**p-value**
Nickel	3.07	−1.41	7.55	0.17	5.68	1.38	9.98	0.01 *
Lead	1.28	−3.14	5.70	0.56	2.05	−2.83	6.93	0.39
Cadmium	0.78	−5.05	6.60	0.79	3.42	−3.06	9.91	0.28
Manganese	0.83	−3.31	4.97	0.68	4.18	−0.89	9.24	0.10
Arsenic	−0.77	−7.74	6.19	0.82	0.16	−8.06	8.39	0.97

Separate linear regression models were fitted for each metal. The adjusted models controlled for number of years as a boilermaker, current smoking intensity, body mass index, race, and age at baseline.

* p-values ≤ Bonferroni corrected α-threshold of 0.01 were considered statistically significant. Arterial Compliance as reflected by Central Augmentation Index was corrected to a heart rate of 75 bpm. Main effects were log-transformed to obtain normally distributed data.