Occupational Exposure to Metals and Serum Adiponectin Levels Among Shipyard Workers: A Cohort Study with Weighted Quantile Sum Regression Analyses

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Research

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Abstract

Background: The influence of welding-associated air pollutants on workers' health is mainly regarded as a core issue in public health and occupational medicine. Previous studies have indicated that workers exposed to metal fumes had an increased risk of metabolic syndrome, which was correlated with decreased serum adiponectin levels. This study aimed to explore whether heavy metal exposure affects the concentration of adiponectin among welding workers.

Methods: The study participants were recruited from a shipyard with 31 office workers and 100 welding workers in 2015. Urinary metal concentrations were measured by inductively coupled plasma–mass spectrometry. Serum adiponectin was measured by enzyme-linked immunosorbent assay. Inferential statistics on repeated measures were performed using generalized estimating equations (GEEs). A weighted quantile sum (WQS) regression model was conducted to examine the joint effect of the association of multimetal exposure with serum adiponectin.

Results: After adjustment for all confounding variables through a GEE analysis, significantly negative associations of numerous urinary metals with serum adiponectin were detected in the welding workers, including Cr ($\beta = -0.088$; 95% CI: -0.148, -0.027), Mn ($\beta = -0.174$; 95% CI: -0.267, -0.081), Co ($\beta = -0.094$; 95% CI: -0.158, -0.029), Ni ($\beta = -0.108$; 95% CI: -0.208, -0.008), Cd ($\beta = -0.067$; 95% CI: -0.115, -0.018), and Pb ($\beta = -0.089$; 95% CI: -0.163, -0.015). The contributions of multiple urinary metal levels to serum adiponectin levels, determined individually by WQS regression, suggested that Pb was the greatest contributor.

Conclusions: Welding workers exposed to heavy metals such as Pb, Cr, Co, Mn, Ni, and Cd might have reduced serum adiponectin levels and an increased risk of cardiovascular disease.

Background

Welding is ubiquitous and indispensable in industrial development, and it consists of joining metals by fusing and melting them; it also includes tasks such as grinding, brazing, and soldering. It is estimated that more than 1 million workers worldwide perform welding as a part of their jobs [1]. Potential health hazards may arise during the welding process, including exposure to physical hazards, ergonomic stress, and chemical poisons. Among these health hazards, the influence of welding-associated air pollutants on workers' health is regarded as a core issue in public health and occupational medicine. Welding fumes are a byproduct of the process, and the rate of generation and the composition of welding fumes are characteristic of the different materials being welded and the soldering components used. Ultrafine and fine welding particles often consist of numerous metals, including iron (Fe), lead (Pb), zinc (Zn), nickel (Ni), copper (Cu), manganese (Mn), cobalt (Co), cadmium (Cd), and chromium (Cr). The size of the welding particles generated differs based on the industrial processes undertaken. Earlier studies have indicated that welding particles are in the ultrafine size range of 0.01 to 0.10 μm [2] and that most of the welding fumes have particles that are $< 0.50 \mu\text{m}$ in aerodynamic diameter [3]. Ultrafine particles have a

higher likelihood of being deposited in the smaller branches of the bronchial airways in the respiratory tract; rapid clearance by the mucociliary system is much more ineffective.

A previous study indicated that welding fumes were known to cause acute pulmonary diseases, such as metal fume fever [4]. Moreover, several studies have reported the adverse impacts of welding fume exposure on the development of chronic health conditions, including pulmonary fibrosis [5], chronic obstructive pulmonary disease [6], and carcinogenesis [7]. At the same time, few studies have shown that long-term heavy metal exposure could raise the risk of developing metabolic syndrome (MetS) [8, 9], which is a constellation of cardiometabolic abnormalities and is recognized as a risk factor for cardiovascular disease and type 2 diabetes mellitus [10]. Additionally, a large cohort study that enrolled 10,059 male metal workers demonstrated that welding processed particles raised the risk of cardiovascular disease [11]. Previous studies have illustrated that the potential mechanisms by which metal fume exposure induces cardiometabolic illness might be correlated with systemic inflammation and the oxidative stress response [12, 13].

Adiponectin is an adipose-derived hormone that is abundantly present in human plasma; it is adversely modulated by the accumulation of visceral fat and is lowered in obesity. Thus, it plays an essential role as a vital messenger in the communication between metabolism-related organs and adipose tissue. Adiponectin is secreted into the circulation, where it exerts insulin-sensitizing, antiatherosclerotic, and anti-inflammatory effects. In addition, adiponectin can increase insulin sensitivity in the skeletal muscle and the liver, and it is associated with reducing atherosclerosis [14]. Aside from these effects, adiponectin seems to display pleiotropic impacts on MetS. Emerging studies have emphasized the role played by hypoadiponectinemia in the pathogenesis of insulin resistance, MetS, diabetes, and cardiovascular disease [15, 16].

Given the awareness of the possible factors controlling adiponectin levels, including genetic, dietary, and lifestyle factors and environmental interventions, limited studies have discussed the relationship between occupational exposure to metals and adiponectin levels. Because welding workers are exposed to multiple heavy metals simultaneously, the combined effects of different heavy metals have not been discussed in previous surveys. By way of weighted quantile sum (WQS) regression, we could assess the weights of environmental chemicals, which allowed us to make clinical assumptions regarding relative chemical importance. Therefore, we designed a longitudinal study to explore the association between welding fume exposure and serum adiponectin levels.

Methods

Data source and participants

We recruited the study subjects from a shipyard in northern Taiwan, and all qualified subjects were classified into two groups based on their job responsibilities in 2014. At baseline, there were 70 welding workers in the exposure group and 26 office workers in the control group. The following year, almost all

the earlier participants were recruited and underwent the same study protocols; moreover, we also included new study subjects in both the exposure and control groups. Finally, in 2015, a total of 131 study participants qualified for this study, namely, 100 welding workers and 31 office workers. Additionally, we excluded female subjects and individuals with diabetes or those receiving antidiabetic agents, as we intended to eliminate the impacts of sex and metabolism as much as possible.

All workers were asked to fill out a self-administered questionnaire that contained demographic and personal information, including medical history, respiratory protective devices used, and lifestyle habits. Furthermore, all study participants underwent physical examinations, morning urine sample collection after one day of exposure between 8 AM and 5 PM with 1 hour of rest between 12 PM and 1 PM on Tuesday, and blood sampling after 8 hours of overnight fasting. Additionally, all workers were required to wear personal air samplers for a 1-day exposure on Monday. The Ethics Committee of the Tri-Service General Hospital-Joint Institutional Review Board approved this research. All individuals in this survey provided written informed consent.

Measurement of field air sampling

Personal air samples were collected by active samplers with filters of cellulose ester (pore size: 0.8 μm and diameter: 37 mm) from the workspaces of all participants; the active samplers had a flow rate of 2 L/min to gather the heavy metals. All workers were required to carry these personal samplers, which were placed in the breathing zone of the participants for a full eight-hour working day. The levels of heavy metals were detected using inductively coupled plasma–mass spectrometry (ICP–MS, Agilent 7500ce, Agilent, Santa Clara, CA, USA).

Assessment of urinary metal concentrations

Morning urine samples were collected after one workday of exposure and stored at -80°C until analysis. ICP–MS also measured the levels of urinary metals, and the procedures were performed twice as independent experiments. Each metal's interday and intraday coefficients of variation were within 5%. In addition, urine creatinine was measured by Jaffe's method for adjusting urinary biomarker concentrations.

Measurement of serum adiponectin levels

Fasting blood samples were collected in EDTA-treated tubes by venipuncture based on standard protocols, kept on ice, and delivered to our laboratory for further assessment. After centrifugation, fractions were separated and kept on ice, snap-frozen in liquid nitrogen, and stored at -80°C until analysis. Serum adiponectin was analyzed with a commercial enzyme-linked immunosorbent kit (ELISA) (Calbiotech, Inc., USA).

Measurement of other covariates

All participants underwent peripheral blood sampling after eight hours of overnight fasting to obtain cardiometabolic parameters, including triglycerides, total cholesterol, fasting glucose, serum albumin, and

uric acid. Body mass index (BMI), expressed in kilograms by meters squared, was determined based on subjects' height and weight. As previously described, interviewer-assessment questionnaires were applied to acquire data on personal information and lifestyle factors.

Statistical analysis

Basic characteristics, biochemistry data, and metal biomarkers between the control group and exposure group were compared using Student's t tests for continuous variables and chi-squared tests for discrete variables. Generalized estimating equations (GEEs) on repeated measures were utilized to investigate the effectiveness of metal exposure in modulating serum adiponectin concentrations. Since urinary metals and serum adiponectin were not normally distributed, log transformation was utilized to achieve a normal distribution. GEEs with a first-order autoregressive working correlation matrix were conducted to model the study outcome while accounting for correlated data within the repeated measures of the study design. The changes in study outcome values from baseline to follow-up were expressed in the exposed and control groups under adjustment for potential confounding factors. The adjusted models compared both groups over time while accounting for age, BMI, serum albumin, total cholesterol, uric acid, fasting glucose, triglycerides, urine creatinine, job tenure, current smoking status, and exercise habits.

Moreover, a WQS regression model was conducted to examine the combined effects of the highly associated multimetal exposures with serum adiponectin. The WQS approach presumed that all metals had the same direction effects on the study outcome, regardless of positive or negative results [17]. A set of weights quantified the weights of the different influences of individual exposures. Each weight was confined within 0 and 1, and all the weights were summed to 1. WQS regression estimates were calculated from 1,000 bootstraps with the sample separated into validation and training datasets by a split proportion of 4:6. Statistical analysis was performed using IBM SPSS statistics software for Windows version 22.0 (IBM Corp., Armonk, NY, USA). Additionally, WQS regression was implemented by means of the gWQS package for R 3.5.1. The definition of statistical significance was a two-sided P value of < 0.05.

Results

Demographic and clinical characteristics of the subjects

The ratios of the ambient air sampling of heavy metals for comparing the exposure and control groups are shown in **Fig. 1**. Fe was the most abundant metal, which displayed a 134.7-fold change following exposure, followed by Mn in decreasing order with an 81.9-fold change. All metals in the ambient air sampling showed higher concentrations in the exposure group to varying degrees. The demographic characteristics of all participants, including office and welding workers, are listed in Table 1. Compared with the office workers, the welding workers in this study were likely to be younger, had less job tenure, and had significantly lower blood albumin and higher urine creatinine levels. The mean ages of the office and welding workers were 52.74 ± 12.28 and 44.08 ± 11.15 years old, respectively.

Table 1
Characteristics of welding and office workers at baseline

	Total workers (n=96)	Welding workers (n=70)	Office workers (n=26)	<i>p</i> values
Continuous variables				
Age (years)	46.43 (12.04)	44.08 (11.15)	52.74 (12.28)	0.001
BMI	25.21 (3.33)	25.15 (3.37)	25.36 (3.27)	0.784
Albumin (g/dL)	4.71 (0.21)	4.74 (0.21)	4.62 (0.19)	0.011
Total cholesterol (mg/dL)	190.40 (56.77)	192.79 (64.07)	183.96 (29.33)	0.501
Triglyceride (mg/dL)	144.73 (201.03)	150.66 (231.96)	128.77 (68.58)	0.638
Uric acid (mg/dL)	6.69 (1.50)	6.68 (1.56)	6.70 (1.32)	0.952
Fasting glucose (mg/dL)	94.55 (8.75)	94.56 (9.32)	94.54 (7.15)	0.993
Urine creatinine (mg/dL)	133.82 (72.36)	143.53 (76.32)	107.70 (53.36)	0.030
Job tenure (years)	22.75 (15.40)	20.75 (15.28)	28.12 (14.70)	0.037
Adiponectin (ug/dL)	13.69 (6.93)	13.55 (7.30)	14.16 (5.62)	0.666
Categorical variables				
Current Smoking	49 (51.0)	39 (55.7)	10 (38.5)	0.170
BMI, body mass index.				
^a Values were expressed as mean (standard deviation)				
^b Values in the categorical variables were expressed as number (%)				

	Total workers (n=96)	Welding workers (n=70)	Office workers (n=26)	<i>p</i> values
Current Exercise	26 (27.1)	17 (24.3)	9 (34.6)	0.359
BMI, body mass index.				
^a Values were expressed as mean (standard deviation)				
^b Values in the categorical variables were expressed as number (%)				

Nevertheless, these groups did not have significant differences in BMI, total cholesterol, triglycerides, uric acid, fasting glucose, or personal habits. In addition, all welding workers had used respiratory protective devices at work by self-report (data not shown). The comparison of urinary metals in the office and welding workers at baseline is shown in Table 2. Although there were no significant differences between the groups for all urinary metals, the concentration of urinary metals in the welding workers seemed to be higher than that in office workers.

Table 2
The concentration of urinary metals in welding and office workers at baseline

Urinary metals	Total Workers (n=96)	Welding workers (n=76)	Office Workers (n=20)	<i>p</i> values
Urine Cr ^a (μg/L)	89.99 (799.95)	119.32 (941.01)	13.71 (57.21)	0.578
Urine Mn ^a (μg/L)	28.96 (229.42)	36.44 (269.27)	9.53 (35.90)	0.621
Urine Co ^a (μg/L)	1.42 (5.88)	1.58 (6.88)	0.99 (1.17)	0.675
Urine Ni ^a (μg/L)	209.48 (1652.45)	266.66 (1942.89)	60.82 (166.72)	0.599
Urine Zn ^a (μg/L)	601.06 (560.91)	631.57 (619.45)	521.72 (366.60)	0.408
Urine Cd ^a (μg/L)	1.77 (9.36)	2.11 (11.00)	0.86 (0.95)	0.571
Urine Pb ^a (μg/L)	32.92 (10.16)	33.37 (11.19)	31.45 (5.63)	0.360
Urine Cu ^a (μg/L)	150.45 (265.48)	157.13 (311.22)	133.07 (51.46)	0.703
^a Values were expressed as mean (standard deviation)				

Correlations of urinary metal levels with serum adiponectin

The GEE results for the correlations among metal exposure and serum adiponectin are shown in Table 3. After full adjustment for age, BMI, albumin, total cholesterol, triglycerides, fasting glucose, uric acid, urine creatinine, job tenure, exercise habits, and current smoking status, significantly negative associations of numerous urinary metal levels with serum adiponectin concentration were detected among the welding workers, including Cr ($\beta = -0.088$; 95% CI: -0.148, -0.027, $p = 0.004$), Mn ($\beta = -0.174$; 95% CI: -0.267, -0.081, $p < 0.001$), Co ($\beta = -0.094$; 95% CI: -0.158, -0.029, $p = 0.004$), Ni ($\beta = -0.108$; 95% CI: -0.208, -0.008, $p = 0.033$), Cd ($\beta = -0.067$; 95% CI: -0.115, -0.018, $p = 0.007$), and Pb ($\beta = -0.089$; 95% CI: -0.163, -0.015, $p =$

0.018). However, there were no significant associations between urinary metals and serum adiponectin among office workers. Taken together, these findings indicated that occupational exposure to specific metals might have an impact on the reduction in serum adiponectin levels.

Table 3
Association between urinary metal concentrations and serum adiponectin levels by generalized estimating equation

Exposure markers	Welding workers		Office workers	
	Serum adiponectin (log $\mu\text{g/ml}$)			
	β^b (95% CI)	p value	β^b (95% CI)	p value
Urine Cr ^a (log $\mu\text{g/L}$)	-0.088 (-0.148, -0.027)	0.004	0.022 (-0.088, 0.133)	0.695
Urine Mn ^a (log $\mu\text{g/L}$)	-0.174 (-0.267, -0.081)	<0.001	0.020 (-0.116, 0.156)	0.776
Urine Co ^a (log $\mu\text{g/L}$)	-0.094 (-0.158, -0.029)	0.004	0.017 (-0.082, 0.116)	0.731
Urine Ni ^a (log $\mu\text{g/L}$)	-0.108 (-0.208, -0.008)	0.033	-0.004 (-0.157, 0.148)	0.956
Urine Zn ^a (log $\mu\text{g/L}$)	-0.095 (-0.213, 0.022)	0.112	-0.030 (-0.173, 0.112)	0.677
Urine Cu ^a (log $\mu\text{g/L}$)	-0.025 (-0.214, 0.165)	0.800	-0.127 (-0.273, 0.527)	0.533
Urine Cd ^a (log $\mu\text{g/L}$)	-0.067 (-0.115, -0.018)	0.007	0.007 (-0.068, 0.083)	0.850
Urine Pb ^a (log $\mu\text{g/L}$)	-0.089 (-0.163, -0.015)	0.018	0.029 (-0.068, 0.126)	0.554
^a Adjusted covariates including age, BMI, serum albumin, total cholesterol, uric acid, fasting glucose, triglyceride, urine creatinine, job tenure, smoking habit, recreational activity.				
^b β coefficient was interpreted as a change of log(adiponectin) level for each increased log(urinary metal concentration).				

The contributions of multiple metal exposures to serum adiponectin

Table 4 illustrates an estimate of -0.0435 ($p = 0.048$) per WQS unit in the unadjusted model and an estimate of -0.0478 ($p = 0.026$) per WQS unit in the adjusted model in the inverse correlation. The contributions of multiple urinary metal levels to serum adiponectin levels individually by the WQS regression model are illustrated in **Fig. 2**. As displayed in **Fig. 2A**, the highest contributors to serum adiponectin were Pb, Mn, Ni, Cd, Cr, and Co, making up 49.4%, 22.4%, 15.3%, 6.3%, 5.3%, and 1.4% of the total contribution, respectively, in the unadjusted model. Among these metal exposures, Pb and Mn were the crucial influencing factors. After adjusting for confounders in the WQS regression model, an inverse association was found between urinary heavy metals and serum adiponectin. **Fig. 2B** shows that Pb, Co, and Cr were 30.9%, 27.2%, and 25.7% contributors to serum adiponectin, respectively. Collectively speaking, regardless of these unadjusted or adjusted WQS regression models, among metal exposures, Pb was the most negative contributor and had the greatest influence on serum adiponectin levels.

Table 4
 β coefficients from the weighted quantile sum (WQS) regressions for serum adiponectin levels

	β	p	Weight (%)					
	coefficients	value	log Pb	log Mn	log Ni	log Cd	log Cr	log Co
Unadjusted	-0.0435	0.048	49.4	22.4	15.3	6.3	5.3	1.4
Adjusted	-0.0478	0.026	30.9	8.6	2.1	5.5	25.7	27.2
β coefficients are per increase of an interquartile range of the logarithmically transformed urinary metals. Variables adjusted for include age, BMI, and job tenures.								

Discussion

In this two-year longitudinal study, the most prominent finding was that occupational exposure to specific metals was negatively linked to serum adiponectin levels in welding workers. Additionally, among heavy metal exposures by WQS regression analyses, Pb was the most negative contributor to serum adiponectin levels. To the best of our knowledge, this study was the first to examine the impacts of occupational metal exposure on serum adiponectin levels using GEE and WQS regression models.

An earlier study reported occupational and environmental exposure to Pb as a probable risk factor for cardiovascular disease [18]. Recent experimental and epidemiological studies have indicated that heavy metal exposure was considered a risk factor for cardiovascular disease and raised the public health burden [19–21]. These review articles discussed the potential correlation between chronic heavy metal exposure—including exposure to Pb, Cd, mercury (Hg), and arsenic (As)—and cardiovascular disease, although the mechanism through which heavy metals act to elevate cardiovascular risks remains disputed. These nonessential heavy metals were all nonthreshold toxins and could display toxic effects

at trace concentrations [22]. A review article by Xu et al. proposed that exposure to increased levels of As, Cd, Pb, and Hg was significantly correlated with MetS or comorbid conditions [23]. Another cross-sectional study analysis derived from the Korea National Health and Nutrition Examination Survey of 1,405 subjects indicated that a higher prevalence of MetS was correlated with increased blood Pb concentrations in Koreans [24]. Additionally, a prospective cohort study that enrolled 2,500 young adults of African descent reported that blood As and Pb were significantly associated with elevated fasting glucose with adjustment for percent body fat [25]. In 2000, a review article that contained cell, animal, and human study results suggested the damaging role of Cd in the organic impairment of glucose metabolism; therefore, it contributed to insulin resistance [26]. Numerous studies have established the adverse impacts of toxic heavy metals as potential biomarkers for developing cardiometabolic illnesses.

However, limited literature has explored the relationship between heavy metals and adiponectin levels, especially in occupational exposure. An animal/mouse model executed by Kawakami et al. revealed that Cd exposure caused abnormal adipocyte differentiation, expansion, and function, which lowered the gene expression levels of adiponectin and might contribute to insulin insensitivity [27]. In 2013, the same study group designed another mouse model with Cd administration, which also indicated that Cd exposure induced abnormally smaller adipocytes and decreased adiponectin levels [28]. Another mouse model by the same author found that in vivo exposure to inorganic Co might exhibit a protective function in obesity-related diseases by increasing the expression of adiponectin [29]. This finding was inconsistent with our study results, which demonstrated that occupational exposure to Co might reduce serum adiponectin levels in welding workers. Apart from the animal studies, a longitudinal study by Wang and his colleagues that enrolled 1,228 midlife women without specific heavy metal exposure illustrated that exposure to Cd was associated with an adverse adiponectin profile [30]. Taken together, exposure to Cd was reported as a negative influencing factor on the expression levels of adiponectin, and based on the few studies available, it might also worsen insulin sensitivity and lead to the development of diabetes. In line with earlier reports, our study results revealed that Cd exposure was correlated with decreased serum adiponectin levels, while Co exposure also demonstrated a negative adiponectin profile.

Our preceding study reported that Fe, Zn, Mn, and Cu were dominant among the welding fumes in a shipyard and that welding workers had higher urinary concentrations of Co, Cu, Ni, Mn, Cd, and Zn [31]. Thus, we selected the eight metals to test for in the postexposure urinary samples of the participants in this survey. Among these heavy metal exposures, Pb had the most negative influence on serum adiponectin levels according to the WQS model. One of the mechanisms was probably related to lipid disturbance in occupational Pb exposure. An earlier cross-sectional study by Ademuyiwa et al. suggested that Pb exposure increased cholesterol synthesis and transport to peripheral tissues among petrol station workers [32]. Additionally, aside from conventional mechanisms, telomere shortening and lipid disturbance were also regarded as unignorable roles in the pathway whereby low-level Pb exposure contributed to cardiovascular disease [33]. Moreover, a cross-sectional study of 986 subjects by Sirivarasai et al. indicated that exposure to low Pb levels correlated with deficiency of the enzyme catalase and oxidative stress, which might lead to high blood pressure [34]. In addition to toxic heavy metals, occupational exposure to some essential metals, such as Co, Ni, Cr, and Mn, also negatively

affected serum adiponectin levels in our study. Generally, essential metals are necessary for proper cellular growth and function; otherwise, they play a crucial role as cofactors in various enzymes engaged in metabolism and energy production and respond to oxidative stress. Nevertheless, long-standing overexposure to and deficiencies in trace micronutrients could cause adverse health outcomes. Exposure to Mn, Ni, Cr, and Co has increased because of their use as industrial metals in commercial applications over the last century. A recent study summarized that the main detrimental health impact of Mn, Ni, and Co, to a lesser extent, was on lipid peroxidation arising from oxidative stress [35]. Cr had multiple oxidation states ranging from -2 to $+6$, in which the trivalent and hexavalent forms were primarily stable structures. Cr(VI) was connected with toxicity and carcinogenicity, while Cr(III) was essential in trace amounts for protein and lipid metabolism and acted as a cofactor for insulin action [36]. Similar to other metals, Cr(VI)-induced oxidative stress and reactive oxygen species production at high concentrations affected the lipid content and DNA of cells, which resulted in lipid peroxidation and DNA damage, respectively [37]. Taken together, the typical negative health effects of exposure to heavy metals seemed to be lipid peroxidation resulting from oxidative stress, although heavy metals could also disturb metabolic functions in various ways.

Some limitations of this study should be considered. First, all welding workers were asked to use respiratory protective devices at work, but office workers were not compelled to wear masks when they were in the shipyard. Therefore, some office workers might have contacted metal fumes during their workdays if they walked through the welding sites; this might have increased the exposure levels to heavy metals among the office workers more than we expected. Second, to eliminate sampling bias, we confined the work experience of office workers to those who had not held welding jobs within the past two years. However, some office workers in the shipyard had worked in the welding department when they were younger; therefore, the potential effects of earlier exposures to heavy metals on serum adiponectin levels could not be thoroughly assessed, although we corrected the covariates of job tenures. Next, some heavy metals, such as Cr, had multiple oxidation states, but urinary metals analyzed in this study by ICP-MS could not distinguish the amounts of individual oxidation states. Additionally, the welding aerosol composition varied depending on the specific type of welding process and materials used. Nevertheless, the work content of welding workers in this study could not be set up as a uniform welding process. Last, we did not include individual food intake or record dietary recall as confounding variables in this study. However, almost all workers obtained their lunch from factory-provided meals, which diminished the individual differences in the food consumption of the study subjects.

Conclusions

In conclusion, our study findings suggest that exposure to heavy metals decreases serum adiponectin levels in welding workers. Furthermore, Pb acted as the highest adverse contributor to lower adiponectin levels. Thus, we highlighted an important issue in the prevention of cardiometabolic diseases and occupational illnesses that deserves public attention. In the future, more basic research is needed to clarify the disease pathology and cellular and molecular pathways involved.

Declarations

Authors' Contributions

Chen-Jung Wu contributed to the design of the study, was responsible for the management and retrieval of data, contributed to initial data analysis and interpretation, drafted the initial manuscript. Chen-Jung Wu, A-Chuan Ho, Shih-Ya Chen, Chih-Hong Pan, Hsiao-Chi Chuang, Wei-Liang Chen, and Chung-Ching Wang decided upon the data collection methods. Chen-Jung Wu and Ching-Huang Lai were also responsible for the data analysis decisions. Ching-Huang Lai conceptualized and designed the study, supervised all aspects of the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors meet the [ICMJE](#) criteria for authorship.

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Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Tri-Service General Hospital (TSGH) (IRB No 1-102-05-013). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Conflict of interest

The authors declared that they had no competing interests.

References

1. Antonini JM: **Health effects of welding.** *Critical reviews in toxicology* 2003, **33**(1):61–103.

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):350–360.
3. Akselsson KR, Desaeleer GG, Johansson TB, Winchester JW: **Particle size distribution and human respiratory deposition of trace metals in indoor work environments.** *The Annals of occupational hygiene* 1976, **19**(3-4):225–238.
4. Wardhana, Datau EA: **Metal fume fever among galvanized welders.** *Acta medica Indonesiana* 2014, **46**(3):256–262.
5. Cosgrove MP: **Pulmonary fibrosis and exposure to steel welding fume.** *Occupational medicine (Oxford, England)* 2015, **65**(9):706–712.
6. Koh DH, Kim JI, Kim KH, Yoo SW: **Welding fume exposure and chronic obstructive pulmonary disease in welders.** *Occupational medicine (Oxford, England)* 2015, **65**(1):72–77.
7. Zeidler-Erdely PC, Falcone LM, Antonini JM: **Influence of welding fume metal composition on lung toxicity and tumor formation in experimental animal models.** *Journal of occupational and environmental hygiene* 2019, **16**(6):372–377.
8. Planchart A, Green A, Hoyo C, Mattingly CJ: **Heavy Metal Exposure and Metabolic Syndrome: Evidence from Human and Model System Studies.** *Current environmental health reports* 2018, **5**(1):110-124.
9. Bulka CM, Persky VW, Daviglius ML, Durazo-Arvizu RA, Argos M: **Multiple metal exposures and metabolic syndrome: A cross-sectional analysis of the National Health and Nutrition Examination Survey 2011-2014.** *Environmental research* 2019, **168**:397-405.
10. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ: **Prevalence of the metabolic syndrome in the United States, 2003-2012.** *Jama* 2015, **313**(19):1973–1974.
11. Ibfelt E, Bonde JP, Hansen J: **Exposure to metal welding fume particles and risk for cardiovascular disease in Denmark: a prospective cohort study.** *Occupational and environmental medicine* 2010, **67**(11):772–777.
12. Luo JC, Hsu KH, Shen WS: **Inflammatory responses and oxidative stress from metal fume exposure in automobile welders.** *Journal of occupational and environmental medicine* 2009, **51**(1):95–103.
13. Brand P, Bauer M, Gube M, Lenz K, Reigen U, Spiegel-Ciobanu VE, Kraus T: **Relationship between welding fume concentration and systemic inflammation after controlled exposure of human subjects with welding fumes from metal inert gas brazing of zinc-coated materials.** *Journal of occupational and environmental medicine* 2014, **56**(1):1–5.
14. Kadowaki T, Yamauchi T: **Adiponectin and adiponectin receptors.** *Endocrine reviews* 2005, **26**(3):439–451.
15. Lara-Castro C, Fu Y, Chung BH, Garvey WT: **Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease.** *Current opinion in lipidology* 2007, **18**(3):263–270.

16. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K: **Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome.** *The Journal of clinical investigation* 2006, **116**(7):1784–1792.
17. Carrico C, Gennings C, Wheeler DC, Factor-Litvak P: **Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting.** *Journal of agricultural, biological, and environmental statistics* 2015, **20**(1):100-120.
18. Poręba R, Gać P, Poręba M, Andrzejak R: **Environmental and occupational exposure to lead as a potential risk factor for cardiovascular disease.** *Environmental toxicology and pharmacology* 2011, **31**(2):267–277.
19. Alissa EM, Ferns GA: **Heavy metal poisoning and cardiovascular disease.** *Journal of toxicology* 2011, **2011**:870125.
20. Burroughs Peña MS, Rollins A: **Environmental Exposures and Cardiovascular Disease: A Challenge for Health and Development in Low- and Middle-Income Countries.** *Cardiology clinics* 2017, **35**(1):71–86.
21. Yang AM, Lo K, Zheng TZ, Yang JL, Bai YN, Feng YQ, Cheng N, Liu SM: **Environmental heavy metals and cardiovascular diseases: Status and future direction.** *Chronic diseases and translational medicine* 2020, **6**(4):251–259.
22. Rahman Z, Singh VP: **The relative impact of toxic heavy metals (THMs) (arsenic (As), cadmium (Cd), chromium (Cr)(VI), mercury (Hg), and lead (Pb)) on the total environment: an overview.** *Environmental monitoring and assessment* 2019, **191**(7):419.
23. Xu P, Liu A, Li F, Tinkov AA, Liu L, Zhou JC: **Associations between metabolic syndrome and four heavy metals: A systematic review and meta-analysis.** *Environmental pollution (Barking, Essex: 1987)* 2021, **273**:116480.
24. Rhee SY, Hwang YC, Woo JT, Sinn DH, Chin SO, Chon S, Kim YS: **Blood lead is significantly associated with metabolic syndrome in Korean adults: an analysis based on the Korea National Health and Nutrition Examination Survey (KNHANES), 2008.** *Cardiovascular diabetology* 2013, **12**:9.
25. Ettinger AS, Bovet P, Plange-Rhule J, Forrester TE, Lambert EV, Lupoli N, Shine J, Dugas LR, Shoham D, Durazo-Arvizu RA *et al*: **Distribution of metals exposure and associations with cardiometabolic risk factors in the "Modeling the Epidemiologic Transition Study".** *Environmental health: a global access science source* 2014, **13**:90.
26. Buha A, Đukić-Čosić D, Ćurčić M, Bulat Z, Antonijević B, Moulis JM, Goumenou M, Wallace D: **Emerging Links between Cadmium Exposure and Insulin Resistance: Human, Animal, and Cell Study Data.** *Toxics* 2020, **8**(3).
27. Kawakami T, Sugimoto H, Furuichi R, Kadota Y, Inoue M, Setsu K, Suzuki S, Sato M: **Cadmium reduces adipocyte size and expression levels of adiponectin and Peg1/Mest in adipose tissue.** *Toxicology* 2010, **267**(1-3):20–26.
28. Kawakami T, Nishiyama K, Kadota Y, Sato M, Inoue M, Suzuki S: **Cadmium modulates adipocyte functions in metallothionein-null mice.** *Toxicology and applied pharmacology* 2013, **272**(3):625–

29. Kawakami T, Hanao N, Nishiyama K, Kadota Y, Inoue M, Sato M, Suzuki S: **Differential effects of cobalt and mercury on lipid metabolism in the white adipose tissue of high-fat diet-induced obesity mice.** *Toxicology and applied pharmacology* 2012, **258**(1):32–42.
30. Wang X, Karvonen-Gutierrez CA, Mukherjee B, Herman WH, Park SK: **Urinary metals and adipokines in midlife women: The Study of Women's Health Across the nation (SWAN).** *Environmental research* 2021, **196**:110426.
31. Lai CY, Lai CH, Chuang HC, Pan CH, Yen CC, Lin WY, Chen JK, Lin LY, Chuang KJ: **Physicochemistry and cardiovascular toxicity of metal fume PM2.5: a study of human coronary artery endothelial cells and welding workers.** *Scientific reports* 2016, **6**:33515.
32. Ademuyiwa O, Ugbaja RN, Idumebor F, Adebawo O: **Plasma lipid profiles and risk of cardiovascular disease in occupational lead exposure in Abeokuta, Nigeria.** *Lipids in health and disease* 2005, **4**:19.
33. He L, Chen Z, Dai B, Li G, Zhu G: **Low-level lead exposure and cardiovascular disease: the roles of telomere shortening and lipid disturbance.** *The Journal of toxicological sciences* 2018, **43**(11):623–630.
34. Sirivarasai J, Kaojarern S, Chanprasertyothin S, Panpunuan P, Petchpoung K, Tatsaneeyapant A, Yoovathaworn K, Sura T, Kaojarern S, Sritara P: **Environmental lead exposure, catalase gene, and markers of antioxidant and oxidative stress relation to hypertension: an analysis based on the EGAT study.** *BioMed research international* 2015, **2015**:856319.
35. Sule K, Umbaar J, Prenner EJ: **Mechanisms of Co, Ni, and Mn toxicity: From exposure and homeostasis to their interactions with and impact on lipids and biomembranes.** *Biochimica et biophysica acta Biomembranes* 2020, **1862**(8):183250.
36. Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M: **Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic.** *Frontiers in pharmacology* 2021, **12**:643972.
37. Wise SS, Aboueissa AE, Martino J, Wise JP, Sr.: **Hexavalent Chromium-Induced Chromosome Instability Drives Permanent and Heritable Numerical and Structural Changes and a DNA Repair-Deficient Phenotype.** *Cancer research* 2018, **78**(15):4203–4214.

Figures

Figure 1

Ratio of metals of exposure/control group from personal air samples in the metal fumes particulate matter

Figure 2

The associations between urinary metal levels and serum adiponectin levels based on weighted quantile sum regression analysis (A) unadjusted, (B) adjusted.