Metal mixtures with longitudinal changes in lipid profiles: findings from the manganese-exposed workers healthy cohort

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Abstract

The majority of epidemiological investigations on metal exposures and lipid metabolism employed cross-sectional designs and focused on individual metal. We explored the associations between metal mixture exposures and longitudinal changes in lipid profiles and potential sexual heterogeneity. We recruited 250 men and 73 women, aged 40 years at baseline (2012), and followed them up in 2020, from the manganese-exposed workers healthy cohort. We detected metal concentrations of blood cells at baseline with inductively coupled plasma mass spectrometry. Lipid profiles were repeatedly measured over 8 years of follow-up. We performed sparse partial least squares (sPLS) model to evaluate multi-pollutant associations. Bayesian kernel machine regression was utilized for metal mixtures as well as evaluating their joint impacts on lipid changes. In sPLS models, a positive association was found between manganese and change in total cholesterol (TC) (beta = 0.169), while a negative association was observed between cobalt (beta = −0.134) and change in low density lipoprotein cholesterol (LDL-C) (beta = −0.178) among overall participants, which were consistent in men. Interestingly, rubidium was positively associated with change in LDL-C (beta = 0.273) in women, while copper was negatively associated with change in TC (beta = −0.359) and LDL-C (beta = −0.267). Magnesium was negatively associated with change in TC (beta = −0.327). We did not observe the significantly cumulative effect of metal mixtures on lipid changes. In comparison to other metals, manganese had a more significant influence on lipid change [group PIP (0.579) and conditional PIP (0.556) for TC change in men]. Furthermore, male rats exposed to manganese (20 mg/kg) had higher levels of LDL-C in plasma and more apparent inflammatory infiltration, vacuolation of liver cells, nuclear pyknosis, and fatty change than the controls. These findings highlight the potential role of metal mixtures in lipid metabolism with sex-dependent heterogeneity. More researches are needed to explore the underlying mechanisms.

Keywords Dyslipidemia · Metal mixtures · Manganese · Longitudinal study

Abbreviations

MEXWHC Manganese-exposed workers healthy cohort
ICP-MS Inductively coupled plasma mass spectrometry
sPLS Sparse partial least squares
BKMR Bayesian kernel machine regression
TC Total cholesterol

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TG Triglycerides
HDL-C High-density lipoprotein cholesterol
LDL-C Low-density lipoprotein cholesterol
LOD Limit of detection
ICC Intraclass correlation coefficient
BMI Body mass index
OLS Ordinary least squares
PIP Posterior inclusion probabilities
Mg Magnesium
Mn Manganese
Fe Iron
Co Cobalt
Cu Copper
Zn Zinc
Se Selenium
Rb Rubidium
Cd Cadmium
Pb Lead
ROS Reactive oxygen species
SHBG Sex hormone-binding globulin
ERRα Estrogen-related receptor alpha

Introduction

Dyslipidemia has experienced a remarkable increase in the last two decades, particularly in developing countries. Over the last decade, the prevalence of dyslipidemia of Chinese adults has risen from 18.6 to 40.4% (Huang et al. 2019). Based on the data from Global Burden of Disease Study in 1990–2019, elevation in low density lipoprotein cholesterol has risen from the 14th to the 8th leading risk factor of attributable disability-adjusted life-years worldwide (Collaborators GBDRF 2020). New evidence has emerged and suggested the link between elevated triglyceride-rich lipoprotein and low-grade inflammation, atherosclerotic cardiovascular disease as well as all-cause mortality (Nordestgaard 2016). Unfavorable lipid trajectories throughout adulthood (35 years) were supposed to be related to a higher cardiovascular and mortality risk in later life (Duncan et al. 2019). There is an urgent need for exploring the pathogenesis for dyslipidemia, particularly the early and minor alteration in lipid profiles.

The roles of related factors have been well studied, such as diet and lifestyles; however, the impacts of exposures from environment remain understudied. Growing evidences emerged and suggested links between environmental factors, including metals, and alteration in lipid levels or dyslipidemia (Chen et al. 2020; Karim et al. 2013; Ledda et al. 2018; Yang et al. 2017; Yue et al. 2022; Zang et al. 2018; Zhou et al. 2016). The majority of previous studies were restricted by exposure to single metal and few cross-sectional researches have investigated relationships of multiple metals with dyslipidemia risk or metabolic syndrome components (Bulka et al. 2019, Moon 2014, Park and Kim 2019, Xu et al. 2020, Zhu et al. 2021). However, no conclusive results were drawn from the previous researches owing to potentially reverse causation by cross-sectional design or bias. Though several researches were available on the longitudinal associations of metal exposures with incident of dyslipidemia (Bai et al. 2015; Jiang et al. 2021; Kuo et al. 2018; Stranges et al. 2011; Xiao et al. 2019), scarce evidence was available on alteration in lipid profile.

It is known that people are faced with metal mixture exposures in reality. More evidences emerged suggesting the toxic effects of metal mixture exposures were not the same as that of a single metal (Silva et al. 2002; Wu et al. 2016). Therefore, we should pay more attention to the potential health effects related to metal mixture exposures in the development of dyslipidemia or alteration in lipid profile. Given sparse partial least squares (sPLS) regression can be used in dimension reduction and variable selection (Chun and Keles 2010), while Bayesian kernel machine regression (BKMR) can flexibly assess combined effects of mixture components (Bobb et al. 2015), we utilized sPLS and BKMR models to reduce dimension of metal mixtures and identify effect of metal mixtures on lipid change. Here, we aimed to assess the associations of metal mixture exposures with changes in lipid profiles in the subjects from the manganese-exposed workers healthy cohort (MEWHC).

Materials and methods

Study participants

The participants were gathered from the MEWHC. More details on the cohort were provided in previous studies (Lv et al. 2014; Zhou et al. 2018). In brief, the prospective cohort started in 2011 focusing on exploring early health effects, potential biomarkers of exposure, disease and susceptibility, and diseases related to occupational metal exposure. A total of 1888 individuals were enrolled into manganese-exposed workers healthy cohort (MEWHC). The same information as gathered at baseline will be collected through questionnaires, physical examination, and biological specimens. Participants (n = 573) were selected both in baseline (September 2012) and follow-up (May 2020) visits, whose information on demographics, lifestyles, and physical examination were available. We excluded people who changed occupation type during the time interval (n = 164), lacked data on lipid profile (n = 30) or metal concentrations in blood cells (n = 43),
and outliers with abnormal metal level [higher than three times percent 99 of metals (n = 13)]. Finally, 323 participants were remained in final analysis.

Written informed consent was signed by each participant, and this study was approved by the Ethics and Human Subject Committees of Guangxi Medical University.

**Blood collection**

After overnight fast, 5 mL blood sample from peripheral venous was collected. Then, the blood samples were centrifugated at 3500 rpm for 10 min and subsequently separated into plasma, serum, and blood cells. The samples were refrigerated at –80°C prior to analysis.

**Determinations of metal concentrations in blood cells**

We measured 22 metal concentrations of blood cells following protocols (Xiao et al. 2021). The certified reference materials (Seronorm™ Trace Elements Whole Blood RUO no. 210105, 210205, and 210305, ALS Scandinavia, Sweden) and standard reference material (SRM1640a, Trace Elements in Natural Water from Natural Institute of Standard Technology, Gaithersburg, MD, USA) were used to assess the accuracy and instrument stability of detection method. And we also used procedural blanks, duplicates as quality controls. The limit of detection (LOD) of 22 blood metals ranged from 0.001 to 2.020 μg/L. The value, equaling to LOD divided by $\sqrt{2}$, was imputed for the sample whose concentration was below the corresponding LOD. The detection rates of 22 metals in blood cells were 100% except aluminum, tin, and antimony whose detection rate were 78.2%, 0.3%, and 47.8%, respectively. Therefore, we did not include these metals for further analysis.

**Metal concentration variability assessments**

We evaluated the variabilities of metal concentrations by comparing levels in 2012, 2017, and 2020, respectively. More details were available elsewhere (He et al. 2022). We calculated correlation coefficients from Spearman’s rank-order analysis and intraclass correlation coefficient (ICC) to assess variation across the visits. The ICCs ranged from 0.000 (vanadium) to 0.979 (cadmium). And the correlation coefficient ranged from 0.233 (arsenic) to 0.948 (cadmium) in 2012–2017 and from 0.122 (strontium) to 0.948 (cadmium) in 2017–2020. As a result, 10 metals (magnesium, manganese, iron, cobalt, copper, zinc, selenium, rubidium, cadmium and lead) with ICCs higher than 0.4 were remained in final analysis.

**Determination of lipid parameters**

Levels of lipid profiles, including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), were determined with an automatic biochemical analyzer (Hitachi 7600–020, Kyoto, Japan). The longitudinal change in lipid was defined as lipid level at follow-up minus lipid level at baseline.

**Definition of covariates**

Socio-demographic characteristics and lifestyle habits were collected by face-to-face questionnaire. Seniority was defined as the length (year) of subjects worked for the ferro-manganese refinery. Participants were defined as a current drinker who drank alcohol at least once each week for more than 3 months, and a current drinker (no) always never drank or formerly drank (less than 5 mL once). Those who smoked at least one cigarette daily for more than 3 months were defined as a current smoker, and a current smoker (no) was the rest (never smoked or a former smoking habit with cessation for more than 3 months) (Zhou et al. 2018).

**Animal experiments**

Eighty Sprague–Dawley rats (3-week old, male and female in half, 125–150 g, purchased from the Experimental Animal Center of Guangxi Medical University) were used, and procedures were as described in the previous study (Cheng et al. 2018). Male and female rats were randomly subdivided into 4 groups of 10 animals each, which were treated with 2 ml/kg of sterile saline, 5.0 mg/kg, 10.0 mg/kg, and 20.0 mg/kg of MnSO₄•H₂O (St. Louis, MO, USA), respectively, via intraperitoneal injection for 24 weeks. On the next day after 24 weeks of MnSO₄•H₂O treatment, the rats were sacrificed by cervical dislocation, plasma and the liver were immediately excised and stored at –80°C. Inductively coupled plasma mass spectrometry (ICP-MS) was employed to detect concentrations of hepatic manganese in rats. Briefly, approximately 50 mg of each hepatic tissue from the rat was transferred to a microwave cuvette, and the exact mass was measured. Digestion was carried out by a microwave accelerated reaction system (MARS6 Classic, GEM, USA), and samples were decomposed in 5 mL of nitric acid (65%, Merck, Germany) at 180°C, by applying the following temperature program: step 1, 10 min warm-up to 120°C and heating for additional 5 min; step 2, 15 min warm-up to 180°C and heating for additional 20 min. After cooling, decomposed samples were transferred into
the centrifuge tubes (Eppendorf, Germany) and diluted to 25 mL with ultrapure water (resistance of 18.2 MΩ, obtained from Cascada III.I 10 system, PALL, USA). The method of quality control refers to the previous study (Stojsavljevic et al. 2020). We used the certified reference materials (Seronorm™ Trace Elements Whole Blood RUO no. 210105, 210205, and 210305, SERO, Norway) and Standard Reference Material (SRM1640a, Trace Elements in Natural Water, National Institute of Standards and Technology, USA) as standard reagent for quality assurance in tissue measurement.

Lipid profiles in plasma of rats were measured with an automatic biochemical analyzer (Hitachi 7600–020, Kyoto, Japan). After fixing the tissue, hepatic tissue from 3 animals of each group were transversely sectioned, dehydrated in ethyl alcohol (75%) and cleared by toluene, then embedded in paraffin wax, and sectioned in 5 μm slices. The slices were stained with hematoxylin and eosin for histological analysis. The samples were examined under a light microscope (ZEISS IMAGER A2-M2, Germany), and images were taken at 40× magnification.

Statistical analysis

We used mean (standard deviation) or frequency (percent) to present demographic information. In order to reduce skewed distributions of metal concentrations in blood cells, the metals were log10-transformed and represented as median [25th (P25), 75th percentiles (P75)]. Spearman’s rank-order correlation analysis was performed for correlation assessment across the metals. We conducted inverse-normal transformed of the levels of lipid changes to improve normality.

For single-metal model, linear regression model (ordinary least squares, OLS) was performed to assess the relationships of 10 metals with lipid changes with the metal entering the model as a separated predictor. Gender and baseline age, seniority, BMI, smoking habits, drinking habits, and lipid levels were adjusted for covariates. For multiple-metal model, the relationships of 10 metals with lipid changes adjusted covariates as in single-metal model and metals were simultaneously entered into the model.

In multi-pollutant model, sPLS regression was employed for assessing the relationships of metal mixtures with lipid changes (continuous variable). The number of latent components in the model (K) and thresholding parameter (eta) was determined by a tenfold cross-validation in the optimal model.

BKMR model was also employed by splitting the 10 metals into 2 groups: essential metals (Mg, Mn, Fe, Co, Cu, Zn, and Se) and non-essential metals (Rb, Cd, and Pb). In BKMR model, we assessed the nonlinear and interactive effects as well as cumulative effects of 10 metals on lipid changes.

First, we used posterior inclusion probabilities (PIP) analyses to assess the importance of metals on lipid changes. The univariate dose–response curve of specific metal with lipid change was showed when the remaining was fixed at P50. The difference (95% CI) in lipid change related to increase in metal concentration from its P25 to P75 was determined with the remaining metals fixed at P25, P50, or P75, respectively. The overall effects of metal mixtures at particular quantiles were estimated in comparison to their P50s. We evaluated the interactions between metals on lipid changes. To investigate potential sexual heterogeneity, gender-stratified analysis was performed in all models.

For animal experiments, tow-way ANOVA and LSD post hoc tests were used to test the difference between manganese-exposed groups and the controls. All graphs were plotted using GraphPad Prism 6.

All statistical analyses were performed with R (Version 4.0.3) and SPSS (version 26.0, IBM). P value <0.05 was considered as statistically significant.

Results

Characteristics of the participants

Table 1 summarizes the demographic characteristics and metal concentrations of 323 participants (men = 250, women = 73). The majority of participants were likely to be married or in cohabitation, with a normal BMI and high school education level or above. Current smokers and current drinkers were almost found in men. None of the women were current smokers and less was current drinkers. The lipid at followed-up were significantly higher than that at baseline except HDL-C (all P <0.001) (Fig. S1).

Metal concentrations and corresponding correlations

The metal concentrations in blood cells are showed in Table 1. Highest of median concentration was observed for iron (1058.52 mg/L), and lowest was observed for cobalt (0.09 μg/L). The concentrations of rubidium, cadmium, and lead in men were higher as compared to women, while manganese, cobalt, and copper were opposite (all P <0.05).

We also performed spearman’s rank-order correlations analysis to reveal the correlations between the metals in blood cells (Fig. 1).

Associations of metals in blood cells with lipid changes in single-metal model

In overall, manganese showed a positive association with TC change (beta=0.808); cobalt was negatively associated with LDL-C change (beta= −0.518). For men, manganese showed
a positive association with TC change (beta = 0.899); cobalt was negatively associated with LDL-C change (beta = −0.725). However, we found no significant relationship between metal and lipid change for women (Table S1).

**Associations of metals in blood cells with lipid changes in multi-metal model**

In overall, manganese showed a positive association with TC change (beta = 0.909), while cobalt showed a negative association with TC change (beta = −0.636). A negative association was found for cobalt and LDL-C change (beta = −0.716). In gender-stratified analysis, a negative association was found for zinc and TC change only in men (beta = −1.947). Cobalt showed a negative association with LDL-C change in men (beta = −0.813). Copper was negatively associated with TC change only in women (beta = −7.304) (Table S2).

**Associations of metals in blood cells with lipid changes in sPLS model**

In sPLS regression model, we selected predictive metals with lipid changes with adjustment for covariates. The optimal model was selected for the minimum mean squared prediction error according to the ten fold cross-validation.
The error path and the selected metals were available in Fig. S2 and Table 2, respectively. In overall participants, we observed a positive association between manganese (beta = 0.169) and TC change, whereas a negative association was established between cobalt (beta = −0.178) and LDL-C change (both P < 0.05). In men, the associations of manganese (beta = 0.156) with TC and cobalt with LDL-C change (beta = −0.133) were in line with that in overall (both P < 0.05). In women, magnesium (beta = −0.327) and copper (beta = −0.359) showed negative associations with TC changes, and rubidium (beta = 0.273) showed a positive association with LDL-C change.

**Bayesian kernel machine regression analysis**

No significant cumulative effect of the metal mixtures was observed on changes for TC, TG, or LDL-C (Fig. 2). To investigate the dose–response relationship, we estimated the univariate relationship of specific metal with changes in lipid markers with other metals fixed at P50 (Fig. S3).
The results indicated dose–response relationships between specific metal and changes in lipid markers appeared to be approximately linear, except for cadmium and change in TC among women. We then sought to learn the difference (95% CI) of lipid changes caused by specific metal increasing from its P25 to P75 with the remaining fixed at P25, P50, or P75, respectively. We observed manganese displayed a significantly positive association with TC change in overall participants (Fig. S4A). We also detected potential interaction effects but there was little evidence for interactions between the metals on changes in lipid profiles (Fig. S5).

**Associations of chronic manganese exposure and lipid profile in rats**

To further verify the association between manganese exposure and lipid profiles, we firstly detected the concentration of manganese in rats' liver (Fig. S6). When compared with the control group, only male rats that treated with 20 mg/kg MnSO₄•H₂O were observed a significantly higher level of manganese (P = 0.002), and there was a significant difference in manganese deposition between sexes at this dose. In addition, only the plasma LDL-C levels significantly increased in male rats that received the highest dose (P = 0.026). None significant difference was found in lipid levels between the groups of female rats (Fig. S7).

Finally, the liver histopathological analysis was pretended in Fig. S8. No major abnormalities were observed in the control group. Rats that received 5 mg/kg MnSO₄•H₂O showed minor sinusoidal dilatation with slightly inflammatory infiltrates in both sexes. The medium and high-dose group rats presented apparent inflammatory infiltration, vacuolation of liver cells, nuclear pyknosis, fatty changes, and fibrosis (Fig. S8).

**Discussion**

The strongest finding in the present study is to identify of sex-specific metals related to lipid changes among the participants from MEHWC. The consistent findings from sPLS and BKMR analysis indicated significantly positive associations of manganese with elevated TC and LDL-C among overall participants and men. The BKMR model showed manganese dominated the positive cumulative effect of ten metal mixtures.
on elevated TC and LDL-C, though the effects including the null. Interestingly, we found significantly negative associations of copper with elevated TC and LDL-C among women. In addition to sex differences in metal levels, previous researches have also revealed sex differences in lipid levels or lipid patterns. A higher risk of cardiovascular disease was observed in men compared with women, even if with comparable serum lipid concentrations (Johnson et al. 2004). It was reported higher TC and HDL-C were observed in women from the Multi-Ethnic Study of Atherosclerosis study (Goff et al. 2006). Moreover, higher large HDL-C, large HDL-C to total HDL-C ratio, and less small HDL-C were found in women in comparison to men (Johnson et al. 2004). Furthermore, men have a higher fraction of small dense LDL-C and larger VLDL particles, and small dense LDL-C has been implicated as a major cardiovascular disease risk factor. Based on the sex-difference in the metals and lipids, we performed the stratified analysis by sex. Interestingly, we found some associations between metal exposures and changes in lipid profiles with sex-specific heterogeneity.

By selecting the predictive metals associated with lipid changes, our study may provide additional clinical value to identify individuals with elevated lipid profile. The use of sPLS model helped to identify the associations between metals and lipid changes, which might be covered up by high correlation or data dimension in traditional statistical models, such as copper and rubidium for LDL-C in women and cobalt for TC in overall participants. Furthermore, the importance of each metal on the lipid change was quantified accounting for inter-metal interactions. As showed in PIP analysis, manganese might play the most important role in association of metal mixture exposures with change in TC in men, given the both highest group PIP and conditional PIP (0.579 and 0.556) among metals. It is interesting given that the association of manganese with lipid change was independent, suggesting the complexity in relationship may not be noticed in conventional analysis strategy. However, manganese serves as both essential metals and neurotoxins depending on doses (Li and Yang 2018). Compared to the levels of metals reported in previous researches, the concentration of manganese in current study (median, 29.30 μg/L) was higher than that in erythrocyte of the general population (mean, 17.4 μg/L) (Heitland and Koster 2021); however, it was still lower than the levels of smelters or welders in other

![Fig. 2 Cumulative effects of metal mixtures for changes in lipid profiles in BKMR model. In overall participants, A TC; B TG; C LDL-C. In men, D TC; E TG; F LDL-C. In women, G TC; H TG; I LDL-C. Abbreviations: TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol](image-url)
places (mean or median, ranging from 79 to 1300 μg/L) (Jiang et al. 2007; Long et al. 2014; Ou et al. 2018). The variation in the shape of relationship may weaken the overall association with change of lipid profile. Moreover, MEWHC was performed among occupational workers in China; the harmful effects of heavy metals might be less profound among general population.

Moreover, our study assessed the potential sexual heterogeneity in the association of manganese with lipid changes. For instance, a positive association was found between manganese and change in lipid in men but not women. Oxidative stress leading to lipid peroxidation is a well-known mechanism for manganese toxicity, and manganese imbalance may promote more reactive oxygen species (ROS) producing, leading to oxidative stress, inflammation, and endothelial dysfunction (Bornhorst et al. 2013). In line with our previous research (Cheng et al. 2018), the activities of SOD, GSH-Px, and CAT in plasma of rats exposed to chronic manganese decreased, while the level of MAD increased, suggesting that chronic manganese exposure can reduce the antioxidant level. However, the production of ROS increased, which exceeds the antioxidant capacity of the body, resulting in excessive lipid peroxidation products and ultimately leading to mitochondrial damage and energy metabolism disorders. An animal experiment found that manganese enhanced cholesterol biosynthesis in the rats’ liver microsome and stimulated farnesyl pyrophosphate synthase activity, which was an important synthesis pathway for regulating cholesterol biosynthesis and metabolism (Bell and Hurley 1973). Differences in response to hormones between men and women might account for the sex-specific association of manganese with lipids changes. Manganese was positively associated with sex hormone binding globulin (SHBG) (Rotter et al. 2016). Previous researchers indicated higher SHBG level showed significant relation to an elevated lipid profile. For instance, a positive association was found in men but not women. This is the first to evaluate the associations of metal mixture exposures with lipid changes by a prospective longitudinal study. In addition, we used different methods (sPLS and BKMR models) to remedy the gaps in traditional approaches, and we observed consistent findings. However, there were several limitations in our study. First, the sample size was relatively small, limiting the power for interpretation of results, particularly in women. Second, baseline levels of metals might not completely represent the exposure level in a long term. However, metals levels could be considered to be relatively stable because the occupation type of the participants were fixed. Moreover, metals in blood cells showed fair reproducibility (ICC > 0.4). Last but not the least, this study was based on an occupational population who were exposed to relatively high level of metals, and the findings need to be further confirmed in the general population.

Conclusions

To conclude, these findings highlight the potential role of metal mixtures in lipid metabolism with sex-dependent heterogeneity. More researches are needed to explore the underlying mechanisms.
Supplementary Information  The online version contains supplementary material available at https://doi.org/10.1007/s11356-022-21653-5.

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Data availability The datasets used or analyzed and materials during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval The Medical Ethics Committee of Guangxi Medical University (ID: 20200021) have approved all study procedures.

Consent to participate All participants have signed the informed consents for this study.

Consent for publication The manuscript is approved by all the authors for publication.

Competing interest The authors declare no competing interests.

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