High manganese exposure decreased the risk of high triglycerides in male workers: a cross-sectional study

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Abstract

Manganese (Mn) is to be involved in lipids metabolism. However, few epidemiological studies have investigated the association between elevated exposure to Mn and the risk of dyslipidemia. Methods: This was a cross-sectional study based on follow-up of the manganese-exposed workers healthy cohort (MEWHC) in 2017. A total of 803 Mn-exposed workers were divided into the low-exposure, and high-exposure group according to Mn-Time Weighted Average (Mn-TWA) ≤0.15mg/m3 or >0.15mg/m3. And we evaluated the associations between Mn-TWA levels and dyslipidemia, and assessed the interaction between Mn-TWA levels and each of the potential interacting factors. Results: After adjustment for potential confounders, we observed mainly significant negative association between high triglycerides (TG) risk and Mn-TWA levels in male (OR = 0.60; 95% CI: 0.39, 0.94; p <0.01). In interaction analyses of male, we did not observe a significant interaction between Mn-TWA levels and pack-years on high TG risk (relative excess risk for the interaction (RERI) = -1.30, 95% CI: -3.29, 0.70, RERI = -1.62, 95% CI: -3.92, 0.67). Similarly, analysis of smoking status, drinking status, high-fat diets frequency, and BMI were nonsignificant interaction with Mn-TWA levels on high TG risk as well. Conclusions: Our study indicated that high Mn exposure was significantly associated with low risk of hyper TG in male workers.Keywords: Manganese; Occupation; Dyslipidemia; Triglycerides

Background

Manganese (Mn) is an important trace element that plays an important role in immune system function, cell energy regulation, bone and connective tissue growth, blood coagulation, and reproductive hormones[1-3]. Meanwhile, excessive Mn has also been proved to have toxic effects on the human central nervous system, affecting specific areas of the central nervous system. Mn exposure in workers have been shown to induce neurotoxic effects resulting in neurobehavioral impairment and neuromotor deficits [4-7].

Mn has also been reported to be involved in lipids metabolism. However, the mechanism of effect of Mn on lipid metabolism is not clear for the time being. Some studies have reported that Mn reduced the total antioxidant status and increased brain lipids peroxidation in rats [8, 9]. At the same time, Mn was found to stabilize lipoprotein particles in cell research and involved in the development of normal lipids composition and structure in rats [10, 11]. Furthermore, Mn was found to enhance cholesterol biosynthesis in rats liver microsome and stimulate the activity of farnesyl pyrophosphate synthase. The important synthesis pathway for many lipids was the mevalonate pathway, and this enzyme was the first branch of this pathway [12-15]. However, studies on the effect of Mn on serum lipids were rare. A recent report found that rats exposed to low doses of Mn can reduce serum TG levels [16]. Meanwhile, epidemiological data were all focused on studies on dietary Mn intake. A dietary survey of Chinese people, Mn intake was negatively correlated with hypertriglyceridemia in male, while Mn was positively associated with low HDL-C only in female [17]. Similarly, in a study of obese men, high serum Mn was also found to significantly reduce HDL-C concentrations [18]. Another survey on polymetallic dietary intake in China found that Mn intake was negatively correlated with serum TG and T-CHO [19]. Welding,

mining and smelting have long been considered occupations of manganese overexposure [20]. In addition, with the use of methyl cyclopentadienyl manganese tricarbonyl (MMT) as an antiknock agent in gasoline, the exposure of ordinary residents to manganese is also increasing[21]. The public health issues related to Mn are raising more and more concern in public health. However, no studies have assessed the relationship between Mn exposure and the changes in the levels of serum lipids in occupationally Mn-exposed workers.

Manganese-exposed workers healthy cohort (MEWHC) was a longitudinal prospective and multidisciplinary study that began in July to October 2011 in an iron and manganese smelters [22]. The primary goal of MEWHC was to explore early or long-term health effects, potential exposure biomarkers, and the diseases associated with Mn exposure. Therefore, we conducted this study to investigate Mn external exposure with dyslipidemia to explore the relationship between Mn exposure and serum lipids in occupationally Mn-exposed workers.

Methods

Date collection

This was a cross-sectional study based on follow-up of the manganese-exposed workers healthy cohort (MEWHC) in 2017, detailed description of the inclusion criteria and exclusion criteria for this cohort can be found in the previous study [22, 23]. Face-to-face interviews were conducted by trained staff, and we used standardized and structured questionnaires to collect the basic information, including demographic information, smoking, drinking status, high-fat diets frequency, medicine intake in the past two weeks, and self-report chronic diseases. We measured height and weight, waist circumference, and blood pressure using standard methods. Body mass index (BMI, kg/m^2) was calculated from the height and weight measurements. The history of hypertension was defined according to the subjects' self-reported history and the results of blood pressure measured in the field, and the standard methods and definition of the Chinese guidelines for the prevention and treatment of hypertension to define hypertension (revised in 2018) was used[24]. We conducted a high animal fat diets frequency questionnaire to assess high fat diets intake. We divided the weekly high animal fat diets frequency into two groups, low high-fat diets frequency group was defined as the high-fat diets frequency less than 3 times per week, and high high-fat diets frequency group was defined as the high-fat diets frequency 3 times or more per week. Current smoking status was defined as smoking at least one cigarette per day for 6 consecutive months. Current drinker was defined as drinking more than 5 ml at a time and drinking at least 3 times a week for 6 months. Participants were classified as nonsmoker, former smoker or current smoker. A pack-year was defined as 20 cigarettes smoked every day for one year [25]. We further categorized participants' smoking status into three groups on the basis of median pack-years: nonsmoker, <18 pack-years, and ≥18 pack-years.

Our study subjects were recruited from the follow-up of manganese-exposed workers healthy cohort (ME WHC) in 2017. According to the exclusion criteria, subjects with cancer, or coronary heart disease, or

stroke disease, or diabetes were excluded from the 828 workers, as well as those whose biological samples were undetected. Finally, a total of twenty-two subjects were excluded from our study. In the end, a total of 803 occupationally Mn-exposed workers were invited to participate in our study. All biological samples include blood and urine samples were collected after a night of fasting, and immediately were transported to the biobank and stored deep frozen at -80°C until be analyzed.

Measurement of Mn concentration in the respirable dust

We collected a total of 134 samples including 20 categories of relatively typical occupation by personal sampling. We selected three subjects in each occupation and measured their respiratory dust for 3 consecutive days. We used the air sampling pump (SENSIDYNE, GilAirPlus, US) and respirable dust sampling head (HXFC-WH, Wuhan, China), and glass fiber microporous filter membrane (diameter 0.22 mm, 37 mm diameter) to collect the respirable dust of the workers from the breathing zone of participants. Gas flow rates were set to 2 L/min and flow rates checked both before and after the sampling, the average time we collected 6.9h of sample per person per day. We tested only representative types of positions in the main workplace, individual exposure concentration of other positions was replaced by detected concentration with the same or similar workplace. We strictly abided by the national occupational health standard of the People's Republic of China. The standards are “Determination of airborne dust in the workplace part 2: Concentration of respirable dust” (GBZ/T 192.2-2007), and “Specifications of air sampling for hazardous substances monitoring in the workplace” (GBZ159-2004). The determine procedure followed the standard “Ambient air and stationary source emission-Determination of metals in ambient particulate matter-Inductively Coupled Plasma Mass Spectrometry (ICP-MS)” (HJ657-2013).

Digestion of filter membrane: the filter membrane was placed in a Teflon tube and added with 10 ml aqua regia. Microwave digestion instrument was used for digestion at 200 degrees Celsius for 30 minutes, diluted with ultrapure water to 50 ml and measured by ICP-MS (Perkin Elmer, NexION 2000, USA). We used the isotope ^{45}Sc as the internal standard for the determination of Mn. Quality control (QC) measures included analysis of the initial calibration validation criteria, a repeat measurement for every 10 samples, and SRM1640A (natural trace element concentration in water). Mn metal had the limit of detection (LOD) of 0.076 μg/L. All samples concentration was higher than the LOD. Finally, we calculated the time-weighted average of Mn (as MnO_2) (Mn-TWA) based on the three day average concentration. According to the National occupational health standards of the People's Republic of China, the occupational exposure limits permissible concentration-time weighted average（PC-TWA）for Mn and its compounds were set at 0.15mg/m^3 (as MnO_2) based on an 8-hour time weighting.(GBZ 2.1-2007). Therefore, we divided all subjects into two groups, low-exposure group was defined as Mn-TWA ≤0.15 mg/m^3 and high-exposure was defined as Mn-TWA >0.15 mg/m^3. The high-exposure group mainly included smelters, welders, human crushing workers, casting crane workers, material crane workers. The low-exposure group mainly included circulating cooling water system operator, chemical analysts, office workers, security guards and workers in other auxiliary positions.

Measurement of Serum lipids

Serum samples were stored in a deep freeze -80 °C until be tested. Serum lipids were measured by using chemistry automatic analyzer (Hitachi 7600-020, Kyoto, Japan) at the testing center of the Department of Clinical Laboratory at the First Affiliated Hospital of Guangxi Medical University in Nanning. Serum lipids include Total Cholesterol (T-CHO), Triglyceride (TG), Low-density lipoprotein cholesterol (LDL-C), and High-density lipoprotein cholesterol (HDL-C) [26]. Serum lipids were classified according to The 2016 Chinese Guideline for the Management of dyslipidemia in Adults (Chinese guideline). High LDL-C was defined as Low-density lipoprotein cholesterol ≥4.14 mmol/L. high TG was defined as triglyceride ≥2.26 mmol/L, high T-CHO was defined as total cholesterol ≥6.22 mmol/L, and low HDL-C was defined as High-density lipoprotein cholesterol <1.04 mmol/L. Dyslipidemia was well-established with strong risk factors of cardiovascular diseases, and cardiovascular diseases are sequelae of dyslipidemia[27]. The dyslipidemia guideline suggested that a target of LDL-C should be set according to individual ASCVD risk, and the individual ASCVD risk was evaluated adjusted age, gender, BMI, history of hypertension, and smoking status[26].

Statistical analysis

Mann-Whitney U test was used to compare the lipids levels of low Mn exposure and high Mn exposure group. Logistic regression models was used to estimate Mn exposure levels and the adjusted odds ratio (ORs), 95% confidence interval (CIs) of no achieving LDL-lowering targets risk, high LDL-C risk, high TG risk, high T-CHO risk, and low HDL-C risk, respectively. Specifically, because of the high inter variable correlation between age and seniority, the only seniority was adjusted in models. Finally, the potential confounders for models adjustment included gender, seniority, BMI, hypertension, medicine intake in the past two weeks, high-fat diets frequency, smoking status, and drinking status.

We conducted a stratified analysis according to strata of gender, seniority, BMI, hypertension, medicine intake in the past two weeks, high-fat diets frequency, smoking status, and drinking status. In our research, we considered the biologic interaction in potential risk factors. Rothman has argued that we should focus on epidemiological interaction or interaction on an additive scale by testing whether the joint effect from exposure to both factors was greater than the sum of their independent effects, and suggested the use of relative excess risk for interaction (RERI) in assessing additive interaction. The previous reports gave RERI a detailed explanation and calculation method [28-30]. Display quotations of over 40 words, or as needed. In short, RERI was calculated as follows:

$$RERI = e^{(\beta 1 + \beta 2 + \beta 3)} - e^{(\beta 1)} - e^{(\beta 2)} + 1$$

Where β1 is the coefficient of the effect of Mn-TWA levels measure, β2 is the coefficient of potential risk factor and β3 is the coefficient of the cross-product of the Mn-TWA levels and potential risk factor. And we estimated 95% confidence intervals by using the standard delta method. When the relative excess risk for interaction is an estimate of more than zero, there is an additive scale interaction between the two risk factors, and the 95% confidence interval is positive and does not contain zero. RERI of 0 indicates exact

additivity and there is no additive scale interaction. Finally, we assessed the interaction between Mn-TWA levels and each of the potential interacting factors of smoking effects (both smoking status and pack-years), drinking status, high-fat food frequency, and BMI on high TG risk in the logistic regression models by using R software. Analyses were conducted using R (version 3.4) and SPSS (19.0), two-sided, p <0.05 was considered statistically significant.

Results

In our participants, the median seniority was 18.92 years old, and the median age for the low, and high exposure group were 41.75 years, 45.42 years, respectively. The median of seniority was 18.92, and there was no difference in seniority between two groups (p =0.07). Male made up the majority of the low, and high exposure groups at 57.6%, and 72.5%, respectively. Only male smokers in our study and the proportion of current smoker were higher in high exposure group compared with the low exposure group, and the rates was 26.2%, 10.6%, respectively (p <0.01). Similarly, the proportion of ≥18 pack-years was higher in the high exposure group, and the rates was 29.4%, 14.5%, respectively (p <0.01). The current drinker account for a higher proportion of high-exposure group than that in the low-exposure group, and was 32.7%, 23.0%, respectively (p <0.01). In addition, the rates of BMI ≥24.0 kg/m^2 in the low exposure group was higher than that in the high exposure group, and was 64.2%, 53.7%, respectively (p <0.01). However, hypertension and medicine intake in the past two weeks were not different in the two groups (p 0.05) (**Table 1**).

As shown in **Table 2**, the proportion of occupationally Mn-exposed workers with high TG (≥2.3 mmol/L), high T-CHO (≥6.2 mmol/L), high LDL-C (≥4.1mmol/L), and low HDL-C (<1.04 mmol/L) was 25.5%, 15.7%, 6.8 %, and 3.1 %, respectively. LDL-lowering targets were set according to individual ASCVD risk and prevalence rates was 27.3%. The prevalence rates of high TG in low exposure group was higher than in the high exposure group, and was 30.7%, 22.7%, respectively (p <0.01).

In interaction analyses, we did not observe a significant additive scale interaction between Mn-TWA levels and smoking status, or pack-years on high TG risk (relative excess risk for the interaction (RERI) = -1.68, 95% CI: -3.76, 0.40), RERI = -0.78, 95% CI: -2.59,1.04) for smoking status , RERI = -1.30, 95% CI: -3.29, 0.70), RERI = -1.62, 95% CI: -3.92, 0.67) for pack-years, respectively. Results of our study suggested that male in this cohort, the joint effect of with high level of Mn-TWA exposure and current smoking or former smoking was not greater than the sum of their individual effects, consistent results was found in ≥18 pack-years or <18 pack-years. Similarly, we did not observe the significant interaction between Mn-TWA levels and drinking status, high-fat diets frequency, and BMI on high TG risk as well. Although not significant interaction, the risk of high TG seemed to be lower for people with a high level of Mn-TWA exposure who had high-fat diets frequency ≥3 times/week (high) (OR = 0.44; 95% CI: 0.24, 0.79) **(Table 4).**

Discussion

This is the first study to explore the relationship between Mn exposure and dyslipidemia in occupationally Mn-exposed workers. Our results showed that male workers exposed to higher Mn-TWA levels with lower high TG risk, and may no interaction with potential interaction factors. About the effect of Mn on lipids concentration, most studies have focused on dietary Mn intake. A clinical trial showed that after 14 adults supplemented with gluconic acid, Mn can reduce body fat by increasing fecal fat excretion [31]. Another clinical trial in seven young men, adequate intake of Mn can reduce plasma cholesterol levels[32]. A dietary study included 2111 Chinese adults has found a negative correlation between Mn intake and hypertriacylglycerolemia in male and Mn was positively correlated with low HDL-C concentration in female [17]. Another polymetallic dietary intake survey in 258 healthy male and female in China found that Mn intake was inversely correlated with serum TG and T-CHO [19]. In our population, the potential effect of gender was also observed. The negative correlation between Mn exposure and serum TG in male was consistent with previous findings. However, our study did not observe a correlation between Mn exposure and serum T-CHO, HDL-C, LDL-C, and LDL-lowering targets. Previous research results endorsed the important role of Mn in TG metabolism. However, it should be noted that our study subjects were occupational exposure to Mn, thus dietary Mn intake concentration is not directly compared to occupational Mn exposure concentration in population. In order to explore how Mn involved in the regulation of lipids and the toxic dose on lipids, it is necessary to establish mammalian models that inhalation Mn exposure concentration is closer to the occupational exposure in the population.

Mn enters the bloodstream through intestinal absorption or olfactory channels. The liver plays a major role in the excretion of Mn. Mn is absorbed into the liver from the blood and is regulated by homeostasis, excess Mn is mainly excreted into the intestine in combination with bile, finally, Mn in the liver complexes with different molecules and exists in the form of Mn2+[33-36]. At present, it was found previous studies provided biological support for the role of Mn in lipids metabolism. Some studies suggested that metabolism was thought to be related to lipids peroxidation [37-39]. Furthermore, another mechanism by which Mn may be involved in lipids metabolism was the process involved in lipids synthesis [12-15]. In summary, previous studies may suggest that Mn plays an important role in the mechanism of lipids. About lipid synthesis, there are two pathways for the synthesis of TG in the liver. One way is that exogenous fatty acids enter the liver cells and are esterified to synthesize TG, another pathway is produced by the de novo lipogenesis (DNL) pathway. Finally, the TG is placed in a storage pools or a secretory pool. The TG in storage pools is hydrolyzed by lipase, and the TG in the secretion pool is used for very low density lipoprotein (VLDL) assembly [40-43]. Acetyl-coa carboxylase is the key catalyst for the synthesis of de novo lipogenesis (DNL) acids. It requires a phosphatase to activate Acetyl-coa carboxylase, and the phosphatase's activation and dephosphorylation are dependent on Mn2+ [41, 44]. Thus, Mn2+ is an important coenzyme factor in liver synthesis of TG. In human and rodent studies, allosteric inhibition of acetyl-CoA carboxylase in the liver significantly reduced hepatic triglyceride levels, while plasma TG increased [45, 46]. Studies have speculated that the degree of inhibition of acetyl-CoA carboxylase may ultimately determine the mechanism leading to hypertriglyceridemia in rodents and humans [47]. Our population exposed to higher Mn levels, we hypothesized that the Mn2+ stored in their liver may be higher. Therefore, acetyl-CoA carboxylase is more easily to be activated in the liver.

Eventually, the level of triglyceride in the liver may be higher, while the level of triglycerides in serum drops.

Gender is a common factor affecting the absorption of Mn in individuals. Studies have reported that female have higher absorption rates of Mn, and Mn levels in female's blood are significantly higher than male's [48-51]. However, Male are reported to be more prone to triglycerides, lipid abnormalities, and metabolic diseases [52-54]. We hypothesized that there may be differences in Mn-regulated lipid metabolism between male and female, as well as differences in estrogen and androgen levels, resulting in a decrease in the risk of high TG in male only with increased manganese exposure.

Our study is the first to explore the relationship between Mn exposure and dyslipidemia in occupational workers. We carefully measured and analyzed comprehensive information on risk factors and potential confounders associated with lipids metabolism to minimize the possibility of bias. In addition, the stability of the cohort will also provide long-term follow-up of participants in the future to assess the risks dyslipidemia with Mn exposure. Some limitations should be considered. First, the present study did not select a non-Mn exposed population as a control group. Thus, regional diet and genetic and environmental influences cannot be eliminated, which may lead to biased results. Secondly, due to the reform of the job type of our participants, the measurement data cannot accurately calculate Mn cumulative exposure index (Mn-CEI), which makes it impossible to deeply explore the relationship between the cumulative exposure dose of long-term Mn and dyslipidemia.

Conclusions

In summary, we found a good negative correlation between high TG and Mn exposure levels in male workers, and more epidemiological studies are needed to determine the relationship between Mn exposure and dyslipidemia in the population.

Abbreviations

MMT: methyl cyclopentadienyl manganese tricarbonyl; TWA: Time-weighted Average; TG: Triglycerides; T-CHO; Total Cholesterol; LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol;BMI: Body Mass Index; RERI: relative excess risk for the interaction; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; MEWHC: Manganese-exposed Workers Healthy Cohort; QC: Quality control; PC-TWA: permissible concentration-time weighted average; LOD: limit of detection; DNL: de novo lipogenesis; VLDL: Low density lipoprotein; Mn-CEI: cumulative exposure index;

Declarations

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Declarations

Authors' contributions

XBY contributed to conception and design; SFH, YTZ, DFL, LML, XC, LLH, HC, QZH, LLX, CQL and YFZ contributed to acquisition of the data; XYL, ZFL, XTG and analyzed the data and drafted the manuscript. LXY, ZFL and XTG contributed equally to this study. All authors approved the final manuscript of this article prior to submission.

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Availability of data and materials

The data and material are available upon reasonable request from the corresponding author. E-mail: yxbo21021@163.com.

Ethics approval and consent to participate

The Medical Ethics Committee of Guangxi Medical University approved this study. All participants were fully informed about the study purpose and methods and provided written consent to participate.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interest.

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Tables

Table 1 Demographic characteristics of the manganese-exposed workers from MEHWC.

Variables	Total (n=803)	Low exposure group (n=283)	High exposure group (n=520)	*p* – Value*
Age (years)	44.25(39.50,48.42)	41.75(36.58,46.92)	45.42(41.27,49.08)	< 0.01
Seniority (years)				0.07
<18.92	402(50.1)	154(54.4)	248(47.7)	
≥18.92	401(49.9)	129(45.6)	272(52.3)	
BMI (kg/m^2)				< 0.01
<24	317(39.5)	131(46.3)	186(35.8)	
≥24	486(60.5)	152(53.7)	334(64.2)	
Gender				< 0.01
Male	540(67.2)	163(57.6)	377(72.5)	
Female	263(32.8)	120(42.4)	143(27.5)	
Race				0.65
Han	361(45.0)	128(45.2)	233(44.8)	
Zhuang	409(50.9)	141(49.8)	268(51.5)	
Other race	33(4.1)	14(4.9)	19(3.7)	
Education level				< 0.01
Middle school or below	257(32.0)	39(13.8)	218(41.9)	
High school	367(45.7)	103(36.4)	264(50.8)	
Junior college or above	179(22.3)	141(49.8)	38(7.3)	
Smoking status				< 0.01
Nonsmoker	476(59.3)	208(73.5)	268(51.5)	
Former smoker	161(20.0)	45(15.9)	116(22.3)	
Current smoker	166(20.7)	30(10.6)	136(26.2)	
Pack-years[b]				< 0.01
Nonsmoker	431(53.7)	193(68.2)	238(45.8)	
<18 years (low)	178(22.2)	49(17.3)	129(24.8)	

≥18 years (high)	194(24.1)	41(14.5)	153(29.4)	
Drinking status				< 0.01
Former/never drinker	568(70.7)	218(77.0)	350(67.3)	
Current drinker	235(29.3)	65(23.0)	170(32.7)	
High-fat diets frequency				< 0.01
<3times/week	640(79.7)	242(85.5)	398(76.5)	
≥3times/week	163(20.3)	41(14.5)	122(23.5)	
Hypertension				0.23
Yes	251(31.3)	81(28.6)	170(32.7)	
No	552(68.7)	202(71.4)	350(67.3)	
Medicine intake in the past two weeks				0.85
Yes	283(35.2)	69(34.7)	214(35.4)	
No	520(64.8)	130(65.3)	390(64.6)	

Mn-TWA, Mn-Time Weighted Average; Low exposure group, Mn-TWA ≤0.15 mg/m^3; High exposure group, Mn-TWA >0.15 mg/m^3; MEHWC, Manganese-exposed workers healthy cohort; BMI, Body Mass Index; Data were presented as median (25th, 75th) or n (%).

p –Value were derived from Mann-Whitney U tests for continuous variables according to the data distribution, and chi-square test for the categorical variables.

**pack-years: A pack-year was defined as 20 cigarettes smoked every day for 1 year (Bernaards et al. 2001). We further categorized participants' smoking status into three groups on the basis of median pack-years: nonsmoker, <18 pack-years, and ≥18 pack-years.

Table 2 Prevalence of different forms of dyslipidemia among participants from MEHWC.

Variables	Total(n=803)	Low exposure group(n=283)	High exposure group(n=520)	*p* – Value*
Triglycerides				0.01
≥ 2.3 mmol/L	205(25.5)	87(30.7)	118(22.7)	
< 2.3 mmol/L	598(74.5)	196(69.3)	402(77.3)	
Total cholesterol				0.18
≥ 6.2 mmol/L	126(15.7)	51(18.0)	75(14.4)	
< 6.2 mmol/L	677(84.3)	232(82.0)	445(85.6)	
LDL-C				0.44
≥ 4.1 mmol/L	55(6.8)	22(7.8)	33(6.3)	
< 4.1 mmol/L	748(93.2)	261(92.2)	487(93.7)	
HDL-C				0.61
< 1.0 mmol/L	25(3.1)	10(3.5)	15(2.9)	
≥ 1.0 mmol/L	778(96.9)	273(96.5)	505(97.1)	
No achieving LDL-lowering targets				0.57
Yes	220(27.4)	81(28.6)	139(26.7)	
No	583(72.6)	202(71.4)	381(73.3)	

Mn-TWA, Mn-Time Weighted Average; Low exposure group, Mn-TWA ≤0.15 mg/m^3; High exposure group, Mn-TWA >0.15 mg/m^3; LDL-C, Low-density lipoprotein cholesterol. HDL-C, High-density lipoprotein cholesterol; MEHWC, Manganese-exposed workers healthy cohort; No achieving LDL-lowering targets, According to the Chinese guideline-2016 Chinese Guideline for the Management of Dyslipidemia in Adults[26], LDL-lowering targets were set according to individual ASCVD risk levels. Adjusted by age, gender, BMI, history of hypertension, and smoking status.

* *p* –Value were derived from chi-square test.

Table 3 Adjusted odds ratios [95% confidence interval (CI)] for different forms of dyslipidemia according to Mn-TWA levels in MEHWC.

Dyslipidemia	Model 1*		Model 2**	
	OR(95% CI)	*p* – Value	OR(95% CI)	*p* – Value
No achieving LDL-lowering targets	0.91(0.66,1.26)	0.48	0.86(0.62,1.20)	0.37
High LDL-C	0.80(0.46,1.41)	0.80	0.70(0.39,1.28)	0.25
High TG	0.66(0.48,0.92)	0.01	0.59(0.41,0.84)	< 0.01
High T-CHO	0.77(0.52,1.13)	0.18	0.75(0.50,1.14)	0.18
Low HDL-C	0.81(0.36,1.83)	0.61	0.73(0.30,1.76)	0.49

Logistic regression models was used for analysis, with different forms of dyslipidemia as the dependent variable and Mn-TWA levels (categorical variable) as the independent variable. No achieving LDL-lowering targets, low-density lipoprotein cholesterol targets were set according to individual ASCVD risk, and adjusted for the variables as drug status in the past two weeks, and alcohol intake status. According to the Chinese guideline-2016 Chinese Guideline for the Management of Dyslipidemia in Adults[26], high LDL-C was defined as Low-density lipoprotein cholesterol ≥4.14 mmol/L, high TG was defined as triglycerides ≥2.3 mmol/L, high T-CHO was defined as total cholesterol ≥6.2 mmol/L, and low HDL-C was defined as High-density lipoprotein cholesterol <1.0 mmol/L.

*Model 1: Without adjusting covariates.

**Model 2: Adjusted for the variables as gender, seniority, BMI, hypertension, medicine intake in the past two weeks, high-fat diets frequency, smoking status, and drinking status.

Table 4 Adjusted odds ratios [95% confidence interval (CI)] for high TG according to the combined exposure Mn-TWA levels with categories of smoking status, pack-years, drinking status High-fat diets, and BMI in male workers.

Variables	n(high /normal TG)	Low exposure	High exposure	Relative excess risk due to interaction(RERI)** (95%CI)
		OR*(95% CI)	OR*(95% CI)	
Smoking status				
Nonsmoker	88/343	1.00	1.09(0.53,2.26)	
Former smoker	11/34	1.31(0.39,4.34)	0.55(0.18,1.69)	-1.68(-3.76,0.40)
Current smoker	106/221	2.80(1.35,5.81)	1.19(0.64,2.24)	-0.78(-2.59,1.04)
Pack years[c]				
Nonsmoker	88/343	1.00	1.09(0.53,2.25)	
<18 years (low)	56/122	2.27(1.01,5.11)	1.15(0.58,2.28)	-1.30(-3.29,0.70)
≥18 years (high)	61/133	2.63(1.14,6.09)	1.06(0.54,2.08)	-1.62(-3.92,0.67)
Drinking status				-0.46(-1.55,0.62)
Former/never drinker	127/441	1.00	0.68(0.39,1.19)	
Current drinker	78/157	1.52(0.77,3.01)	0.75(0.41,1.36)	
High-fat diets frequency				-0.79(-3.67,2.10)
<3 times/week (low)	165/475	1.00	0.48(0.30,0.77)	
≥3 times/week	40/123	0.24(0.07,0.76)	0.44(0.24,0.79)	

(high)				
BMI				-0.11(-1.22,1.01)
	BMI <24kg/m^2	90/396	1.00	0.50(0.27,0.95)
	BMI ≥24kg/m^2	115/202	2.01(1.02,3.97)	1.34(0.72,2.51)

Low exposure group, Mn-TWA ≤0.15 mg/m^3; High exposure group, Mn-TWA >0.15 mg/m^3. pack-years, A pack-year was defined as 20 cigarettes smoked every day for 1 year[25]. We further categorized participants' smoking status into three groups on the basis of median pack-years: nonsmoker, <18 pack-years, and ≥18 pack-years.

*OR: In our cohort, only participants were male, Mn-TWA levels showed stronger negative associations with high TG risk. And OR across the combined exposure of Mn-TWA levels and the other risks factors of dyslipidemia were obtained in logistic regression models in male. Adjusted for the variables as gender, seniority, smoking status, pack-years, drinking status, hypertension, medicine status in the past two weeks, and BMI; Combined categories variables did not be adjusted.

**RERI: We assessed the presence of interaction between exposure Mn-TWA levels and smoking status, pack-years, drinking status, High-fat diets, and BMI by testing whether the joint effect from exposure to both factors was greater than the sum of their independent effects. When the relative excess risk for interaction is an estimate of more than zero, there is an additive scale interaction between the two risk factors, and the 95% confidence interval is positive and does not contain zero. Otherwise, there was no interaction, and RERI of 0 indicates exact additivity and there is no additive scale interaction.

Figures

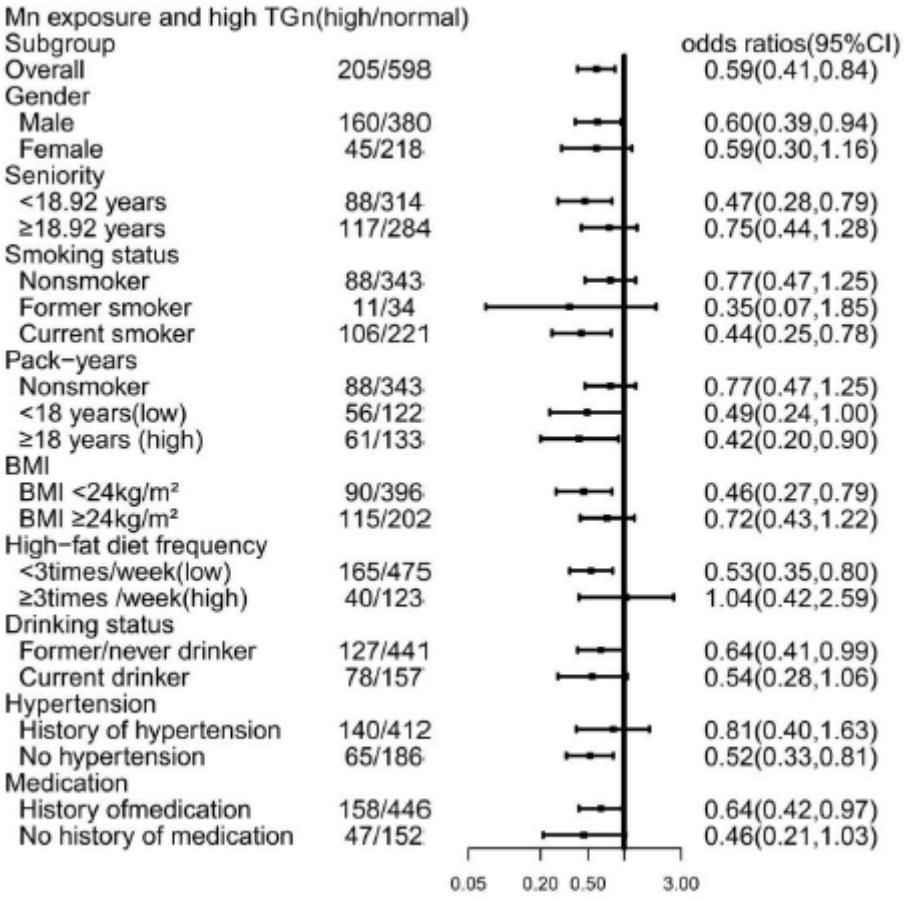

Figure 1

Adjusted ORs for Mn-TWA levels associated with high TG risk in subgroups Logistic regression models was used for analysis, with high TG as the dependent variable and Mn-TWA levels (categorical variable) as the independent variable. We set subgroups according to gender, seniority, smoking status, pack years, drinking status, hypertension, medicine intake in the past two weeks, and BMI. Seniority was divided into two groups by median, and other variables were adjusted. When participants were male, or current smoker, or smoking ≥18 pack-years, seniority <18.92 years, or non-hypertension, or high-fat diets frequency less than 3 times per week, or BMI <24 kg/m2, Mn-TWA levels showed negative associations with high TG risk.