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Associations of essential trace metals with telomere length in general population: a cross-sectional study

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This study investigated the relationship between essential plasma metals (Co, Cr, Cu, Mn, Mo, Se, Zn) and telomere length in 2,194 Chinese adults aged ≥ 30 years. Metal concentrations were measured using ICP-MS, and leukocyte relative telomere length (rTL) was assessed by qPCR. In the elderly, Cr and Mn were significantly positively correlated with rTL, while Mo, Zn, and Cu showed negative correlations. In the 30–59 age group, the overall metal mixture was significantly negatively associated with rTL (estimate = -0.069, *P* = 0.003), with Zn as the dominant contributor. In the elderly, the metal mixture was positively associated with rTL (estimate = 0.040, *P* = 0.031), with Cr and Mn as main contributors. The findings highlight the importance of maintaining adequate Cr and Mn levels in older adults, and the potential adverse impact of Cu, Mo, and Zn on telomere length.

Keywords Trace metal, Telomere length, BKMR, Quantile g-computation

Telomeres are nuclear protein structures composed of specific proteins and tandem repeats of the TTAGGG sequence, located at the ends of the chromosomes[1]. Telomere damage can lead to the inability of DNA polymerase to complete the replication of the telomeric region of eukaryotic DNA. As a result, after several rounds of cell division, telomeres undergo significant shortening, triggering genomic instability and ultimately leading to cell apoptosis or senescence. Telomere shortening is associated with age-related susceptibility to diseases, including type 2 diabetes, atherosclerosis, coronary heart disease, stroke, and cancer[2,3]. The study of the determinants of telomere shortening is crucial for understanding the pathophysiology of chronic diseases.

In recent years, the critical role of essential trace elements in biological and physiological processes has received growing attention. Research indicates that these elements are not only vital for cell division, proliferation, and growth, but may also influence telomere length[4]. Epidemiological studies have provided compelling evidence linking essential metal elements to telomeres. For instance, a birth cohort study conducted in China found that maternal urinary manganese and selenium concentrations were positively correlated with newborn telomere length[5,6]. Another study from Myanmar suggested that selenium has a protective effect and can counteract telomere shortening caused by heavy metal exposure[7]. Existing studies indicate that essential metal elements may affect telomere length through mechanisms including the promotion of oxidative stress, DNA damage, and the regulation of telomerase activity[8]. However, the dose-response relationship between essential metal elements and telomere length is yet to be determined[9], and this aspect requires further exploration. Although many studies focus on the impact of individual metals on telomeres, in real-world scenarios, humans are typically exposed to a combination of metal elements. Therefore, studying the effects of metal mixtures on telomere length offers a more accurate representation of actual human exposure[10]. Existing epidemiological studies have predominantly focused on infants, pregnant women, or specific occupational groups, with fewer studies examining the general population, particularly the elderly. The elderly often face challenges such as inadequate dietary intake and reduced nutrient absorption capacity, making them more sensitive to trace element intake and more vulnerable to both deficiencies and excesses[11].

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Currently, a limited number of epidemiological studies have indicated that mixed exposure to multiple metals can affect telomere length. However, existing studies mainly focus on specific groups, such as infants or occupational populations[12–14]. , Moreover, studies on the relationship between trace metal elements and telomere length in the general population remain limited, and there is a lack of systematic assessment of the elderly population, particularly in countries with significant aging populations, such as China. Considering the unique characteristics of the elderly population, this study aims to evaluate the relationship between combined exposure to eight essential metal elements in plasma and relative leukocyte telomere length in the general population.

Methods

Study population

This cross-sectional study was conducted in rural areas of Guangxi, southern China. From 2018 to 2019, we recruited local residents aged 30 and above in Gongcheng Yao Autonomous County. All procedures involving human subjects in this study were approved by the Ethics Committee of Guilin Medical University (No: 20180702-3). Each participant was informed about the purpose and content of the survey and provided written informed consent. Our exclusion criteria were as follows: (a) participants with incomplete laboratory tests and questionnaire data. (b) individuals with abnormal values in the metal element detection (defined as three times the 99th percentile). (c) Individuals with white blood cell counts exceeding 10 (10^9/L)[15]and C-reactive protein levels surpassing 10 (mg/L)[16], because heightened cell division during infection can result in the depletion of telomeric repeat sequences. Consequently, a total of 2194 subjects were encompassed in the present study.

Blood routine blood biochemical examination

All study participants provided fasting blood samples from the antecubital vein in the morning after a minimum of 12 h of fasting. White blood cell counts were analysed using a haematology analyser (Sysmex CS-1600, Shanghai, China), and C-reactive protein (CRP) levels were examined using a blood biochemistry analyser (Hitachi 7600-020, Kyoto, Japan). The remaining blood samples were aliquoted into 1.5 mL centrifuge tubes and stored in a − 80 ℃ freezer.

Measurement of metals

Plasma samples were analysed for Cobalt(Co), Chromium(Cr), Copper(Cu), Iron(Fe), Manganese(Mn), Molybdenum(Mo), Selenium(Se) and Zin(Zn) using ICP-MS (Thermo Fisher scientific iCAPRQ01408). The detection method has been described in a previous study[17]. An acidic solution containing 1% nitric acid (ultra-pure), 0.01% Triton (Triton X-100, Inc.) and 0.5% butanol (Across, Denmark) was prepared, and 0.1 ml of plasma was diluted 20 times using the acidic solution. A quality control solution (ClinChek human plasma controls for trace metals Level 1 [No.8883] and Level 2 [No.8884]; Recipe Chemicals) was tested every 25 samples. The sample recovery rate ranged from 80.16 to 114.65%. The number of samples with Fe concentrations below the detection limit was 0.06%, whereas the detection values for other elements were above the detection limit. The replacement value of metal concentrations below the detection limit was calculated by dividing the detection limit by the square root of 2[18].

Relative leucocyte telomere length

We used a DNA extraction kit provided by Beijing Edilai Biotechnology Co., Ltd. to extract DNA. The DNA concentration and purity were measured using a UV spectrophotometer from BioTek, USA. Samples with an OD260/OD280 ratio between 1.8 and 2.0 were considered qualified. The primer sequences for the telomere gene (TEL) and 36B4, as well as the qPCR thermal cycling conditions, have been described in detail in previous studies[19–21]. Real-time qPCR was performed using the StepOne-Plus system (Applied Biosystems). The TEL gene and 36B4 gene were analysed separately in individual 96-well plates. Each sample was subjected to duplicate measurements for the TEL gene and the 36B4 gene. Standard reference genomic DNA samples were randomly selected. The standard genomic DNA was diluted to concentrations of 3.125, 6.25, 12.5, 25, 50, 100, and 200 ng/μL, and standard curves were constructed on each 96-well plate. All samples in this study satisfied the following criteria: (a) qPCR amplification efficiency between 90% and 110% (b) a correlation coefficient (R^2) of the standard curve greater than 0.98 (c) CT values of each sample on the 96-well plate within the range of the standard curve and (d) a maximum difference of 0.5 in CT values between replicate wells of the same sample[21,22]. The mean relative TL was calculated by the $2^{-\triangle\triangle Ct}$method[23].

Covariate assessment

Covariates include age, education level (0 years, ≤ 6 years, > 6 years), ethnicity (Yao and other nationalities), smoking status (yes or no), alcohol consumption (yes or no), agricultural physical activity (yes or no), energy intake (continuous), and dietary fiber intake (continuous). Energy intake and dietary fiber intake were assessed using the FFQ questionnaire[24]. Overweight was defined as 23.0 $kg/m^2 \leq BMI < 27.5\ kg/m^2$, and general obesity was defined as BMI ≥ 27.5 kg/m^2[225].

Statistical analyses

Prior to the statistical analysis, the plasma metal detection values were log10 transformed, and the relative telomere length (rTL) was transformed using the natural logarithm (Ln), to improve normality and enhance the model's fit within a relatively concentrated range. We conducted a stratified analysis of the population based on age, considering that age can alter the relationship between metals and metal mixtures with rTL[10].

Initially, the bivariate correlation between metal elements was assessed using Spearman correlation analysis. In addition, restricted cubic spline (RCS) regression was used to explore the linear or nonlinear associations between each metal and RTL. In the RCS, three knots were set at the 10th, 50th and 90th percentiles of the metal concentrations, and the 10th percentile served as the reference. Based on reported confounding factors that affect RTL, we adjusted the gender, age, educational level, ethnicity, smoking status, alcohol consumption, overweight, obesity[10,26] and agricultural physical activity.

Furthermore, we employed Bayesian kernel machine regression (BKMR) and Quantile g-computation (Q-g computation) to evaluate the relationship between multiple metal levels and RTL. BKMR is highly flexible in modelling joint effects, allowing potential interactions and nonlinear effects in mixed components[27]. Q-g computation is capable of effectively inferring the overall impact of mixtures and the individual contributions to mixtures, without requiring a prior assumption of positive or negative effects between mixtures and outcomes[28]. The difference between BKMR and Q-g computation lies in that BKMR represents the overall impact of exposure mixtures using increments of 10th percentiles, without generating mixture dose-response parameters. On the contrary, Q-g computation can estimate mixture dose-response parameters and evaluate the estimated contributions of each metal to the overall impact of the mixture[28,29]. n this study, the BKMR model was iterated 10,000 times, and efficiency was improved with a speed of 50 knots. Finally, we conducted sensitivity analysis by further adjusting the energy intake to examine the stability of the results. All data were analysed using R version 4.1.2. P-values were calculated using two-tailed tests, and values less than 0.05 were considered statistically significant.

Confirm
All procedures involving human subjects and all experimental methods in this study were conducted in accordance with relevant guidelines and regulations and were approved by the Ethics Committee of Guilin Medical University (Approval No: 20180702-3).

Results
Characteristics of the study population
As shown in Table 1, this study included 2194 participants, with 1060 individuals aged 30–59 and 1134 individuals aged 60 and above. The proportion of males was 36.4%, and that of the Yao ethnic group was 74.6%. Participants with at least a junior high school education accounted for 35%. The proportions of smokers, drinkers, overweight individuals, obese individuals, and those engaged in agricultural physical activities were 18.2%, 32.0%, 35.1%, 7.7%, and 65.5%, respectively. The median energy intake was 1435.74 kcal/day. The median concentrations of plasma Cobalt (Co), Chromium (Cr), Copper (Cu), Iron (Fe), Manganese (Mn), Molybdenum (Mo), Selenium (Se), and Zinc (Zn) were 0.25, 2.93, 913.15, 1079.09, 2.07, 1.60, 109.26, and 1082.60 µg/L, respectively.

Correlation of metals
In the population aged 30–59 years (Fig. 1A), we found a strong correlation between Mn and Zn ($rs = 0.60$ and $P < 0.05$). We also observed moderate correlations between Cr and Mn, Mn and Mo, Mo and Zn (all $rs \geq 0.30$, $rs < 0.50$ and $P < 0.05$). In the population aged 60 years and above (Fig. 1B), moderate correlations were observed between Co and Cr, Co and Se, Cr and Mn, Cr and Zn, and Mn and Zn (all $rs \geq 0.30$, $rs < 0.50$ and $P < 0.05$). BKMR and Q-g computation allow interactions between independent variables given that essential metals are interrelated. Therefore, BKMR and Q-g computation were suitable tools for this study.

Association between individual metal and telomere length
The RCS model established the relationship between individual essential trace metals and rTL. As shown in Fig. 2, Zn showed a linear negative correlation with rTL (P for nonlinear > 0.05) in the 30–59 years old population. As shown in Fig. 3, Co, Fe, Mn and rTL displayed nonlinear associations (all P for nonlinear < 0.05), whereas Cr, Mo, and Zn showed linear associations with rTL (all P for nonlinear > 0.05) in the ≥ 60-year-old population.

The shaded area represents the confidence interval, while the P-value indicates the strength of the correlation. In the plots where the line slopes upwards, it indicates a positive correlation between the metal and rTL. This means that as the metal concentration increases, the telomere length (rTL) also increases. In the plots where the line slopes downwards, it indicates a negative correlation between the metal and rTL. This means that as the metal concentration increases, the telomere length (rTL) decreases. Models were adjusted for smoke, drink, sex, age, ethnic, education, overweight and fat.

Association between metal mixture and telomere length
In the 30–59 years old population, the increasing level of the metal mixture was significantly negatively associated with shortened rTL in the 55th to 75th range when compared with the 50th percentile of the metal mixture, The effect estimates range between −0.023 and −0.153 (Fig. 4A). As shown in Fig. 4B, Zn exhibited significant negative associations with rTL when other metals were set at different 25th, 50th, or 75th percentiles, respectively, in the 30–59 years old population. In the ≥ 60-year-old population, the increasing level of the metal mixture was linearly associated with longer rTL in the 25th(estimate= −0.062) to 70th(estimate = 0.009) range (Fig. 4C). As shown in Fig. 4D, when other metals were fixed at specific percentiles, Cr and Mn showed significant positive associations with rTL, while Cu, Mo, and Zn showed significant negative associations with rTL in the ≥ 60-year-old population.

Figure S1 illustrates the exposur–response relationship between individual metals and rTL when other metals are fixed at the median level. In the ≥ 60-year-old population, Co and Fe did not exhibit an evident nonlinear correlation with the length of telomeres. The exposur–response relationship between the remaining essential metals and rTL was generally consistent with the RCS model fitting.

As shown in Fig. 5A, in the 30–59 years old population, Q-g computation indicated a significant correlation between overall exposure to trace metals and rTL (estimate = −0.069, $P = 0.003$). Zn (weight 71.2%) was the relatively dominant metal that contributed to negative association. As shown in Fig. 5B, in the ≥ 60-year-old

Variables	Overall	30–59 years old	≥60 years old
General characteristics			
Gender, n (%)			
Males	799 (36.4)	351 (33.1)	448 (39.5)
Females	1395 (63.6)	709 (66.9)	686 (60.5)
Ethnicity			
Yao	1637 (74.6)	895 (84.4)	742 (65.4)
Other	557 (25.4)	165 (15.6)	392 (34.6)
Education, years, n (%)			
0 years	350 (16.0)	34 (3.2)	316 (27.9)
≤6 years	1076 (49.0)	499 (47.1)	577 (50.9)
>6 years	768 (35.0)	527 (49.7)	241 (21.3)
Smoking status, n (%)			
Yes	399 (18.2)	172 (16.2)	227 (20.0)
No	1795 (81.8)	888 (83.8)	907 (80.0)
Drinking status, n (%)			
Yes	701 (32.0)	302 (28.5)	399 (35.2)
No	1493 (68.0)	758 (71.5)	735 (64.8)
BMI, kg/m2			
<23	1257 (57.3)	530 (50.0)	727 (64.1)
23–27.49	769 (35.1)	421 (39.7)	348 (30.7)
≥27.5	168 (7.7)	109 (10.3)	59 (5.2)
Agricultural physical activity			
Yes	1438 (65.5)	816 (77.0)	622 (54.9)
No	756 (34.5)	244 (23.0)	512 (45.1)
rTL	0.69 (0.56, 0.90)	0.76 (0.60, 1.00)	0.64 (0.53, 0.81)
Energy intake (kcal/day, *n* = 1591)	1435.74 (1032.52, 1972.66)	1554.48 (1118.51, 2187.82)	1315.91 (967.32, 1748.21)
Dietary fiber intake (g, *n* = 1591)	6.97(4.16,11.72)	8.48(4.89,13.92)	6.01(3.72,9.84)
Plasma metals, (μ g/L)			
Cobalt (Co)	0.25 (0.16, 0.5)	0.29 (0.19, 0.52)	0.21 (0.14, 0.43)
Chromium (Cr)	2.93 (1.88, 4.10)	3.43 (2.49, 4.46)	2.41 (1.63, 3.67)
Copper (Cu)	913.15 (796.64, 1030.03)	889.51 (783.95, 1003.20)	932.29 (815.66, 1056.16)
Iron (Fe)	1079.09 (827.42, 1340.30)	1097.20 (827.82, 1365.43)	1068.95 (826.83, 1322.06)
Manganese (Mn)	2.07 (1.55, 2.95)	2.41 (1.79, 3.24)	1.78 (1.43, 2.69)
Molybdenum (Mo)	1.60 (1.23, 2.09)	1.50 (1.21, 1.91)	1.71 (1.31, 2.24)
Selenium (Se)	109.26 (94.38, 123.89)	107.97 (94.56, 122.1)	110.30 (94.24, 126.68)
Zinc (Zn)	1082.6 (766.97, 4714.95)	1352.95 (812.83, 6968.28)	978.95 (736.15, 1878.04)

Table 1. Basic characteristics of study population.

population, a significant correlation between overall exposure to trace metals and rTL was found (estimate = 0.040, $P = 0.031$). The weights of Cr and Mn (weights 59.2% and 32.1%, respectively) were the relatively dominant metals for positive association.

Sensitivity analyses

As shown in Fig. S2, after the additional adjustment of energy intake and detary fiber intake, the independent and overall effects of various essential trace metals on individuals aged 30–59 remain unchanged. As shown in Fig. S3, in the ≥60-year-old population, the strength of the association between Cu and rTL decreased after adjusting the energy intake and detary fiber intake, and the relationships between other metals and rTL were essentially consistent. Meanwhile, the overall effects of trace metals remain unchanged.

Discussion

This study, using the BKMR and Q-g models, reveals a significant association between exposure to essential trace metal mixtures and telomere length (rTL), with notable differences observed across age groups. In the 30–59 age group, a negative correlation between essential trace metal mixtures and telomere length was found, whereas in

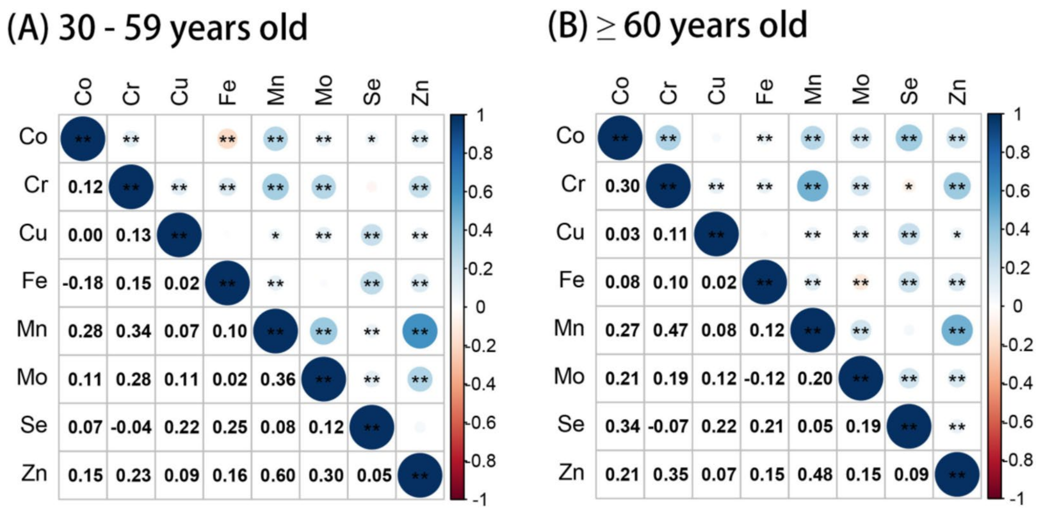


Fig. 1. Correlation analysis between essential trace metal mixtures and telomere length. (**A**) 30–59 years old; (**B**) ≥ 60 years old.Models were adjusted for smoke, drink, sex, age, ethnic, education, overweight and fat.

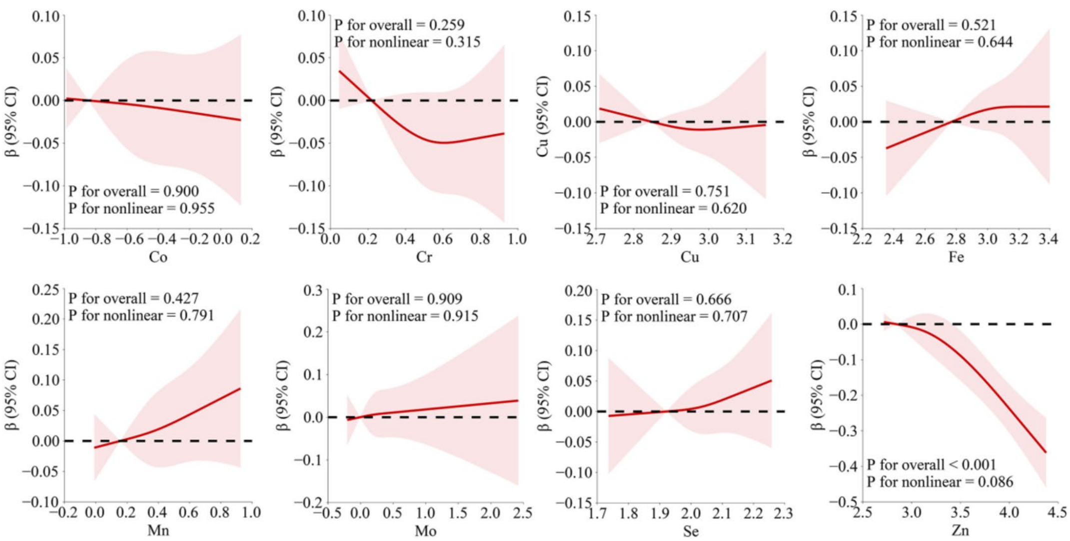


Fig. 2. The RCS model established the relationship between individual essential trace metals and rTL in the 30–59 years old population. The shaded area represents the confidence interval, while the P-value indicates the strength of the correlation. In the plots where the line slopes upwards, it indicates a positive correlation between the metal and rTL. This means that as the metal concentration increases, the telomere length (rTL) also increases. In the plots where the line slopes downwards, it indicates a negative correlation between the metal and rTL. This means that as the metal concentration increases, the telomere length (rTL) decreases. Models were adjusted for smoke, drink, sex, age, ethnic, education, overweight and fat.

the elderly population, a positive correlation was observed. These findings suggest that the relationship between trace metal mixtures and telomere length may change with age, offering further insights into the aging process.

Trivalent Cr is a trace element that has beneficial effects on oxidative stress parameters and inflammation[30]. Oxidative stress causes telomere shortening; it induces single-strand breaks that preferentially accumulate in telomeres, leading to an accelerated loss of telomeres during DNA replication[31]. Cr can reduce oxidative stress by activating glutathione reductase or other antioxidant enzymes[32], and results from cellular experiments also indicate that Cr chloride can prolong telomere length in liver cancer cells[4]. In this study, the median concentration of plasma Cr was 2.93 μg/L, which is higher than in another cross-sectional study (0.15 μg/L)[33], but lower than that of the Dongfeng-Tongji cohort participants (5.07 μg/L)[34], this may be related to the different environmental exposures of the population in our study. Cr levels decrease with age due to reduced energy intake, changes in food patterns, decreased absorption or increased Cr loss[35]. We found a linear positive association between Cr and rTL in older participants. However, epidemiological evidence to confirm the positive relationship between Cr and rTL is currently insufficient. Bai et al.[13]found a significant positive correlation between plasma Cr and

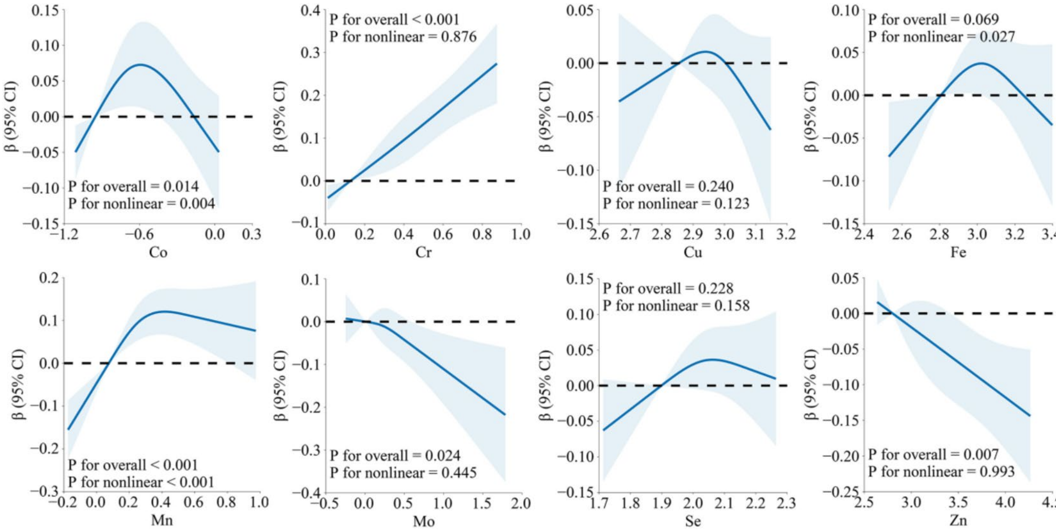


Fig. 3. The RCS model established the relationship between individual essential trace metals and rTL in the ≥60-year-old population.

rTL in blast furnace workers in a single metal model. Unfortunately, after adjusting other metals, no significant association between Cr and rTL was found. In addition, two cross-sectional studies from China and Japan did not find a significant association between urinary Cr and telomere length[29,36]. Further prospective research is required to confirm the anti-aging ability of Cr.

In this study, the BKMR model suggested that Cu was negatively correlated with rTL in the elderly population. Although Cu is a component of superoxide dismutase and has a resistance effect on oxidative stress, abnormal Cu concentration may also induce the generation of hydroxyl radicals and cause oxidative stress[37]. ROS produced by copper exposure can induce telomere shortening in cells[38]. A cross-sectional study conducted by Vriens et al.[39] found a negative correlation between urinary Cu and rTL in Belgian adults aged 50 to 65 years. Lai et al.[10] found in their study on the Dongfeng–Tongji cohort that the median level of plasma copper in middle-aged and elderly individuals was 964.7 μg/L, which is similar to the plasma copper level of 913.15 μg/L in the current study. In this study, we also found a significant negative correlation between copper and rTL. However, we should consider the influence of diet on this relationship because the strength of the association between Cu and rTL decreased after adjusting the energy intake.

Mn, as an auxiliary factor of manganese superoxide dismutase and other antioxidants, participates in protection against DNA damage. Manganese deficiency is extremely rare because adequate amounts of manganese can be obtained from most diets[40]. The median level of Mn in this study was 2.07 μg/L, which is lower than the reference values for blood manganese in the Brazilian population (18.54 μg/L for men and 20.15 μg/L for women)[41]and the National Health and Nutrition Examination Survey (NHANES)in the United States (9.42 μg/L)[42]. In this study, the RCS result indicated that although the correlation coefficient between Mn and rTL decreased when Mn reached a certain concentration in the elderly population, it still maintained a positive correlation. On the contrary, the BKMR model suggested that Mn was positively correlated with rTL in the elderly population. The plasma Mn concentration in this study is similar to the results reported by Bai et al.[13](2.73 μg/L), and the association between Mn and rTL is also consistent. In addition, another study from a Chinese birth cohort reported a positive correlation between urinary Mn concentration in mid-pregnancy women and newborn TL[5]. Animal and cell experiments provide consistent evidence that Mn has a protective effect on telomeres. In animal experiments, specific manganese superoxide dismutase-deficient mice had reduced telomerase activity in heart tissue[43], whereas mice with longer telomeres had higher superoxide dismutase activity[44]. In cell experiments, overexpression of Mn-SOD can reduce the number of cells with shortened telomeres by reducing ROS levels[45].

At present, research on the association between Mo and rTL is limited, and the results are inconsistent. A study from the NHANES in the United States found a positive correlation between urinary Mo and rTL in older adults[46]. However, two other epidemiological studies did not find a significant association between Mo and rTL[10,13]. In this study, we found a negative correlation between plasma Mo and rTL in the elderly population. The association between molybdenum and telomere length lacks in vivo and in vitro experimental evidence, which may be an area worth exploring.

Zn can bind with metallothioneins (MTs) and function as an antioxidant or free radical scavenger. However, the relationship between Zn and telomere length is still controversial[47]. A study from Australia showed no significant correlation between plasma Zn (median concentration 786.5 μg/L) and lymphocyte telomere length in elderly healthy adults[48]. However, a study from China found that an increase in plasma Zn levels (median concentration 1229.6 μg/L) is associated with reduced telomere attrition in middle-aged and elderly individuals[10]. The average level of plasma Zn (1082.6 μg/L) in the participants of this study was between the levels reported in the two aforementioned studies. Our results indicate a significant negative correlation between Zn and rTL. Cellular experiments also yield different conclusions. Liu et al.[4]found that Zn sulphate significantly

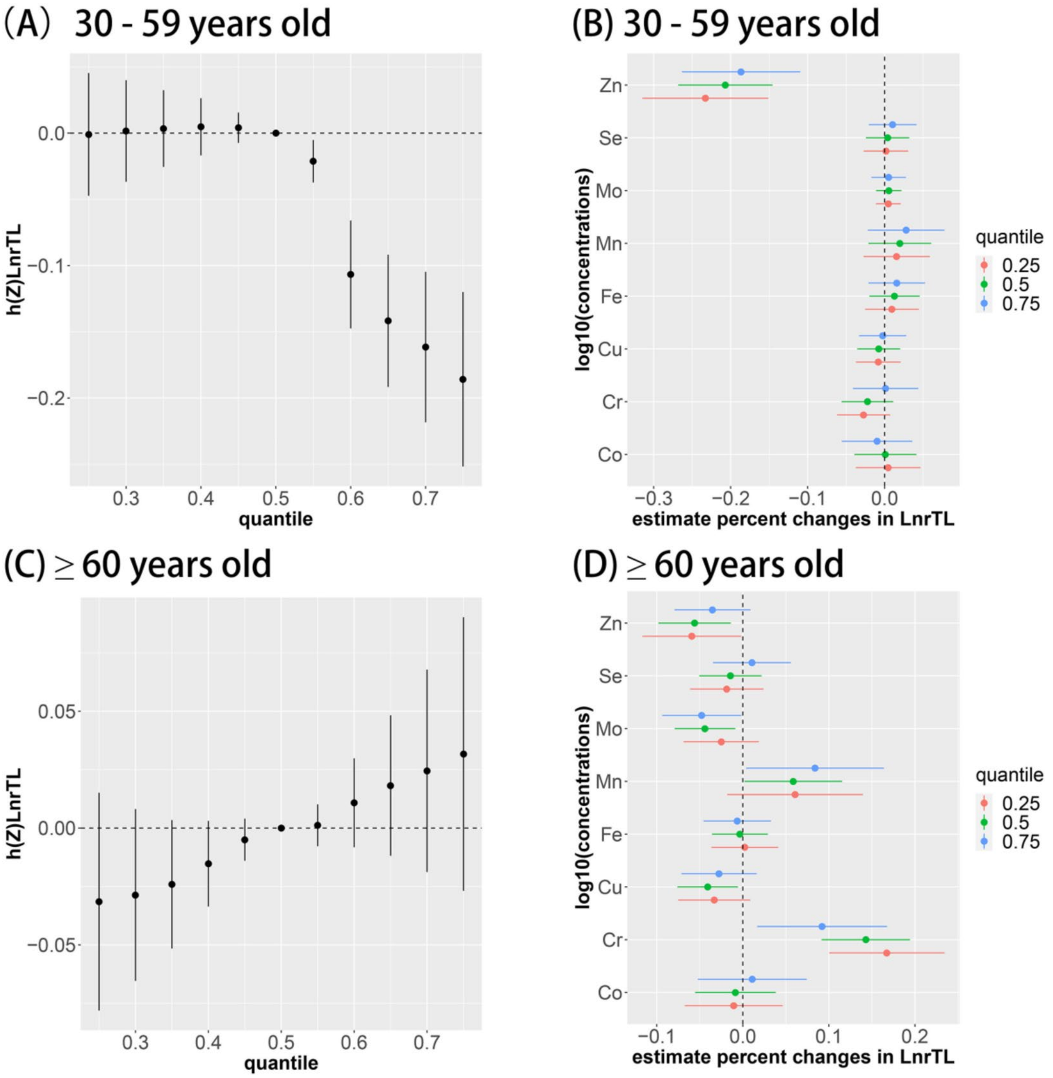
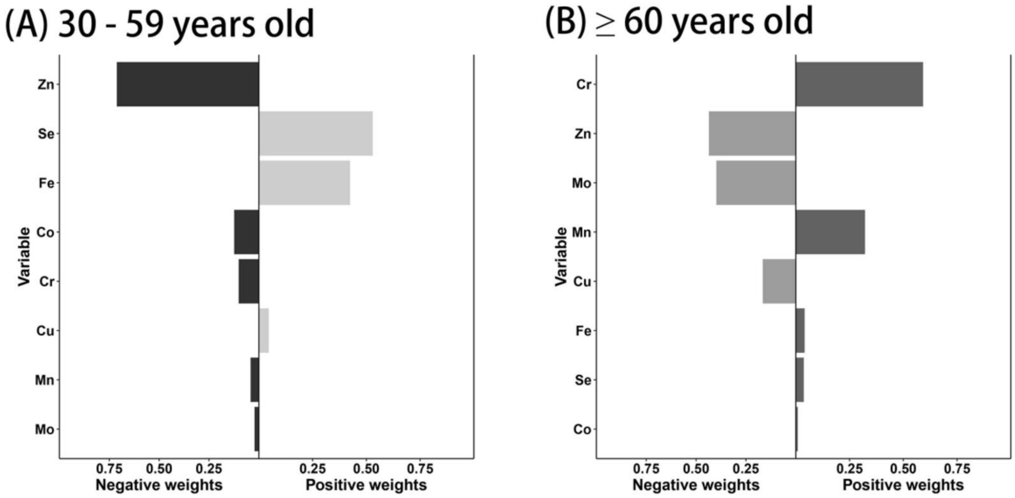


Fig. 4. Shows the combined effect of exposure and 95% confidence intervals using the BKMR model. (**A**) In the 30–59 years old population, the increasing level of the metal mixture was significantly negatively associated with shortened rTL in the 55th to 75th range; (**C**) In the ≥ 60-year-old population, the increasing level of the metal mixture was linearly associated with longer rTL in the 25th to 70th range. Upward trends or positive percent change estimates indicate a positive correlation. Downward trends or negative percent change estimates indicate a negative correlation. In the separate effects model, the outcome variable changed with each interquartile spacing increase in individual metal concentrations when the metal concentration levels were at the 25th, 50th, and 75th percentiles, respectively. (**B**) 30-59years old; (**D**) ≥ 60 years old. The red line represents the 25th percentile, the green line represents the 50th percentile, and the blue line represents the 75th percentile.Models were adjusted for smoke, drink, sex, age, ethnic, education, overweight and fat.

accelerated the loss of telomere length in hepatoma cells. However, Zn can enhance telomerase activity in the human renal cell carcinoma and prostatic cancer cell lines[49]. Further research is required to confirm the exact relationship between Zn and rTL.

In our study, we did not find a significant relationship between selenium levels and telomere length. Although selenium is known for its antioxidant properties and has been reported to be associated with telomere protection during the aging process[7,50], no clear association was observed between changes in selenium concentrations and telomere length in our study. This result may be related to the characteristics of the study population, selenium intake levels, or other potential confounding factors. Therefore, further research is needed to explore the potential link between selenium and telomere length.

Through new methods, such as BKMR and Q-g models, we found a significant correlation between co-exposure to essential trace metals and rTL. We observed a significant negative correlation between essential trace metal mixtures and rTL in the 30–59 age group, while it showed a significant positive correlation in the elderly population. These results indicated that the relationship between trace metal mixtures and rTL was age-dependent. A previous study in a general population found a significant negative correlation between plasma levels of 15 metal mixtures and telomere length[10]. However, after stratifying the analysis by age, no significant



Estimate (95%CI)	P value
-0.069 (-0.114, -0.023)	0.003

Estimate (95%CI)	P value
0.040 (0.004, 0.076)	0.031

Fig. 5. Weight ratio of each metal in the positive-negative association in the Quantile g-computation. (**A**) 30-59years old; (**B**) ≥ 60 years old .Models were adjusted for smoke, drink, sex, age, ethnic, education, overweight and fat.

association between metal mixtures and telomere length was observed in the age group below and above 65. This finding is inconsistent with the results of the present study, probably because of the differences in the metallic composition and concentration in the mixture.

Our research offers new insights into aging biology. Telomere length is widely regarded as a key marker of aging, and the relationship between metal exposure and telomere length may reflect the complex role that trace metals play in the aging process. Our findings suggest that chromium (Cr) and manganese (Mn) are associated with longer telomere length in the elderly, indicating their potential anti-aging effects. In particular, chromium has been shown to exhibit antioxidant and anti-inflammatory properties, which may help mitigate oxidative stress-induced telomere damage, thereby slowing the aging process[30,32]. In contrast, metals such as copper (Cu) and zinc (Zn) were found to be linked to shorter telomere length in our study, likely due to oxidative stress caused by high concentrations of these metals. These findings emphasize the dual nature of metal exposure on telomere health.

However, it is important to note that while our study identifies an association between essential trace metal mixtures and telomere length, these correlations do not necessarily imply causality. Given the cross-sectional design of our study, we are unable to determine whether metal exposure directly causes telomere shortening or lengthening. Cross-sectional studies can only reveal correlations between exposure and outcomes, but they cannot infer causal relationships[10]. Therefore, future studies should incorporate prospective cohort designs to better establish the causal nature of these associations.

Moreover, while we adjusted for several potential confounders, such as age, sex, smoking, and alcohol consumption, the influence of other unaccounted factors, such as genetic background, cannot be entirely ruled out. These residual confounders may partially affect the relationship between metal exposure and telomere length. Therefore, future research should consider incorporating additional biomarkers and genetic data to more comprehensively explore the mechanisms by which metal exposure influences telomere length.

Conclusion

In conclusion, this study provides novel insights into the effects of essential trace metal exposure on telomere length and underscores the importance of maintaining chromium and manganese levels in the elderly. However, further research is needed to confirm the causal relationship between these metals and telomere length and to expand the investigation to include a wider range of biomarkers. This will enhance our understanding of how trace metal exposure contributes to the aging process.

Data availability

Data used in the current study are available from the corresponding author upon reasonable request.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

All procedures involving human subjects in this study were approved by the Ethics Committee of Guilin Medical University (No: 20180702-3).

Consent for publication

Not applicable.

Additional information

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