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Occupational and environmental health in middle-aged and older adults

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Occupational and environmental health in middle-aged and older adults

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Editorial: Occupational and environmental health in middle-aged and older adults

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Editorial on the Research Topic
Occupational and environmental health in middle-aged and older adults

A healthy workplace and conducive living environment are fundamental for the health, wellbeing, and progress of modern society. However, rapid industrialization, rising living demands, and the intensification of globalization have all led to increased occupational hazards and contamination of the air, water, soil, and food, thus posing new challenges for occupational and environmental health. Multiple organs and systems of the human body might suffer short- or long-term adverse effects from occupational hazards and environmental contaminants. For example, particulate matter, one of the primary contributors of air pollution, can harm the respiratory and cardiovascular systems by inducing oxidative stress, inflammation, and activation of the autonomic nervous system (1, 2). Meanwhile, there are too many diverse workplace hazards to exhaust their negative consequences and underlying mechanisms; hence, complex multidisciplinary study approaches are warranted.

Extended and recurrent occupational and environmental exposure can amplify these adverse effects (3). The threat of occupational noise exposure to the cardiovascular system rises with increasing cumulative noise exposure or duration of exposure time (4, 5). Thus, more attention should be given to middle-aged and older adults, who frequently have increased health risks and prolonged exposure to occupational and environmental hazards.

Currently, emerging new technologies and instruments have made it feasible to investigate the underlying mechanisms behind occupational and environmental hazards and their adverse health outcomes. The multi-omics approach, integrating data from multiple levels (genes, mRNAs, regulatory factors, proteins, metabolism, etc.), provides a greater knowledge of the molecular mechanisms and genetic foundation of complex features in biological processes and disease processes (6).

With this Research Topic on "occupational and environmental health in middle-aged and older adults," we aimed to entice more academics to concentrate on the health effects of occupational and environmental hazards along with their underlying potential causal mechanisms. Moreover, we aimed to motivate more scholars to explore early biomarkers of environmental and occupational hazards for both exposure and harmful health impacts. This will offer insights for enhancing hazards prevention and control.

Concerns regarding occupational and environmental health threats are growing. The majority of the submitted manuscripts investigated the adverse effects of hazards on the general population (Bączalska et al.; Xia et al.), specific occupational groups (Chen et al.), or middle-aged and older adults (Li et al.; Wang et al.; Huang et al.; Ren et al.; Shen et al.; Wei et al.); additionally, several studies proposed innovative approaches to identify the hazards (Zhang et al.).

Indoor air pollution from the burning of household solid fuel has been found to be significantly associated with cognitive decline, visual impairment, and depression, which are risk factors for functional disability (FD). Given that older adults typically spend the majority of their time indoors, particularly after retirement age, their health is more likely to be impaired by prolonged exposure to indoor air pollution. In a cohort study with 17,708 participants aged 45 years and older from 450 villages/urban communities across China, Ren et al. identified that household solid fuel use was a risk factor for FD, and switching from solid to clean household fuel could help to reduce the burden of FD in the currently aging society of China.

Volatile organic compounds (VOCs) are a large group of chemicals widely used in people's daily routines. Increasing evidence has revealed the VOCs' accumulating toxicity. In a cross-sectional study based on the United States National Health and Nutrition Examination Survey database, Wei et al. explored the relationship between blood VOCs and a prostate-specific antigen and found a positive association between blood chloroform and the total prostate-specific antigen level.

Telomeres are DNA protein complexes that protect the ends of eukaryotic chromosomes, which shorten each time a cell is divided. Telomere shortening is not only a key mechanism of cell senescence, but it also contributes to aging and diseases.

Xia et al. screened the possible hazardous urinary metals for leukocytes telomere length (LTL) while constructing an artificial neural network model to make the prediction of LTL based on urinary metals, demography, behavior, and disease history.

The prevalence of mild cognitive impairment (MCI), which is the most common early sign of Alzheimer's disease, increases with age. The findings of the study by Wang et al. based on participants aged 60 years and older, imply that exposure to chemical agents such as cesium, manganese, barium, and cadmium may be involved in the pathophysiology of MCI, such as via interfering with potassium channels or protecting neurons.

Noise is defined as an unpleasant or harmful sound. Aircraft noise is characterized as the highest source of annoyance when compared with other environmental noise sources, as addressed by Bączalska et al. who provided an updated literature review on aircraft noise exposure and the consequences for cardiovascular systems in the context of the World Health Organization Environmental Noise Guidelines for the European Region (for the whole of Europe).

Non-Gaussian complex noise is composed of transient high-energy impulsive noise superimposed on Gaussian background noise, which is common in the occupational environment and could lead to more severe hearing damage than steady noise. Conventional noise measurement techniques are not suitable for complex noise measurement due to the peak clipping effect of impulse noise. Thus, based on previous studies and literature reviews, Zhang et al. introduced a draft guideline for occupational workplaces in China to measure workplace non-Gaussian complex noise exposure using kurtosis adjustment of the noise level.

Through a survey of enterprise workers in key industries in China, Chen et al. investigated the prevalence of musculoskeletal diseases of the wrists among occupational workers in different industries. They identified several factors (e.g., female sex, working age, and poor wrist posture) that were associated with wrist injuries and provided a scientific basis for formulating corresponding measures for improving occupational workers' health.

Humans are unavoidably exposed to a range of occupational or environmental hazards every day. Sometimes, even slight modifications to the physical or chemical properties of certain dangerous substances can have a profound effect on human health. Through this Research Topic, we have sought to increase attention and interest in strengthening the potential links between occupational and environmental hazards and population health, from exploring their relationships to investigating potential mechanisms and biomarkers. It provides more knowledge to assist with the development of public health policies, and it also improves tertiary prevention measures and targeted prevention for populations that are especially exposed. Population aging is now a significant global public health concern. From a broader perspective, concentrating on the health hazards faced by older adults can assist in enhancing their quality of life and lessening the burden of disease.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Assessing volatile organic compounds exposure and prostate-specific antigen: National Health and Nutrition Examination Survey, 2001–2010

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Background: Volatile organic compounds (VOCs) are a large group of chemicals widely used in people's daily routines. Increasing evidence revealed the VOCs' accumulating toxicity. However, the VOCs toxicity in male prostate has not been reported previously. Thus, we comprehensively evaluated the association between VOCs and prostate-specific antigen (PSA).

Methods: A total of 2016 subjects were included in our study from the National Health and Nutrition Examination Survey with VOCs, PSA, and other variables among U.S. average population. We constructed XGBoost Algorithm Model, Regression Model, and Generalized linear Model (GAM) to analyze the potential association. Stratified analysis was used to identify high-risk populations.

Results: XGBoost Algorithm model identified blood chloroform as the most critical variable in the PSA concentration. Regression analysis suggested that blood chloroform was a positive association with PSA, which showed that environmental chloroform exposure is an independent risk factor that may cause prostate gland changes [β, (95% CI), $P = 0.007$, (0.003, 0.011), 0.00019]. GAM observed the linear relationship between blood chloroform and PSA concentration. Meanwhile, blood chloroform linear correlated with water chloroform in the lower dose range, indicating that the absorption of water may be the primary origin of chloroform. Stratified associations analysis identified the high-risk group on the chloroform exposures.

Conclusion: This study revealed that blood chloroform was positively and independently associated with total PSA level, suggesting that long-term environmental chloroform exposure may cause changes in the prostate gland.

KEYWORDS

prostate-specific antigen (PSA), volatile organic compounds (VOCs), National Health and Nutrition Examination Survey (NHANES), public health, chloroform

Introduction

Volatile organic compounds (VOCs) are a large group of chemicals used as solvents, degreasers, and cleaning agents through industry and consumer products in people's daily routines (1, 2), including vehicle emissions, cooking, wood burning, various industrial processes, smoking, cleaning supplies, building materials, and other household products (3–5). People monitored human exposure to VOCs through a variety of mechanisms, including traditional routes of assessment and the collection of an individual's blood, urine, breath, or sweat (6).

Previous studies have reported that acute exposures to selected VOCs [1,1-dichloroethane, 1,2-dichloroethane, benzene, bromodichloromethane, bromoform, chloroform, dibromochloromethane, dichloromethane, ethylbenzene, MTBE, tetrachloroethylene (PCE)] lead to kidney damage, cardiovascular disease, leukemia and chromosomal mismatch (7–9). Some studies showed that severe VOCs exposures [benzene, toluene, ethylbenzene, and xylenes (BTEX)] could cause sharp liver injury in humans and animal models and lower environment VOCs exposures may also lead to liver damage (10, 11). Some studies indicated that occupational VOCs (methane, benzene, toluene, ethylbenzene, o-xylene, m/p-xylene, and styrene) levels affect white blood level growth. Meanwhile, this phenomenon also occurs in the general population (4, 12, 13). Increasing evidence revealed the VOCs' accumulating toxicity (14). A study observed that cancer incidence, including stomach, bronchus, lung, and prostate, increased among persons living near a municipal solid waste landfill site that generated many VOCs (15). Although most research used empirical data in the environmental distribution and risk analysis, personal laboratory data was considered the best similar to actual exposure (16, 17). The limitations of the association between the blood VOCs concentration and parameters of liver, kidney, hematologic, endocrine and prostate functions still exist, especially in the average population (18). Studies evaluated occupational exposure to monocyclic aromatic hydrocarbons (MAHs) in prostate cancer (PCa) development indicating elevated risks of PCa with ever exposure to toluene and xylene (BTX) and duration, while marginal increases were found for exposure to styrene or MAHs (19–21). The limitations of the association between the blood VOCs concentration and parameters of liver, kidney, hematologic, endocrine, and prostate functions still exist, especially in the average population (18, 22).

The prostate is an essential reproductive gland in many physiological functions and fertility; it produces prostate fluid containing different enzymes, zinc, and many acids (23, 24). The prostate-specific antigen is one of the enzymes in a prostatic fluid whose functions include coagulation and liquefaction of semen which play a significant role in sperm fertility (25). Mounting PSA levels with an enlarged prostate size is related to benign prostatic hyperplasia (BPH), prostatitis, or prostate cancer (26). PSA concentrations monitoring is considered the most helpful serum biomarker to detect in the early prostate cancer process, clinical staging, and therapeutic outcome observation (27). Now, increasing evidence shows various environmental pollution like agent orange, pesticides, and cadmium are possible risk factors in prostate cancer (28), evidenced by PSA levels growth (29, 30). Air pollution and metal exposure are also known as risk factors for BPH like nitrogen oxide, cadmium, and nickel (31–33).

VOCs are common chemicals and suspected dangerous factors influencing public health. However, till now, there has been no research focus on the environmental VOCs affecting the prostate condition in the average population. However, some studies reveal that urinary volatiles and chemical characteristics for the non-invasive detection of prostate changes (34–37), the association between environmental VOCs exposure and PSA concentrations have not been reported previously. Studies revealed that occupational VOCs might promote PCa development, while environmental VOCs' effect on the prostate is still unclear. We hypothesized that VOCs might cause pathological prostate changes, which lead to PSA concentration changes. In order to verify our hypothesis, we explored the U.S. National Health and Nutrition Examination Survey (NHANES) for secondary analysis. According to previous articles (38–43), we controlled the potential confounders including, age, race, education level, marital status, poverty to income ratio, BMI, alcohol drinks, smoking, diabetes, physical activity, blood urea nitrogen, uric acid, creatinine which might be related to both the exposure as well as the outcome. Then we constructed models to clarify the comprehensive relationship between the volatile organic compounds (VOCs) and prostate-specific antigen (PSA). We aim to illustrate the VOCs influence prostate health among U.S. males.

Methods

Data availability

National Health and Nutrition Examination Survey (NHANES) as a nationwide study was supported by the National Centers for Disease Control (CDC) and Prevention National Health Statistics Center, which aimed to estimate the United States adults' and children's health and nutritional status from 1960 (44). All survey data and methodological details are available on the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm). NHANES protocols were approved by the NAHNES Institutional Review Board (IRB)/NCHS Research Ethics Review Board (ERB). In our study, no external IRB or ethical approval was needed beyond NHANES IRB/ERB approval.

Study population

NHANES is a continuous survey that has released published data files in 2-year cycles since 1999. Our study consisted of five periods of subjects who participated NHANES survey from 2001 to 2010. PSA concentration, water VOCs, blood VOCs, sociodemographic data, medical examination, and personal life history data, comorbidities data, and laboratory data have been included in our study for the secondary analysis. Participants were selected out of the total population and taken into our study according to the following exclusion criteria as: (1) female subjects (n = 26,493); (2) aged below 40 years old (n = 16,844); (3) missing/without PSA testing (n = 2735); (4) diagnosed with enlarged prostate (n = 739); (5) diagnosed with prostate cancer (n = 129); (Participants with enlarged prostate or diagnosed with PSA may cause outliers data which influence analysis results)(6) missing/without VOCs testing (n = 3078); (7) do not have data about covariates at least one of following (n = 161): race/ethnicity; educational level; marital level; family poverty income ratio (38, 43, 45). Inclusion criteria as: (1) male subjects (n = 25,702); (2) 40 years old or older (n = 8,858); (3) Tested for PSA (n = 5,255); (4) Tested for VOCs (n = 2,177); (5) have data about covariates at least one of following (n = 2,016): race/ethnicity; educational level; marital level; family poverty

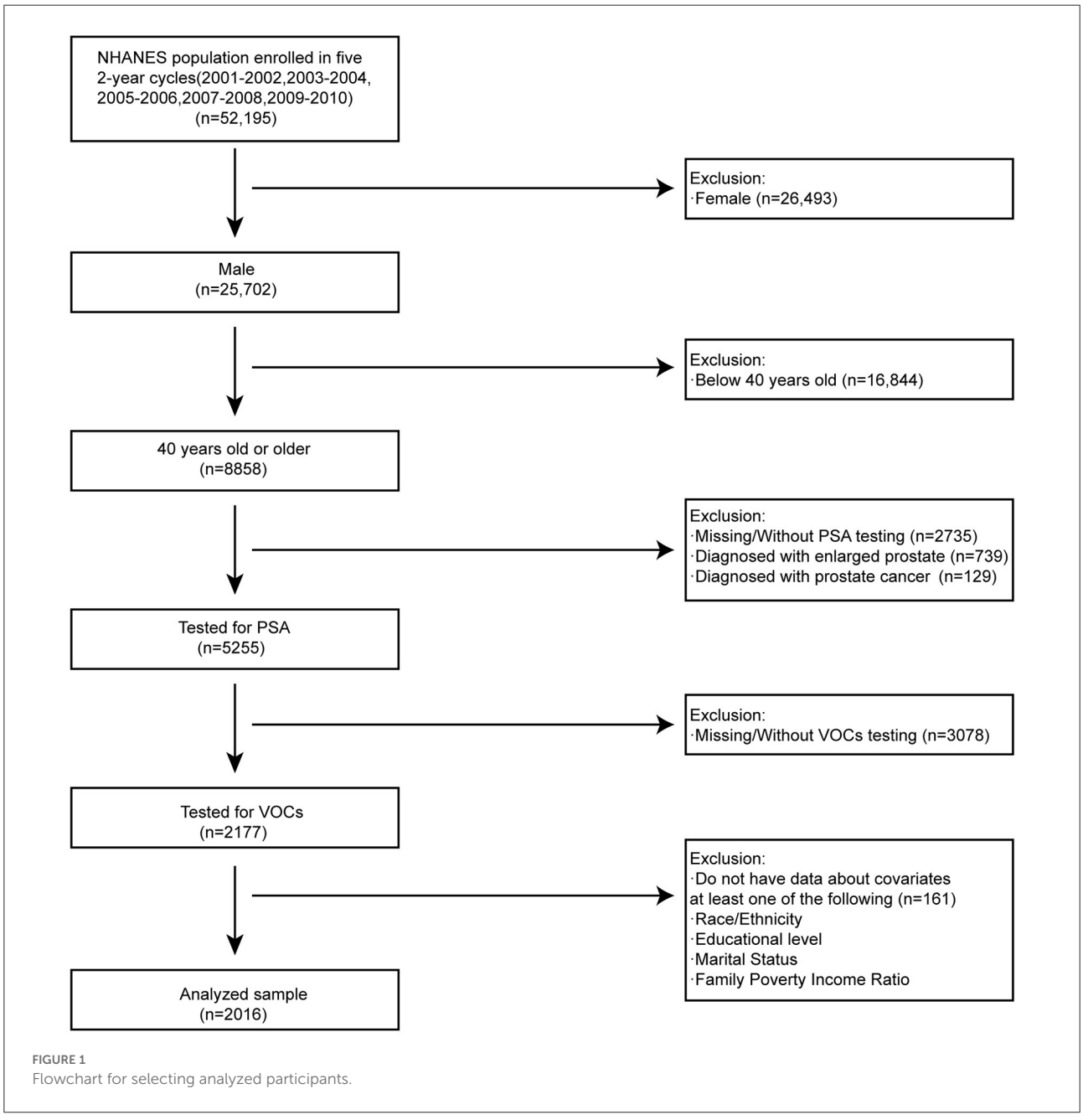

FIGURE 1
Flowchart for selecting analyzed participants.

income ratio. There were 2016 analyzed samples out of 52,195 participants left in our study after screening (Figure 1). In the process of study design and conduction, the study complied with the Helsinki Declaration of the World Medical Association (46).

VOCs measurement

Volatile organic compounds (VOCs) are a large group of chemicals that have been used as solvents, degreasers, and cleaning agents in the industry and consumer products. VOCs measurement consists of human blood VOCs and home tap water VOCs. Tap water VOCs including THMs (chloroform, bromodichloromethane, dibromochloromethane, and bromoform) and MTBE. These were analyzed by automatic method on headspace solid-phase microextraction (SPME) coupled with capillary gas chromatography and mass spectrometry. Blood disinfection by-products (DBP) (chloroform, bromodichloromethane, dibromochloromethane, and bromoform) and MTBE were quantified in human blood using capillary gas chromatography (GC) and high-resolution mass spectrometry (MS) with selected ion mass detection and isotope-dilution techniques which quantified trace levels of THMs and MTBE in human blood. Additional VOCs (tetrachloroethene, benzene, 1,4-dichlorobenzene, ethylbenzene, o-xylene, styrene, trichloroethene, toluene, m-/p-Xylene) were measured in human blood using SPME in conjunction with gas chromatography and benchtop quadrupole mass spectrometer.

PSA measurement

Total PSA concentrations were detected using the Hybritech PSA method on the Beckman Access Immunoassay System, which automatically detected reacted samples' light production. Free PSA concentrations were detected by the Access Hybritech assay, which measures through a two-site immuno-enzymatic "sandwich" assay. Prostate-specific antigen ratio was calculated by dividing the free PSA by the total PSA and then multiplying by 100. Total PSA's cutoff value to dichotomize was 4.0 ng/ mL, and the PSA ratio was 15% (47, 48).

Other variables

We have selected other variables affecting PSA concentration based on the previous surveys regarding the possible connection. Sociodemographic variables included age (year), poverty to income ratio, race/ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, others), an education level (less than high school, high school, more than high school), marital status (married, single, living with a partner). Variables of laboratory data included blood urea nitrogen (mmol/L), uric acid (umol/L), creatinine (umol/L) (41, 49, 50). The LX20 modular chemistry (BUNm) and timed endpoint method were used to quantitatively determine the concentration of blood urea nitrogen and uric acid in serum or plasma. Creatinine was detected by the LX20 modular chemistry side using the Jaffe rate method (kinetic alkaline picrate). Analyzed samples' comorbidities data included drinking (Had at least 12 alcohol drinks/1 year), smoking (Smoked at least 100 cigarettes in life), and diagnosis with diabetes (Yes, No, Borderline). Lastly, we also included medical examination and personal life history data involving body mass index (Kg/m2) and physical activity (MET-based rank). More details of variables can be found on the NHANES official website.

Statistical analysis

We have conducted a statistical analysis of the VOCs (blood and water) and PSA levels based on the CDC guidelines' criteria (https://www.cdc.gov/nchs/nhanes/index.htm). PSA concentration, VOCs and other continuous variables were expressed as the mean ± standard deviation as the normal distribution. The categorical variables were presented as percentage or frequency. First, we divided age as a continuous variable into four quartile concentrations. The weighted chi-square was used to calculate the p-value of the characteristics of the analyzed population's Categorical variables. In the case of continuous variables, we used the Kruskal Wallis rank sum test to calculate the p-value. If the count variable has a theoretical number < 10, we used Fisher's exact probability test to calculate the p-value, Results were shown in Table 1. Second, we constructed the machine learning of the XGBoost algorithm model to predict the relative importance of blood VOCs on the effect of PSA concentration. XGBoost model was performed to analyze blood VOCs contribution (gain) to PSA concentration (51). Third, we constructed three kinds of weighted multiple linear regression models that adjusted various variables shown in Table 2 to classify the relationship between the blood VOCs and PSA concentrations (Model 1: non-adjusted model, Model 2: minimally adjusted model, Model 3: fully adjusted model). Multiple analysis results were based on Rubin's rules and calculated dataset. Then, we found the statistical difference between the blood chloroform and PSA level, so we further constructed the subgroup analysis to identify the stratified associations between blood chloroform and PSA through stratified multivariate logistic regression. Lastly, we based the penalty spline method to construct a smooth curve using a Generalized additive model (GAM) model with a fully adjusted model to explore the potential linear relationship between the blood chloroform and PSA concentration (52). In order to explore the origin of the blood chloroform, we further constructed a smooth curve between the blood chloroform and water chloroform. Using the MICE package accounting for

TABLE 1 Baseline characteristics of the study population.

PSA, total	Q1	Q2	Q3	Q4	*P*-value
N	500	501	511	504	
PSA, total (ng/mL)	0.39 ± 0.12	0.73 ± 0.10	1.24 ± 0.22	4.01 ± 3.85	<0.001
PSA, free (ng/mL)	0.15 ± 0.06	0.24 ± 0.08	0.34 ± 0.13	0.84 ± 0.72	<0.001
Prostate specific antigen ratio (%)	38.37 ± 12.61	32.61 ± 10.88	28.11 ± 10.55	22.95 ± 9.82	<0.001
Sociodemographic variables					
Age, mean±SD (years)	54.38 ± 11.53	53.14 ± 10.92	56.07 ± 11.35	63.85 ± 11.76	<0.001
Poverty to income ratio, mean±SD	2.79 ± 1.64	2.80 ± 1.66	2.70 ± 1.64	2.79 ± 1.62	0.721
Race/Ethnicity (%)					0.128
Hispanic	111 (22.20%)	138 (27.54%)	128 (25.05%)	110 (21.83%)	
Non-Hispanic White	270 (54.00%)	253 (50.50%)	243 (47.55%)	259 (51.39%)	
Non-Hispanic Black	93 (18.60%)	96 (19.16%)	112 (21.92%)	111 (22.02%)	
Other race/ethnicity	26 (5.20%)	14 (2.79%)	28 (5.48%)	24 (4.76%)	
Education (%)					0.534
Less than high school	141 (28.20%)	151 (30.14%)	148 (28.96%)	168 (33.33%)	
High school	122 (24.40%)	132 (26.35%)	124 (24.27%)	120 (23.81%)	
More than high school	237 (47.40%)	218 (43.51%)	239 (46.77%)	216 (42.86%)	
Marital status (%)					0.028
Married	333 (66.60%)	341 (68.06%)	346 (67.71%)	317 (62.90%)	
Single	143 (28.60%)	125 (24.95%)	139 (27.20%)	169 (33.53%)	
Living with a partner	24 (4.80%)	35 (6.99%)	26 (5.09%)	18 (3.57%)	
Variables of laboratory data					
Blood urea nitrogen, mean±SD (mmol/L)	14.15 ± 5.52	13.77 ± 5.52	14.11 ± 5.06	15.69 ± 7.08	<0.001
Uric acid, mean±SD (umol/L)	6.18 ± 1.39	6.06 ± 1.26	6.11 ± 1.29	6.28 ± 1.37	0.043
Creatinine, mean±SD (umol/L)	1.03 ± 0.45	1.02 ± 0.46	1.06 ± 0.54	1.11 ± 0.47	<0.001
Comorbidities (%)					
Had at least 12 alcohol drinks/1 year?					0.357
Yes	379 (82.03%)	397 (84.83%)	402 (84.28%)	363 (80.67%)	
No	379 (82.03%)	397 (84.83%)	402 (84.28%)	363 (80.67%)	
Smoked at least 100 cigarettes in life					0.559
Yes	296 (59.20%)	295 (58.88%)	320 (62.62%)	300 (59.52%)	
No	204 (40.80%)	206 (41.12%)	191 (37.38%)	203 (40.28%)	
Diabetes					0.416
Yes	85 (17.00%)	65 (12.97%)	67 (13.11%)	82 (16.27%)	
No	404 (80.80%)	426 (85.03%)	436 (85.32%)	411 (81.55%)	
Borderline	11 (2.20%)	9 (1.80%)	8 (1.57%)	11 (2.18%)	
Medical examination and personal life history					
Body mass index, mean ± SD (Kg/m2)	29.77 ± 6.06	29.22 ± 5.82	28.32 ± 4.84	28.48 ± 5.32	<0.001
Physical activity (MET-based rank) (%)					0.514
Sits	276 (70.41%)	271 (68.61%)	286 (73.33%)	263 (76.01%)	
Walks	68 (17.35%)	75 (18.99%)	68 (17.44%)	46 (13.29%)	
Light loads	29 (7.40%)	31 (7.85%)	21 (5.38%)	21 (6.07%)	
Heavy work	19 (4.85%)	18 (4.56%)	15 (3.85%)	16 (4.62%)	
Water VOCs					
Water Bromoform, mean ± SD (ng/mL)	1.50 ± 3.43	1.54 ± 3.13	1.55 ± 3.74	1.85 ± 5.14	0.476
Water Chloroform, mean ± SD (ng/mL)	13.07 ± 18.24	14.31 ± 18.82	14.67 ± 19.78	12.63 ± 17.37	0.245
Water Bromodichloromethane, mean ± SD (ng/mL)	8.98 ± 13.26	8.19 ± 11.03	8.05 ± 11.13	8.07 ± 11.31	0.557
Water Dibromochloromethane, mean ± SD (ng/mL)	3.35 ± 5.34	4.05 ± 6.79	3.69 ± 5.42	3.90 ± 6.35	0.295

(Continued)

TABLE 1 Continued

PSA, total	Q1	Q2	Q3	Q4	*P*-value
Water MTBE, mean ± SD (ng/mL)	0.11 ± 0.49	0.12 ± 0.80	0.09 ± 0.11	0.08 ± 0.08	0.563
Blood VOCS					
Blood Tetrachloroethene, mean ± SD (ng/mL)	0.09 ± 0.49	0.07 ± 0.18	0.07 ± 0.23	0.06 ± 0.15	0.37
Blood Bromoform, mean ± SD (pg/mL)	2.21 ± 8.82	2.29 ± 12.40	2.64 ± 20.73	1.67 ± 3.34	0.018
Blood Bromodichloromethane, mean ± SD (pg/mL)	2.95 ± 4.08	3.30 ± 4.90	3.16 ± 5.06	3.01 ± 4.32	0.654
Blood Benzene, mean ± SD (ng/mL)	0.08 ± 0.12	0.07 ± 0.12	0.09 ± 0.15	0.06 ± 0.10	<0.001
Blood Chloroform, mean ± SD (pg/mL)	14.95 ± 35.36	14.32 ± 20.31	15.98 ± 25.91	14.38 ± 21.36	0.002
Blood Dibromochloromethane, mean ± SD (pg/mL)	2.13 ± 4.33	2.20 ± 3.91	2.22 ± 4.34	2.18 ± 3.60	0.284
Blood 1,4-Dichlorobenzene, mean ± SD (ng/mL)	1.08 ± 4.26	1.51 ± 9.79	1.60 ± 7.94	1.51 ± 7.16	0.692
Blood Ethylbenzene, mean ± SD (ng/mL)	0.05 ± 0.06	0.07 ± 0.31	0.10 ± 0.42	0.08 ± 0.48	0.01
Blood MTBE, mean ± SD (pg/mL)	8.87 ± 44.02	9.51 ± 34.54	7.70 ± 34.10	6.06 ± 33.86	0.197
Blood o-Xylene, mean ± SD (ng/mL)	8.04 ± 57.09	8.59 ± 36.36	12.17 ± 85.32	14.50 ± 181.15	0.015
Blood Styrene, mean ± SD (ng/mL)	0.05 ± 0.05	0.05 ± 0.05	0.07 ± 0.23	0.05 ± 0.04	0.033
Blood Trichloroethene, mean ± SD (ng/mL)	0.02 ± 0.05	0.02 ± 0.03	0.02 ± 0.04	0.02 ± 0.03	0.281
Blood Toluene, mean ± SD (ng/mL)	0.24 ± 0.37	0.23 ± 0.46	0.27 ± 0.50	0.22 ± 0.57	0.009
Blood m-/p-Xylene, mean ± SD (ng/mL)	0.17 ± 0.25	0.21 ± 0.90	0.31 ± 1.23	0.21 ± 0.90	<0.001

Q1–Q4: Grouped by quartile according to the total PSA. Our data included PSA concentrations, Sociodemographic variables, Variables of laboratory data, Comorbidities data, Medical examination and personal life history, comorbidities data Water VOCs and Blood VOCs for the second analysis.

TABLE 2 Multivariate weighted linear model analysis reveals the association between the blood VOCs and PSA concentration.

Exposure	Model 1 β (95% CI) P	Model 2 β (95% CI) P	Model 3 β (95% CI) P
Blood VOCs			
Blood Tetrachloroethene	−0.139 (−0.522, 0.245) 0.47927	−0.074 (−0.438, 0.290) 0.68923	−0.079 (−0.442, 0.283) 0.66777
Blood Bromoform	−0.002 (−0.010, 0.007) 0.71939	0.001 (−0.007, 0.009) 0.83055	0.001 (−0.007, 0.008) 0.88882
Blood Bromodichloromethane	−0.001 (−0.025, 0.022) 0.90277	0.007 (−0.016, 0.029) 0.54772	0.010 (−0.013, 0.033) 0.40911
Blood Benzene	−0.623 (−1.450, 0.203) 0.13952	−0.058 (−0.883, 0.768) 0.89119	0.033 (−0.855, 0.921) 0.94213
Blood Chloroform	**0.005 (0.001, 0.009) 0.00782**	**0.007 (0.003, 0.011) 0.00019**	**0.007 (0.003, 0.011) 0.00019**
Blood Dibromochloromethane	0.006 (−0.021, 0.032) 0.68547	0.013 (−0.013, 0.038) 0.33540	0.015 (−0.010, 0.041) 0.24261
Blood 1,4–Dichlorobenzene	0.006 (−0.009, 0.021) 0.43682	0.000 (−0.014, 0.015) 0.95258	0.004 (−0.011, 0.020) 0.57235
Blood Ethylbenzene	−0.090 (−0.394, 0.214) 0.56140	0.018 (−0.273, 0.308) 0.90565	0.040 (−0.262, 0.342) 0.79429
Blood MTBE	−0.003 (−0.006, 0.000) 0.07231	−0.000 (−0.003, 0.003) 0.84867	−0.000 (−0.003, 0.002) 0.75679
Blood o-Xylene	0.000 (−0.001, 0.001) 0.94056	−0.000 (−0.001, 0.001) 0.94836	−0.000 (−0.001, 0.001) 0.88010
Blood Styrene	−0.164 (−1.209, 0.881) 0.75820	0.169 (−0.835, 1.172) 0.74176	0.073 (−0.937, 1.083) 0.88759
Blood Trichloroethene	−1.606 (−4.529, 1.317) 0.28174	−0.976 (−3.768, 1.816) 0.49327	−0.894 (−3.692, 1.905) 0.53134
Blood Toluene	−0.096 (−0.339, 0.147) 0.43788	0.017 (−0.219, 0.254) 0.88598	0.018 (−0.224, 0.260) 0.88570
Blood m-/p-Xylene	−0.052 (−0.177, 0.073) 0.41568	−0.008 (−0.128, 0.111) 0.88984	−0.001 (−0.124, 0.121) 0.98312
Water VOCs			
Water Bromoform	0.017 (−0.010, 0.044) 0.20826	0.008 (−0.018, 0.034) 0.52935	0.012 (−0.017, 0.041) 0.40627
Water Chloroform	0.001 (−0.004, 0.007) 0.66229	0.003 (−0.003, 0.008) 0.32078	0.001 (−0.006, 0.009) 0.72821
Water Bromodichloromethane	0.004 (−0.005, 0.013) 0.40601	0.003 (−0.006, 0.011) 0.53086	0.004 (−0.006, 0.014) 0.46444
Water Dibromochloromethane	0.016 (−0.002, 0.033) 0.08270	0.011 (−0.006, 0.028) 0.19207	0.016 (−0.004, 0.035) 0.11278
Water MTBE	−0.088 (−0.318, 0.141) 0.45088	−0.076 (−0.295, 0.143) 0.49621	−0.221 (−0.635, 0.194) 0.29709

Model 1: Non-adjusted model adjusts for none. Model 2: Minimally adjusted model adjusts for age, race/ethnicity, education level, marital status and poverty to income ratio. Model 3: Fully adjusted model adjusted age, race/ethnicity, education level, marital status, poverty to income ratio, BMI (kg/m2), Had at least 12 alcohol drinks/1 year, smoked at least 100 cigarettes in life, diabetes, physical activity (MET-based rank) (%), blood urea nitrogen, uric acid, creatinine. Bold values means statistically significant.

missing data, we curated the data and improved the accuracy of analysis results (53). There is no significant difference between the complete data and origin data. Multiple analysis results were based on the calculated dataset and Rubin's rules. All kinds of statistical analyses were conducted by R software (Version 4.0.2) using the R package (http://www.R-project.org, The R Foundation) (54). The software of EmpowerStats provided significant help in the process of our research (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA). In our study, the level of statistical significance was set p-value below 0.05.

Results

Characteristics of selected population

Table 1 shows the baseline characteristics of the chosen population from the NHANES dataset (2001-2010), which is weighted distribution. Variables included sociodemographic variables, laboratory data, comorbidities, medical examination and personal life history, water VOCs, blood VOCs, and PSA data. We grouped the population by quartile according to the total PSA (Q1-Q4). We found the distribution of poverty to income ratio, race/ethnicity, education level, drinking situation, smoking situation, diabetes, and physical activity in four quartiles indicated no statistical difference with p values > 0.05, and prostate-specific antigen ratio, age, marital status showed statistical difference with p values < 0.05. The older population showed a higher level of total PSA concentrations, which accorded to previous papers. Compared with the various groups, VOCs including blood bromoform, blood benzene, blood chloroform, blood ethylbenzene, blood o-Xylene, blood styrene, blood toluene, blood m-/p-Xylene showed distribution difference with a statistical significance which may indicate exposure difference between four groups while blood tetrachloroethene, blood bromodichloromethane, blood dibromochloromethane, blood 1,4-dichlorobenzene, blood MTBE and blood trichloroethene showed no exposure difference. Water VOCs including water bromoform, water chloroform, water bromodichloromethane, water dibromochloromethane, and water MTBE showed no statistical difference in the four groups. In our research, non-Hispanic Whites were the main population, and the following were the non-Hispanic Black. (This race/ethnicity variable was derived from responses to the survey questions on race and Hispanic origin. Respondents who self-identified as "Mexican American" were coded as such regardless of their other race-ethnicity identities. Otherwise, self-identified "Hispanic" ethnicity would result in the code "Other Hispanic" variable. We used "Hispanic" category to replace "other Hispanic" and "Mexican American". All other non-Hispanic participants would then be categorized based on their self-reported races: non-Hispanic white, non-Hispanic black, and other non-Hispanic race, including non-Hispanic multiracial).

Using machine learning of XGBoost algorithm model to explore the VOCs' relative importance

In order to select which VOCs affected PSA most, we constructed the machine learning of the XGBoost Algorithm model to determine the relative importance among all blood VOCs. VOCs' variables included blood disinfection by-products (DBP) (chloroform, bromodichloromethane, dibromochloromethane, and bromoform) and additional blood VOCs (tetrachloroethene, benzene, 1,4-dichlorobenzene, ethylbenzene, o-xylene, styrene, trichloroethene, toluene, m-/p-Xylene). We found that blood chloroform was the most critical variable in the PSA concentration, followed by blood1,4-dichlorobenzene, blood styrene, blood benzene, and blood bromodichloromethane (Figure 2).

The regression analysis between VOCs and PSA concentrations

In order to figure out the association between the blood VOCs and PSA concentrations, we constructed the weighted linear model by multivariate regression analysis shown in Table 2. Among all of the results, we found that only blood chloroform shows a positive association with PSA concentrations with statistical significance. In model 1 which adjusts for none, the PSA increase by 0.005 (ng/mL) (0.001, 0.009) for each additional unit of blood chloroform (pg/mL) with p less than 0.05. In model 2 (minimally adjusted model) and model 3 (fully adjusted model), results from both indicated that PSA increased by 0.007 (ng/mL) (0.003, 0.011) for each additional unit of blood chloroform (pg/mL) with p less than 0.05. This result suggested that long-time environmental chloroform exposure as an independent risk factor may cause male reproductive damage, especially in the prostate gland.

Stratified associations between PSA concentrations and blood chloroform

We further analyzed stratified associations between PSA concentrations and blood chloroform in a specific subgroup by age, race, education level, and the ratio of family income and BMI shown in Table 3. Surprisingly, we found an association between the blood chloroform and the PSA concentration concentrated in the specific subgroup. PSA concentrations of the population whose ages from 60 to 70 increase by 0.050 (ng/mL) for each unit of blood chloroform in model 1, by 0.049 in model 2, and 0.060 in model 3 with $p < 0.05$. This positive association also represents the non-Hispanic black, education level more than high school, BMI from 25 to 28. In the non-Hispanic black, PSA increase by 0.036 (ng/mL)

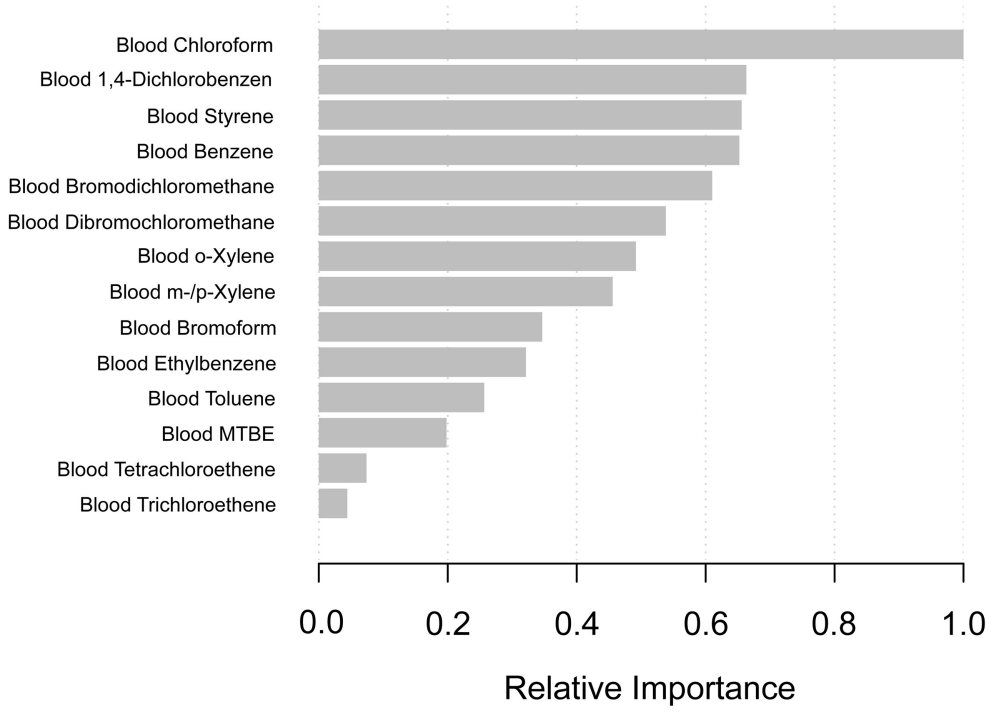

FIGURE 2
XGBoost model reveals the relative importance of blood VOCs on the PSA concentration and the corresponding variable importance score. The X-axis indicates the importance score, the relative number of a variable used to distribute the data; the Y-axis shows the blood VOCs.

(0.025, 0.047) for each additional unit of blood chloroform (pg/mL) in model 1, increase by 0.035 (ng/mL) (0.024, 0.045) in model 2 and increase by 0.055 (ng/mL) (0.041, 0.070) with statistical difference. Moreover, people with education level more than high school had same trend whose PSA increase by 0.021(ng/mL) in model 1, increase by 0.022(ng/mL) (0.017, 0.028) in model 2 and increase by 0.027(ng/mL) (0.021, 0.033) in model 3 with statistical difference. Moreover, Population with BMI between 25 to 28 indicated that PSA concentrations increase by 0.009 (ng/mL) (0.004, 0.015) in model 1, increase by 0.011(ng/mL) (0.006, 0.016) in model 2 and 0.011(ng/mL) (0.005, 0.016) in model 3.

Linear relationship between the blood chloroform and PSA concentrations/water chloroform using GAM

The Generalized linear model (GAM) is sensitive to identifying the linear relationship or non-linearity. To confirm the stability of the analysis results, we constructed the linear relationship using the GAM model between the blood chloroform and PSA concentrations. Based on the fully adjusted model (Figure 3), we used a smooth fit curve to investigate the possible association. Adjusting for all variables, we observed the linear relationship between blood chloroform and PSA concentration, and most of the data were distributed in the blood chloroform between 0 to 100 (pg/mL). We also constructed the GAM model to explore the linear relationship between blood chloroform and water chloroform. We observed the linear relationship between the blood chloroform and water chloroform when the water chloroform concentration was below 40 (pg/mL). When water chloroform concentration was above 40 (pg/mL), we observed a non-linear relationship between the two variables, which indicated that the origin of blood chloroform might come from various sources when water chloroform is above 40 (pg/mL). Thus, this positive correlation suggested that absorption of water might be the primary origin of chloroform in the specific range.

Discussion

VOCs serve as common chemicals in people's daily routines, including vehicle emissions, cooking, wood burning, various industrial processes, smoking, cleaning supplies, building materials, and other household products (55–59). More and more evidence revealed that VOCs might be the dangerous

TABLE 3 Stratified associations of blood chloroform on PSA in the prespecified and exploratory subgroup.

Blood Chloroform	N	Model 1 β (95% CI) P	Model 2 β (95% CI) P	Model 3 β (95% CI) P
Stratified by age				
<60	1170	0.000 (−0.002, 0.002) 0.8393	0.000 (−0.002, 0.002) 0.8041	−0.000 (−0.002, 0.002) 0.8647
60–69	**363**	**0.050 (0.035, 0.065) <0.0001**	**0.049 (0.034, 0.065) <0.0001**	**0.060 (0.040, 0.080) <0.0001**
70–79	292	0.005 (−0.021, 0.032) 0.6855	0.007 (−0.020, 0.034) 0.6012	0.001 (−0.060, 0.062) 0.9720
≥80	23	−0.043 (−0.113, 0.027) 0.2378	−0.016 (−0.111, 0.078) 0.7419	NA
Stratified by race				
Hispanic	445	−0.002 (−0.008, 0.003) 0.3444	−0.001 (−0.006, 0.004) 0.6431	−0.001 (−0.006, 0.004) 0.7159
Non-Hispanic White	940	−0.001 (−0.007, 0.005) 0.6943	0.002 (−0.003, 0.008) 0.4284	0.002 (−0.005, 0.009) 0.5653
Non-Hispanic Black	**380**	**0.036 (0.025, 0.047) <0.0001**	**0.035 (0.024, 0.045) <0.0001**	**0.055 (0.041, 0.070) <0.0001**
Other race/ethnicit	83	−0.022 (−0.053, 0.009) 0.1745	−0.010 (−0.036, 0.016) 0.4362	−0.021 (−0.059, 0.018) 0.3109
Stratified by education				
Less than high school	554	−0.002 (−0.009, 0.006) 0.6716	0.000 (−0.007, 0.007) 0.9282	0.000 (−0.008, 0.009) 0.9153
High school	457	−0.001 (−0.008, 0.005) 0.6406	0.002 (−0.004, 0.008) 0.4545	0.005 (−0.004, 0.014) 0.2980
More than high school	**837**	**0.021 (0.015, 0.027) <0.0001**	**0.022 (0.017, 0.028) <0.0001**	**0.027 (0.021, 0.033) <0.0001**
Stratified by ratio of family income				
Low	608	−0.001 (−0.008, 0.005) 0.6947	0.000 (−0.006, 0.007) 0.9685	−0.000 (−0.008, 0.007) 0.9090
Middle	624	−0.004 (−0.013, 0.005) 0.3821	−0.001 (−0.009, 0.008) 0.8989	0.001 (−0.009, 0.010) 0.9047
High	**616**	**0.017 (0.011, 0.023) <0.0001**	**0.018 (0.013, 0.023) <0.0001**	**0.031 (0.024, 0.038) <0.0001**
Stratified by BM				
<25	409	−0.002 (−0.017, 0.012) 0.7515	0.001 (−0.013, 0.016) 0.8670	0.005 (−0.015, 0.026) 0.6111
25–28	**467**	**0.009 (0.004, 0.015) 0.0006**	**0.011 (0.006, 0.016) <0.0001**	**0.011 (0.005, 0.016) 0.0001**
>28	942	0.000 (−0.005, 0.005) 0.9477	0.002 (−0.003, 0.007) 0.3938	0.004 (−0.003, 0.011) 0.2411

Note 1: Model 1: Non-adjusted model adjusts for none. Model 2: Minimally adjusted model adjusts for age, race/ethnicity, education level, marital status and poverty to income ratio. Model 3: Fully adjusted model adjusted age, race/ethnicity, education level, marital status, poverty to income ratio, BMI (kg/m2), Had at least 12 alcohol drinks/1 year, smoked at least 100 cigarettes in life, diabetes, physical activity (MET-based rank) (%), blood urea nitrogen, uric acid, creatinine.
Note 2: In each case, the model was not adjusted for the stratification variable itself. Bold values means statistically significant.

factors influencing public health. Although some studies reveal that urinary volatiles and chemical characteristics may help detect prostate changes in a non-invasive way (60–62), the association between environmental VOCs exposure and PSA concentrations has not been reported previously. Our research was an extensive secondary analysis of national studies to explore the potential relationship between volatile organic compounds (VOCs) and prostate-specific antigen (PSA) based on the United Stated cross-sectional NHANES database. We proposed the hypothesis that the toxicity of environmental VOCs might cause influent the function of the male reproductive gland. Until now, there is no previous epidemiological research that reported this association. Blood VOCs analysis was considered the accurate indicator used in the environmental pollution exposures assessment through toxic or harmful VOCs checked in human blood (63, 64).

VOCs in our study contained disinfection by-products (DBPs) (chloroform, bromodichloromethane, dibromochloromethane, and bromoform), MTBE, and other VOCs (tetrachloroethene, benzene, 1,4-dichlorobenzene, ethylbenzene, o-xylene, styrene, trichloroethene, toluene, m-/p-Xylene). DBPs are formed when chlorine interacts with natural organic materials found in water. Primary sources of DBPs mainly come from chlorinated drinking water and recreational water bodies (65, 66). DBPs showed the possibility of cytotoxicity, mutagenicity, teratogenicity, and carcinogenicity (67). Methyl-tert-butyl ether (MTBE) was used as an additive in gasoline to replace lead, but it was banned after widespread groundwater contamination was discovered (68). Other VOCs (tetrachloroethene, benzene, 1,4-dichlorobenzene, ethylbenzene, o-xylene, styrene, trichloroethene, toluene, m-/p-Xylene) usually used in industrial and chemical synthetic processes such as benzene has been used to produce DDT, phenol, and nitrobenzene, 1,4-dichlorobenzene is also used as a moth repellent and as a deodorizer (69). Some studies reported that occupational exposure to VOCs may correlate with cancers. A study indicated that blood THM species, particularly brominated THMs, were significantly associated with total cancer mortality in adults (70). A case-control study on occupational exposure to chlorinated solvents revealed elevated odds ratios (ORs) between perchloroethylene and prostate cancer (71). A study reported that cancer incidence increased among Finnish workers exposed to halogenated hydrocarbons (72).

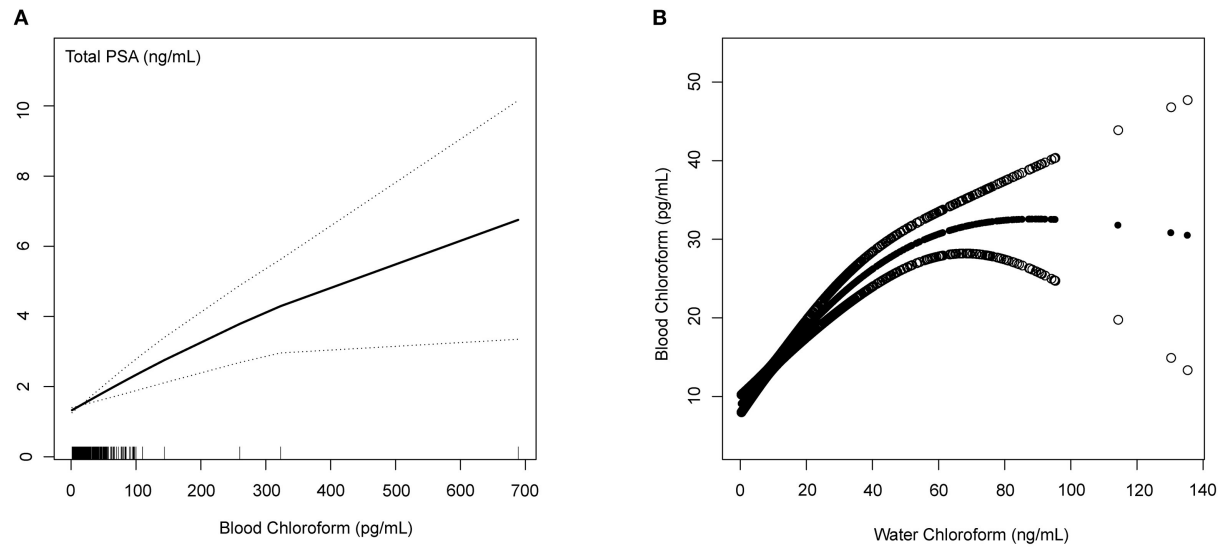

FIGURE 3
Blood Chloroform and PSA concentrations/Water Chloroform **(A)** The linear relationship between the blood chloroform and total PSA; **(B)** The nonlinear relationship between the blood chloroform and water chloroform.

Our research aimed to explore the toxicity of environmental VOCs exposures on the PSA level. We consisted of five periods of subjects who participated NHANES survey from 2001 to 2010 (2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010). In order to classify the above VOCs' relative importance on the PSA level, we first constructed the machine learning of the XGBoost model to determine the order of selected variables. We identified blood chloroform as the most important VOCs on PSA concentrations, followed by blood 1,4-dichlorobenzene, styrene, benzene, and bromodichloromethane. Then, we constructed a weighted linear model by multivariate regression analysis to identify which VOCs is the independent risk factor. Among all of the results, we found that only blood chloroform shows a positive association with PSA concentrations with a statistical significance which indicated that PSA increased by 0.007 (ng/mL) (0.003, 0.011) for each additional unit of blood chloroform (pg/mL) in model 3 (fully adjusted model). This result suggested that long-time environmental chloroform exposure as an independent risk factor may cause male reproductive damage, especially in the prostate gland. Results mean that if 200 (pg/mL) of blood chloroform is added, the PSA concentration will increase by 1.4 (ng/mL).

Chloroform is the most prevalent biomarker of DBPs which can be absorbed through ingestion, inhalation, and dermal contact (73). A prospective cohort study revealed a positive relationship between total brominated THMs, including Br-THMs, the sum of (BDCM, DBCM, and TBM) and TTHM concentrations, and the risk of cancer death (74). Some studies showed that long-term chloroform exposures are linked to colorectal cancer and bladder cancer (75, 76). Animal models indicated that lower exposures of chloroform causing maternal toxicity could not lead to offspring developmental effects (77, 78). Some studies also accounted for the association of chloroform with reproductive development outcomes at the human group level (79, 80). Till now, the toxicity effect of chloroform on the male reproductive gland has not been explored. Through constructing the Generalized linear model (GAM) model, we observed the linear relationship between blood chloroform and PSA concentration which indicated that the damage to the prostate is associated with the accumulation of chloroform exposures. Moreover, we observed the linear relationship between the blood chloroform and water chloroform when water chloroform is below 40 (pg/mL), indicating the absorption of water may be the primary origin of chloroform in the low dose range. Furthermore, we found that the association between chloroform on PSA level has population differences. We identified the high-risk group on the chloroform exposures through stratified analysis, including age between 60 and 70, BMI between 25 and 28, non-Hispanic black, education level more than high school, and education level more than high school.

Our survey has some limitations which should be acknowledged. First, although our study is national broad, most of the data is based on Unite State population. Data on Asian or other populations is still lacking, and the results of the VOCs exposures may be different due to the country's development. Second, this research is a cross-sectional design, and more research is needed to guarantee associations based on causal relationships. Third, VOCs had a relatively short

half-life. Time differences may occur between the PSA concentrations and blood VOCs exposures. Although we comprehensively evaluated the association between VOCs exposure and damage to the prostate, was selected chloroform as a significant risk factor. Nevertheless, the number of analyzed subjects was still too small. It may be a deviation from the results. Therefore, the reproductive toxicity of VOCs and chloroform should be conducted in another large-scale study and *in-vivo/ in-vitro* experiments. In our research, we have excluded patients who contain factors that could affect PSA concentrations including diagnosed with enlarged prostate or with prostate cancer. However, our include patients may contain other factors that could affect PSA concentrations including the presence of prostatitis, drug treatment or recent prostate biopsy and surgery. Meanwhile, our study is based on the secondary analysis of published data, so variables that are not included in the data set cannot be adjusted for. With the development of VOCs consumption, it is necessary to monitor the VOCs concentration in serum and urine. We propose to construct more predicted models between VOCs and body biomarkers, including PSA, in the future clinical setting to guide clinical prevention and treatment.

Conclusion

Our study comprehensively evaluated the association between VOCs exposure and serum PSA level. We found blood chloroform positively and independently associated with total PSA level, which suggested long-time environmental chloroform exposure may cause male reproductive damage, especially in the prostate gland. Furthermore, we found that blood chloroform positively correlates with water chloroform in the lower dose range, which indicated that the absorption of water might be the primary origin of chloroform. We also identified the high-risk group on the chloroform exposures. Our research wished to attract more attention to the toxicity of VOCs and prostate health among the average population.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

CW: conceptualization, data curation, formal analysis, methodology, software, visualization, writing-original draft, and writing-review & editing. YC: conceptualization, methodology, and writing-review & editing. YY: validation and writing-review & editing. DN, YH, and MW: writing-review & editing. XY and ZC: conceptualization, funding acquisition, methodology, supervision, and writing-review & editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Relationships between urinary metals concentrations and cognitive performance among U.S. older people in NHANES 2011–2014

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Background: Epidemiological evidence on Urine metals and cognitive impairment in older individuals is sparse and limited. The goal of this study was to analyze if there was a link between urinary metal levels and cognitive performance in U.S. people aged 60 and up.

Methods: The National Health and Nutrition Examination Survey (NHANES) data from 2011 to 2014 were utilized in this cross-sectional analysis. Memory function was quantified using the following methods: Established Consortium for Word Learning in Alzheimer's Disease (CERAD-WL) (immediate learning and recall and delayed recall), Animal Fluency Test (AFT), and Digit Symbol Substitution Test (DSST). An inductively coupled plasma mass spectrometry (ICP-MS) was used to estimate urine metal concentrations. The connection of Urine metals level with cognitive function was investigated employing binary logistic regression and restricted cubic spline models.

Results: A total of 840 participants aged 60 years and over were enrolled in this study. After controlling for confounders, the association between cadmium, barium, cobalt, cesium, manganese, and thallium and poor cognitive performance showed significance in multiple logistic regression compared to the lowest quartile of metals. In the DSST test, the weighted multivariate adjusted ORs (95% CI) for cadmium in the highest quartile, barium and cesium in the third quartile were 2.444 (1.310–4.560), 0.412 (0.180–0.942) and 0.440 (0.198–0.979), respectively. There were L-shaped associations between urine cesium, barium, or manganese and low cognitive performance in DSST. Urine lead, molybdenum and uranium did not show any significant relationships with cognitive impairment, respectively, compared to the respective lowest quartile concentrations.

Conclusion: The levels of barium (Ba), cobalt (Co), cesium (Cs), manganese (Mn), and thallium (Tl) in urine were found to be negatively related

to the prevalence of impaired cognitive performance in our cross-sectional investigation. Higher cadmium (Cd) levels were associated with cognitive impairment.

KEYWORDS

urine metals, cognitive function, NHANES, older people, mild cognitive impairment (MCI)

Introduction

Cognitive function is the ability of the human brain to recognize and reflect objective things, including various abilities such as perception, attention, memory, thinking, and language. In the process of aging, the cognitive function of the elderly changes significantly, which will have a certain degree of impact on the quality of life of the elderly, and even affect their daily life in severe cases (1). How to effectively maintain the cognitive function of the elderly has become one of the focuses of public health research and attention of the elderly.

Mild cognitive impairment (MCI) is usually used to describe the phenomenon of cognitive impairment, manifested as memory impairment and/or mild impairment of other cognitive functions (2). The American Academy of Neurology (AAN) announced a revised edition of its MCI clinical recommendations in 2018, stating that the prevalence of MCI ranged from 6.7 to 25.2% in people aged 60–84, and that the prevalence increased with age (3). MCI is the most prevalent early indication of Alzheimer's disease (AD) (short-term memory loss), which seriously affects the physical and mental health of the older, poses a significant threat to their quality of life, and often leads to a series of adverse health outcomes in the older people, such as dementia, falls, disability, decreased activities of daily living, increased hospital admissions, increased medical costs, and death (4–6). Unpaid dementia care was estimated to be worth $256.7 billion in 2020. Its costs, however, extend to an increased risk of emotional distress and unfavorable mental and physical health outcomes for home carers, which is compounded by COVID-19. In 2021, it was anticipated that the entire cost of long-term care, healthcare, and hospice services for those 65 and older with dementia would be $355 billion (7).

At present, the central pathogenesis hypothesis of Alzheimer's disease is that β amyloid (Aβ) undergoes extracellular deposition and intracellular Tau protein phosphorylation under the action of various enzymes, which has a toxic effect on neurons, and activates the glial cells in the brain to produce inflammatory factors to induce an inflammatory response (8). In this process, the participation of various enzymes is required. The trace metals involved in this study, such as barium, cadmium, and cesium, may have effects not only on ion pathways, but also directly or indirectly on proteins involved in various life activities (9, 10). These proteins may be involved in DNA repair processes, prevent DNA oxidative damage, and maintain DNA methylation, thereby affecting changes in cognitive function.

Heavy metals are widely distributed in the environment and can enter the human body through various means, such as food, drinking water and air (11, 12). Due to urbanization and industrialization, emissions from metal smelters and leachate from landfills containing toxic metals can have serious impacts on the environment and human health by contaminating groundwater, soil, surface water and natural ecosystems (13, 14). The metals and their compounds covered in this study are widely used in various products. For instance, barium salts are used to make plastics (15), and the manganese industry mainly produces batteries, ceramics, steel, cosmetics, leather, fireworks and glass, and cadmium is commonly used in battery making (16). They have been linked to the development of neurological illnesses in prior research, excessive intake of heavy metals, such as mercury and manganese are neurotoxic, and promote neurodegeneration (17, 18). Furthermore, another study showed that Cd-induced neuronal death in cortical neurons is caused by a collective mechanism of apoptosis and necrosis involving the production of reactive oxygen species and lipid peroxidation (19).

In a previous study (20), based on a similar NHANES dataset, by log-transforming levels of metals and their metabolites, Sasaki et al. analyzed the relationship between levels of metals and their metabolites (including 7 kinds in blood and 19 kinds in urine) and cognitive test scores (CERAD and DSST), using linear correlation. Their results showed that urinary metal concentrations of lead, cadmium and tungsten were significantly and negatively associated with cognitive function. Although similar data sets were used in this study, different statistical inference methods were used, and the original data were corrected, resulting in different statistical results. Moreover, besides CERAD and DSST, we also included the AFT score as an outcome variable in the statistical model. This is a more comprehensive assessment of cognitive function and selected different potential confounders, such as body mass index (BMI) and poverty-income ratio (PIR), based on previous studies (21, 22).

We analyzed the NHANES dataset from 2011 to 2014, with data from non-institutionalized U.S. civilians aged 60 and older, to look into the association between urinary metal levels and

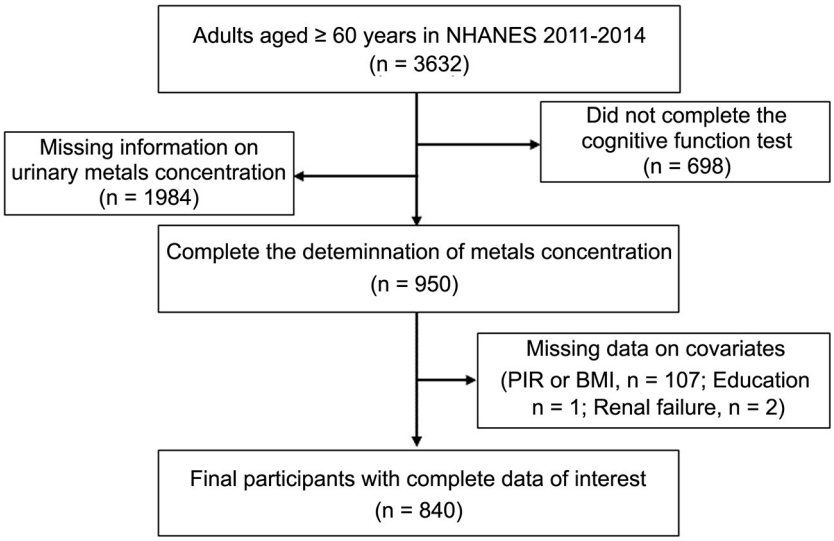

FIGURE 1
Flow chart of the selection of eligible subjects.

cognitive impairment, providing a new perspective for studying the pathological mechanism of MCI.

Methods

Study population

NHANES was conducted biannually in the United States from 1999 onwards, using a stratified multistage probability cluster design to provide a representative sample of the civilian, non-institutionalized U.S. population (23). Two cycles of NHANES (2011–2012 and 2013–2014) were included in this study because Cognitive Function Tests were measured in those cycles. Participants with missing data on urinary metal levels, cognitive tests, and covariates were excluded from the analysis. During this inclusion screening process, for age, 3,632 participants were available for analysis. We excluded 1,984 and 698 participants when examining Urine metal concentration and cognitive tests, respectively, due to the lack of completion of relevant tests. In the final research population, we assessed data from 840 adults aged 60 years and older (Figure 1). NHANES was performed by the Centers for Disease Control and Prevention (CDC), the National Center for Health Statistics (NCHS) Ethics Review Board authorized the study, and all participants gave their informed permission.

Cognitive performance test

NHANES uses the following methods to assess memory function: the Consortium to Establish a Registry for Alzheimer's Disease Word Learning (CERAD-WL) (immediate learning and recall and delayed recall), Animal Fluency Test (AFT), and Digital Symbol Substitution Test (DSST). Cognitive function data was retrieved from the Cognitive Function Questionnaire to assess the working memory/executive, semantic memory, and episodic memory function of study subjects.

CERAD-WL is a high-reliability and validity cognitive function evaluation scale that consists of three learning trials, alone with a delay trial. Participants were instructed to read aloud ten random and unrelated words, which are displayed on a monitor one at a time after visually or auditorily showing the participant ten words, then recall as many as possible immediately. After three rounds of testing, total scores for immediate learning and recall (range: 0–30) were calculated by summing the number of correct answers per round by each participant. Delayed trials begin ∼8–10 min after the first round of immediate recall trial (Tests are usually carried out after AFT and DSST are completed). Participants were required to call to mind as many of the ten words as they could. The CERAD-Total was calculated by adding the scores from the three immediate trials and one delayed trial, with a maximum score of 40 (24, 25).

Verbal Fluency Test (VFT) is a neuropsychological testing method, which involves the patient's memory, language (including naming, comprehension, semantic knowledge, etc.), execution and other cognitive functions during its operation. Animal Verbal Fluency Test is a simple method to measure semantic fluency in VFT, this test often used in clinical and research. The patient was asked to say as many names of animals as they can in 1 min, with each listed animal worth one score (24, 25).

Develop the Digit Sign Substitution Test as an experimental tool for understanding human associative learning. The DSST is currently one of the most regularly used tests in clinical neuropsychology to evaluate working memory, processing speed, and sustained attention due to its simplicity and excellent discriminant validity. Participants were given an examination paper with 9 numbers at the top coupled with symbols that functioned as a key, an array of 133 numbers below the key, and they were required to draw the proper symbol next to each number as soon as they could in 2 min. A point is awarded for each correct match, up to a maximum of 133 points (24, 25).

For CERAD, animal fluency, and DSST outcomes, there is currently no gold standard cut-off threshold; however, prior research (26) utilizing the NHANES database identified persons in the study group with the lowest score in the quartile as cognitively impaired. As a result, the 25th percentile was chosen as the threshold for poor cognitive function in this study. Participants with a CERAD-Total score of 21, an AFT score of 13, and a DSST score of 33 were characterized as having impaired cognitive function.

Measurement of urinary metals levels

After confirming that there was no background contamination in the collected material, the research team collected a urine sample for each respondent at the sampling site. At 4°C transport environment, these samples were transported to the Division of Laboratory Science at the US Centers for Disease Control and Prevention in Atlanta, Georgia. Inductively coupled plasma mass spectrometry (ICP-MS) was used to analyze all urine samples in this investigation for metals. ICP-MS is a multi-element analysis technology that may be paired with Dynamic Reaction Cell (DRC) for trace element analysis (27, 28). In this research, we used ICP-MS for the determine the levels of cadmium (U-Cd), lead (U-Pb), barium (U-Ba), cobalt (U-Co), cesium (U-Cs), manganese (U-Mn), molybdenum (U-Mo), thallium (U-Tl) and uranium (U-Ur) in urine. If the urine metal content was below the limit of detection (LOD), the value for this variable was the limit of detection divided by the square root of two (27, 28). Metal concentrations were standardized by urine creatinine and presented as μg/g creatinine when accounted for changes in urine dilution in spot urine samples between participants.

Covariates

The cause of cognitive impairment has been intensively researched over the last several decades. Various personal and environmental variables, such as age, PIR, education, obesity, and so on, have been linked to poor cognitive function. To control for the effect of confounders on the study results, the statistical model was adjusted for covariates to minimize any potential confounding bias caused by these factors. Covariates, such as demographic characteristics [age (60–70, 70–80, and ≥80 years); race (Mexican American, non-Hispanic white, non-Hispanic black, other Hispanic and other race); sex (male and female); marital status (married/living with partner and widowed/divorced/separated/never married) and educational level (less than high school, high school, and higher than high school)], lifestyle [smoking status (current, ever, never); BMI (normal: <25 kg/m^2, overweight: 25 to <30 kg/m^2, obese: ≥30 kg/m^2) and PIR (under poverty level: ≤1, above poverty level: >1) (29)], and questionnaire findings (Self-reported physician diagnosis of hypertension, renal failure and diabetes is considered to be a history of hypertension, renal failure and diabetes), were gathered by uniform interviews, physical and laboratory testing, and questionnaires administered by competent medical personnel.

Statistical analysis

Since NHANES employs a probability sampling strategy, we selected a 2-year weight (wtsa2yr) for the subsamples for urine metal concentration testing in NHANES 2011–2012 and 2013–2014 according to the analysis guidelines of the NHANES database. When the two survey cycles were joined, the ultimate weight (1/2 wtsa2yr for NHANES 11-14) was adjusted (30).

Descriptive statistics for variables, Chi-square tests were chosen to compare the categorical variables that were represented by numerical and frequency distribution, including age, race, sex, education levels, alcohol consumption, marital status, history of hypertension, diabetes and renal failure. The lowest quartile (Q1) was used as the reference group for each urine metal, then we fitted the multivariate logistics regression to evaluate the effect of a single urinary metal on cognitive function by comparing Q2, Q3, Q4 to Q1 and to generate odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the prevalence of urine metals-related cognitive impairment. Based on previous research and theoretical concerns, in logistic regression, different potential confounders were adjusted in Model 1 (no confounders were adjusted), Model 2 (adjustments in Model 1 plus age and sex) and Model 3 (Model 3 was the same as Model 2 with additional adjustment for BMI, education, PIR, marital status, race, smoke, renal failure, hypertension and diabetes). A restricted cubic spline regression was performed to accommodate the non-linearity of the association between urinary metal concentrations and cognitive function, using four nodes in the model.

Weighted and RCS analyses were operated with the "survey" and "rms" package, respectively, in the R software (version 4.1.1, R Foundation for Statistical Computing). All *p*-values are two-tailed, with 0.05 chosen as the statistical significance level.

Results

Four hundred seventeen males and 423 females from NHANES (2011–2014) participated in our research. Respondents' sociodemographic data were described and categorized by sex, age, education level, ethnicity, marital status, smoking habits, PIR and BMI. There were significant differences in the distributions of age, ethnicity, education, hypertension, and PIR between those with poor and normal cognitive performance for all three measures of cognitive function. In contrast, The BMI of those with normal cognitive performance and those with low cognitive performance did not differ significantly, according to Chi-square testing. Diabetes, renal failure, and hypertension were more common in adults with poor cognitive performance than in people with normal cognitive performance. We made statistical inferences about whether there were differences in the distribution of basic characteristics between the three groups of cognitively impaired populations, based on three different tests. We observed significant differences in the distribution of gender, race, and educational attainment among the three groups. Table 1 and Supplementary Table S1 provides detailed baseline data for this investigation. Geometric means, quartiles and detection rates of urine metals were presented in Table 2. The median concentrations and geometric means of the 10 metals in urine were ranged from 0.0065 to 39.2500 μg/g creatinine, and 0.0072–39.6731 μg/g creatinine, respectively.

The relationship between urinary metal concentration and cognitive function is outlined in Table 3 and Supplementary Table S2. The Table 3 presented the associations between U-Ba, U-Co, U-Tl, U-Mn, U-Cs and U-Cd concentration and low cognitive performance as judged by different measures. After controlling for confounders, the association between cadmium and thallium in the third quartile and low cognitive performance in CERAD showed significance in multiple logistic regression compared to the lowest quartile of metals. The ORs (95% CIs), respectively, were 2.407 (1.137–5.099) and 0.509 (0.277–0.936). In the crude Model (Model 1) and adjusting for Model (Model 2 and Model 3) of Animal Fluency Test, the third quartiles (Q3) and the highest quartile (Q4) of U–Cd were linked to an increased prevalence of cognitive impairment. Our data also revealed that the relationship between U–Co and low cognitive function was significant in the crude model, with the crude OR and 95% CIs of low cognitive performance indicating that U–Co was associated with low cognitive performance in the DSST and AFT. After adjusting for age and sex, compared to the lowest quartile of U–Co, the weighted multivariate adjusted ORs (95% CI) of the third quartile were 0.454 (0.232–0.886) and 0.464 (0.260–0.829). In the DSST test, cadmium in the highest quartile, barium and cesium in the third quartile, and cobalt in the second quartile, the OR (95% CI) of the logistic regression showed significance in each model.

Analysis of the continuous relationship between urinary metal levels and cognitive test scores based on a restricted cubic spline regression model (Figure 2; Supplementary Figure S1). We discovered L-shaped associations between test scores and creatinine-adjusted urine cesium and manganese for cognitive performance in the DSST. The prevalence of low cognitive performance decreased with increasing urinary Ba, Cs, and Mn levels, whereas it increased with urinary Cd concentration, and showed a non-linear dose-response relationship. The association between CERAD cognitive impairment and urinary Cd, Mn, Cs, and Ba concentrations was insignificant (Supplementary Figures S2, S3).

Discussion

In this large sample, NHANES-based, cross-sectional study of U.S. participants aged 60 years or older, the association between urinary metals and cognitive function was analyzed with three measures of cognitive performance. Although Sasaki and Carpenter (20), also used this dataset to illustrate the correlation between metal concentrations and cognitive scores, however, we varied widely in the selection of study subjects for inclusion, and corrected the original data. The detailed changes are listed below. Firstly, we corrected the urine metal content using urine creatinine, which was used to exclude the effect of urine concentration or dilution on the metal content. In addition, we transformed cognitive test scores into a binary variable, normal cognitive status vs. low cognitive performance. Trends in the prevalence of cognitive impairment at different urine metal levels were explored using logistic regression with restricted cubic spline models. Secondly, additional covariates were chosen in this study on the grounds that the results of Momtaz et al. support a significant association between BMI and cognitive function in the older population (22) and that higher cognitive ability is associated with increased household income (21). This allows for better control for confounding factors in the study results. Finally, to treat all participants equally, Sasaki and Carpenter performed an unweighted analysis. Our research team weighted the raw data to account for complex survey design (including oversampling), survey non-response and post-stratification before statistical extrapolation for the purpose of making the estimates representative of the non-institutionalized civilian population in the United States (30).

Many investigations have concluded that metals have a role in nervous system disorders (31). However, as far as we know, analyses focused on urine cesium exposure levels and poor cognitive performance were rare, and only a few studies have looked at the link between cesium levels in the cerebrospinal fluid and cognitive function or Alzheimer's disease (32). More recently, Almulla et al. conducted a case-control study of 120 adults with schizophrenia and 54 healthy controls, and measured cesium and cognitive impairments [using the

TABLE 1 Characteristics of the study population, National Health and Nutrition Examination Survey (NHANES) 2011–2014 ($N = 840$).

Catalogs	CERAD test			Animal fluency test			Digit symbol test		
	Normal Cognitive Performance	Low Cognitive Performance	*p*-value	Normal Cognitive Performance	Low Cognitive Performance	*p*-value	Normal Cognitive Performance	Low Cognitive Performance	*p*-value
Number of subjects (%)	633	207		640	200		642	198	
Age (%)			<0.01			<0.01			<0.01
60–70 years	375 (59.24)	83 (40.10)		376 (58.75)	82 (41.00)		373 (58.10)	85 (42.93)	
70–80 years	200 (31.60)	63 (30.43)		192 (30.00)	71 (35.50)		192 (29.91)	71 (35.86)	
≥80 years	58 (9.16)	61 (29.47)		72 (11.25)	47 (23.50)		77 (11.99)	42 (21.21)	
Sex (%)			<0.01			0.990			<0.01
Male	280 (44.23)	137 (66.18)		318 (49.69)	99 (49.50)		296 (46.11)	121 (61.11)	
Female	353 (55.77)	70 (33.82)		322 (50.31)	101 (50.50)		346 (53.89)	77 (38.89)	
Race (%)			0.049			<0.01			<0.01
Mexican American	45 (7.11)	24 (11.60)		49 (7.66)	20 (10.00)		35 (5.45)	34 (17.18)	
Other Hispanic	54 (8.53)	27 (13.04)		62 (9.69)	19 (9.50)		50 (7.79)	31 (15.66)	
Non-Hispanic White	312 (49.29)	95 (45.89)		332 (51.88)	75 (37.50)		345 (53.74)	62 (31.31)	
Non-Hispanic Black	161 (25.43)	41 (19.81)		137 (21.41)	65 (32.5)		138 (21.49)	64 (32.81)	
Other race	61 (9.64)	20 (9.66)		60 (9.38)	21 (10.5)		74 (11.53)	7 (3.54)	
Educational level (%)			<0.01			<0.01			<0.01
Below high school	126 (19.91)	86 (41.55)		141 (22.03)	71 (35.50)		101 (15.74)	111 (56.06)	
High school	143 (22.59)	43 (20.77)		129 (20.16)	57 (28.50)		143 (22.27)	43 (21.72)	
Above high school	364 (57.50)	78 (37.68)		370 (57.81)	72 (36.00)		398 (61.99)	44 (22.22)	
Marital status (%)			0.744			0.014			<0.01
Married/living with partner	369 (58.29)	124 (59.90)		391 (61.09)	102 (51.00)		396 (61.68)	97 (48.99)	
Widowed/divorced/separated/ never married	264 (41.71)	83 (40.10)		249 (38.91)	98 (49.00)		246 (38.32)	101 (51.01)	
Poverty–income ratio (%)			0.025			<0.01			<0.01
≤1	112 (17.69)	52 (25.12)		106 (16.56)	58 (29.00)		96 (14.95)	68 (34.34)	
>1	521 (82.31)	155 (74.88)		534 (83.44)	142 (71.00)		546 (85.05)	130 (65.66)	
Body mass index (%)			0.121			0.524			0.337
<25 kg/m^2	164 (25.91)	61 (29.47)		166 (25.94)	59 (29.50)		177 (28.04)	43 (22.73)	
25–30 kg/m^2	223 (35.23)	82 (39.61)		238 (37.19)	67 (33.50)		227 (35.67)	75 (38.38)	
≥30 kg/m^2	246 (38.86)	64 (30.92)		236 (36.87)	74 (37.00)		227 (36.29)	74 (38.89)	
Smoking status (%)			0.362			0.704			0.036
Never	309 (48.82)	101 (48.79)		309 (48.28)	101 (50.50)		318 (49.53)	92 (46.46)	
Former	251 (39.65)	89 (43.00)		264 (41.25)	76 (38.00)		265 (41.28)	75 (37.88)	
Current	73 (11.53)	17 (8.21)		67 (10.47)	23 (11.50)		59 (9.19)	31 (15.66)	
Hypertension (%)	385 (60.82)	141 (68.12)	0.072	373 (58.44)	152 (76.00)	<0.01	388 (60.44)	138 (69.70)	0.023
Diabetes (%)	137 (21.64)	52 (25.12)	0.345	127 (19.84)	62 (31.00)	<0.01	127 (19.78)	62 (31.31)	<0.01
Renal failure (%)	34 (5.37)	18 (8.70)	0.12	34 (5.31)	18 (9.00)	0.085	28 (4.36)	24 (12.12)	<0.01

p-value was tested by Chi-square test or Fisher's exact.

Brief Assessment of Cognition in Schizophrenia (BACS)]. The findings imply that cesium was favorably linked with the results of the neurocognitive investigation (33). Our study showed that urinary cesium levels were inversely associated with the prevalence of cognitive impairment. The exact mechanism of the association between urinary cesium and low cognitive performance is unclear, but some speculations may be as follows. Cesium prevents neuronal apoptosis by inactivating glycogen synthase kinase 3 beta (GSK3b) through phosphorylation of serine 9. Furthermore, it inhibited caspase-3 activation and neuronal apoptosis in a dose-dependent manner, as well as H2O2-induced neuronal death, thereby boosting neuronal

TABLE 2 Geometric means, quartiles and detection rates of urine metals.

Urine metals (μg/g creatinine)	GM (95% CI)[a]	Median (IQR)[b]	Detection rate (%)[c]
Ba	1.0749 (1.0013, 1.1539)	1.0833 (0.5375, 2.2100)	99.76
Cd	0.3432 (0.3255, 0.3618)	0.3435 (0.2039, 0.5733)	96.07
Co	0.3889 (0.3702, 0.4087)	0.3517 (0.2431, 0.5539)	99.76
Cs	4.7195 (4.5599, 4.8847)	4.6490 (3.4080, 6.4410)	100
Mo	39.6731 (37.8596, 41.5734)	39.2500 (26.4600, 59.5000)	100
Mn	0.1413 (0.1336, 0.1494)	0.1317 (0.0808, 0.2302)	46.07
Pb	0.5237 (0.4997, 0.5489)	0.5138 (0.3358, 0.7857)	98.93
Sn	0.8660 (0.8068, 0.9295)	0.7457 (0.4174, 1.7333)	92.5
Tl	0.1532 (0.1470, 0.1598)	0.1546 (0.1026, 0.2294)	99.4
Ur	0.0072 (0.0068, 0.0077)	0.0065 (0.0038, 0.0122)	78.33

[a] G-Mean (95%).
[b] Median (25th, 75th percentiles).
[c] Proportion above the lower limit of detection (LLOD, in μg/L).

survival (34). Moreover, cesium (Cs+) prevented the apoptotic volume decrease, caspase-3 activation and cell death induced by K5 and camptothecin. It may have a role in the activation of the apoptotic volume decrease and apoptotic death of Cerebellar granule neurons (35).

The substantial association between U-Ba levels and many subdomains and cognitive impairment, such as immediate and delayed learning capacity, categorical linguistic fluency, episodic memory, and attention, is another noteworthy conclusion of this study. These findings also point to barium as a possible contributor to cognitive function. Gu et al. carried out a baseline survey of the Elderly Health and Environment Risk Factor Cohort, and reported that trace elements Ba could be a protective factor for cognitive function (36). This conclusion is in line with the view of our research. However, there are also other findings that blood barium may not be associated with cognitive function when concomitant exposure to other metals is considered (37). There are several possible explanations for different conclusions stated above. Due to the deficient concentration of Ba in the human body and the significant influence of external factors, statistical results cannot correctly reflect the truth, different types of samples (the metals samples in blood and urine are not the same), cognitive function testing methods are inconsistent, and so on. It's unknown what role Ba plays in cognitive function; however, one study (38) suggests that serum Ba may be associated with increased glutathione reductase (GR) activity, which protects the brain from damage.

Manganese is one of the essential trace elements in the human body and participates in forming various proteins and physiological functions. Previous studies have not given a clear answer on whether manganese exposure can lead to impaired cognitive function in humans. Altered manganese status in the body is associated with changes in human neuronal physiology and cognition, either overexposure or underexposure leading to neurological dysfunction (39). One result from a meta-analysis showed that serum manganese levels in AD patients were lower than those in controls (40). However, one study on 40 older people in China showed that high manganese level may be a causative factor for AD (41). Manganese may cause glutamate accumulation by damaging glutamate transport and reducing glutamine synthetase activity, and ultimately lead to neurotoxicity (42, 43). We found that optimum exposure to manganese may be a protective factor for cognitive dysfunction, which can be explained by the physiological function of manganese. Superoxide dismutase 2 (SOD2) with manganese as a prosthetic group is mainly distributed in mitochondria, SOD2 has antioxidant function and can reduce oxidative stress, amyloid deposition, and memory deficits in AD transgenic mouse models (44).

Cadmium, a carcinogenic heavy metal, can not only cause a variety of diseases, but also enter the brain and lead to neurological damage. An analysis of 2011–2014 data from the NHANES database showed an inverse relationship between blood cadmium and cognitive function in older adults over 60 years of age (45). By using the relevant data from the NHANES database, Min et al. found that there is a correlation between the blood cadmium level and the incidence of AD (46). Furthermore, Peng et al. provided updated evidence to support the association between cadmium and AD mortality (47). These publications echo our findings that urinary cadmium levels are associated with cognitive impairment. Both blood cadmium and urine cadmium can be employed as biomarkers for researching the relationship between body cadmium content and outcome variables, because both can accurately reflect the degree of cadmium burden in the body in terms of long-term consequences (48). The mechanism by which cadmium affects the central nervous system is still unclear. The mainstream view is that cadmium may induce neuronal apoptosis by inducing activation of astrocytes and secretion of inflammatory mediators (49, 50).

Our study had several benefits, besides the sophisticated NHANES urine metal concentration measurement technique. A major strength is that our sample of older adults is derived from the nationally representative NHANES database, which is known for its high-quality survey methodologies and quality control. In addition, considering the potential bias, we selected the main confounders in terms of lifestyle and physical condition based on previous findings to adjust the regression model, avoiding the interference of covariates to a certain extent. Besides, NHANES collected performance data on well-studied cognitive tests in different domains, although not comprehensive in scope, it may be a valuable indicator of underlying brain pathology and therefore worth investigating.

TABLE 3 Weighted odds ratios (95% confidence intervals) of low cognitive performance by quartiles of metals level, NHANES 2011–2014.

Group	CERAD test			Animal fluency test			DSST		
	Model1	Model2	Model3	Model1	Model2	Model3	Model1	Model2	Model3
Urine-Ba (μg/g creatinine)									
Q1 (<0.5375)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (≥0.5375 and <1.0833)	0.699 (0.364–1.339)	0.884 (0.474–1.650)	1.212 (0.601–2.444)	**0.499 (0.278–0.893)**	0.568 (0.321–1.003)	0.790 (0.417–1.498)	0.574 (0.326–1.011)	0.668 (0.395–1.134)	1.023 (0.550–1.901)
Q3 (≥1.0833 and <2.21)	**0.405 (0.209–0.784)**	0.559 (0.284–1.103)	0.768 (0.359–1.646)	**0.250 (0.124–0.505)**	**0.279 (0.135–0.580)**	0.408 (0.164–1.016)	**0.248 (0.123–0.497)**	**0.297 (0.150–0.586)**	**0.412 (0.180–0.942)**
Q4 (≥2.21)	0.838 (0.389–1.805)	1.052 (0.518–2.134)	1.662 (0.720–3.836)	0.624 (0.358–1.088)	0.631 (0.371–1.072)	1.031 (0.510–2.083)	**0.393 (0.191–0.811)**	**0.414 (0.212–0.808)**	0.728 (0.314–1.686)
Urine-Cd (μg/g creatinine)									
Q1 (<0.20391)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (≥0.20391 and <0.34352)	0.957 (0.594–1.542)	1.037 (0.567–1.897)	1.065 (0.588–1.932)	1.396 (0.783–2.49)	1.376 (0.746–2.540)	1.463 (0.806–2.655)	1.242 (0.675–2.287)	1.295 (0.685–2.448)	1.335 (0.630–2.831)
Q3 (≥0.34352 and < 0.5733)	**1.993 (1.154–3.441)**	**2.187 (1.137–4.204)**	**2.407 (1.137–5.099)**	**2.074 (1.22–3.524)**	**1.844 (1.168–2.912)**	**2.016 (1.233–3.297)**	1.631 (0.777–3.423)	1.570 (0.797–3.093)	1.720 (0.777–3.806)
Q4 (≥0.5733)	1.398 (0.777–2.516)	1.634 (0.816–3.270)	1.818 (0.710–4.657)	**2.33 (1.557–3.487)**	**2.211 (1.445–3.384)**	**2.384 (1.349–4.215)**	**1.875 (1.063–3.308)**	**1.974 (1.160–3.358)**	**2.444 (1.310–4.560)**
Urine-Co (μg/g creatinine)									
Q1 (<0.2431)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (≥0.2431 and < 0.3517)	1.159 (0.598–2.247)	1.118 (0.568–2.198)	1.274 (0.639–2.539)	**0.524 (0.278–0.987)**	**0.454 (0.232–0.886)**	0.485 (0.218–1.079)	**0.524 (0.297–0.924)**	**0.464 (0.260–0.829)**	**0.461 (0.227–0.937)**
Q3 (≥0.3517 and <0.5539)	0.519 (0.209–1.289)	0.582 (0.244–1.388)	0.611 (0.241–1.702)	0.904 (0.483–1.689)	0.889 (0.466–1.694)	1.013 (0.486–2.110)	0.599 (0.318–1.130)	0.623 (0.339–1.142)	0.718 (0.329–1.569)
Q4 (≥0.5539)	0.835 (0.456–1.532)	0.792 (0.421–1.490)	0.899 (0.456–1.771)	0.746 (0.419–1.327)	0.582 (0.328–1.032)	0.676 (0.317–1.440)	0.518 (0.256–1.051)	**0.440 (0.207–0.935)**	0.542 (0.219–1.341)
Urine-Cs (μg/g creatinine)									
Q1 (<3.408)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (≥3.408 and <4.649)	0.841 (0.433–1.634)	0.753 (0.391–1.453)	0.775 (0.368–1.634)	0.804 (0.500–1.293)	0.703 (0.451–1.096)	0.803 (0.497–1.297)	0.751 (0.403–1.399)	0.674 (0.389–1.169)	0.823 (0.458–1.479)
Q3 (≥4.649 and <6.441)	0.724 (0.395–1.326)	0.701 (0.385–1.276)	0.773 (0.387–1.546)	0.657 (0.394–1.094)	0.609 (0.359–1.032)	0.813 (0.451–1.466)	**0.397 (0.197–0.800)**	**0.370 (0.201–0.679)**	**0.440 (0.198–0.979)**
Q4 (≥6.441)	0.646 (0.319–1.308)	0.772 (0.372–1.601)	0.947 (0.410–2.189)	0.612 (0.338–1.109)	0.613 (0.351–1.072)	0.861 (0.469–1.582)	**0.318 (0.187–0.540)**	**0.332 (0.195–0.567)**	0.492 (0.240–1.009)
Urine-Mn (μg/g creatinine)									
Q1 (<0.08078)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (≥0.08078 and <0.13165)	0.810 (0.484–1.354)	1.189 (0.606–2.333)	1.239 (0.629–2.442)	0.870 (0.497–1.524)	1.031 (0.571–1.860)	1.084 (0.557–2.110)	0.958 (0.559–1.643)	1.201 (0.676–2.133)	1.369 (0.750–2.497)
Q3 (≥0.13165 and <0.23019)	0.684 (0.384–1.220)	0.802 (0.411–1.565)	0.820 (0.401–1.758)	0.944 (0.574–1.551)	0.902 (0.530–1.535)	0.988 (0.541–1.806)	0.821 (0.381–1.770)	0.851 (0.405–1.787)	0.982 (0.473–2.040)
Q4 (≥0.23019)	0.588 (0.326–1.060)	1.039 (0.466–2.315)	1.093 (0.499–2.396)	0.848 (0.489–1.473)	0.981 (0.529–1.817)	1.141 (0.544–2.397)	**0.442 (0.234–0.837)**	0.564 (0.298–1.069)	0.637 (0.267–1.520)
Urine-Tl (μg/g creatinine)									
Q1 (<0.1026)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (≥0.1026 and <0.15455)	0.930 (0.598–1.446)	0.886 (0.506–1.552)	0.956 (0.520–1.758)	0.683 (0.360–1.294)	0.648 (0.321–1.307)	0.679 (0.308–1.497)	0.702 (0.386–1.276)	0.673 (0.365–1.243)	0.739 (0.375–1.457)
Q3 (≥0.15455 and <0.22936)	**0.424 (0.231–0.780)**	**0.464 (0.258–0.835)**	**0.509 (0.277–0.936)**	**0.475 (0.243–0.926)**	**0.474 (0.242–0.929)**	0.582 (0.277–1.225)	0.570 (0.296–1.100)	0.618 (0.317–1.203)	0.958 (0.447–2.053)
Q4 (≥0.22936)	**0.428 (0.245–0.746)**	0.562 (0.313–1.010)	0.662 (0.387–1.133)	**0.546 (0.303–0.985)**	0.576 (0.328–1.011)	0.720 (0.382–1.357)	**0.395 (0.202–0.772)**	**0.462 (0.229–0.935)**	0.773 (0.314–1.828)

Crude model (Model 1) did not adjust any confounders. Model 2 adjusted for age (years), gender. Model 3 was the same as Model 2 with additional adjustment for educational level (less than high school, high school, higher than high school), marital status (married, widowed, divorced, separated, never married, living with partner), BMI, PIR, smoke, race, renal failure (Yes or No), hypertension (Yes or No) and diabetes (Yes or No). The bold values indicate statistically significant values of $p < 0.05$.

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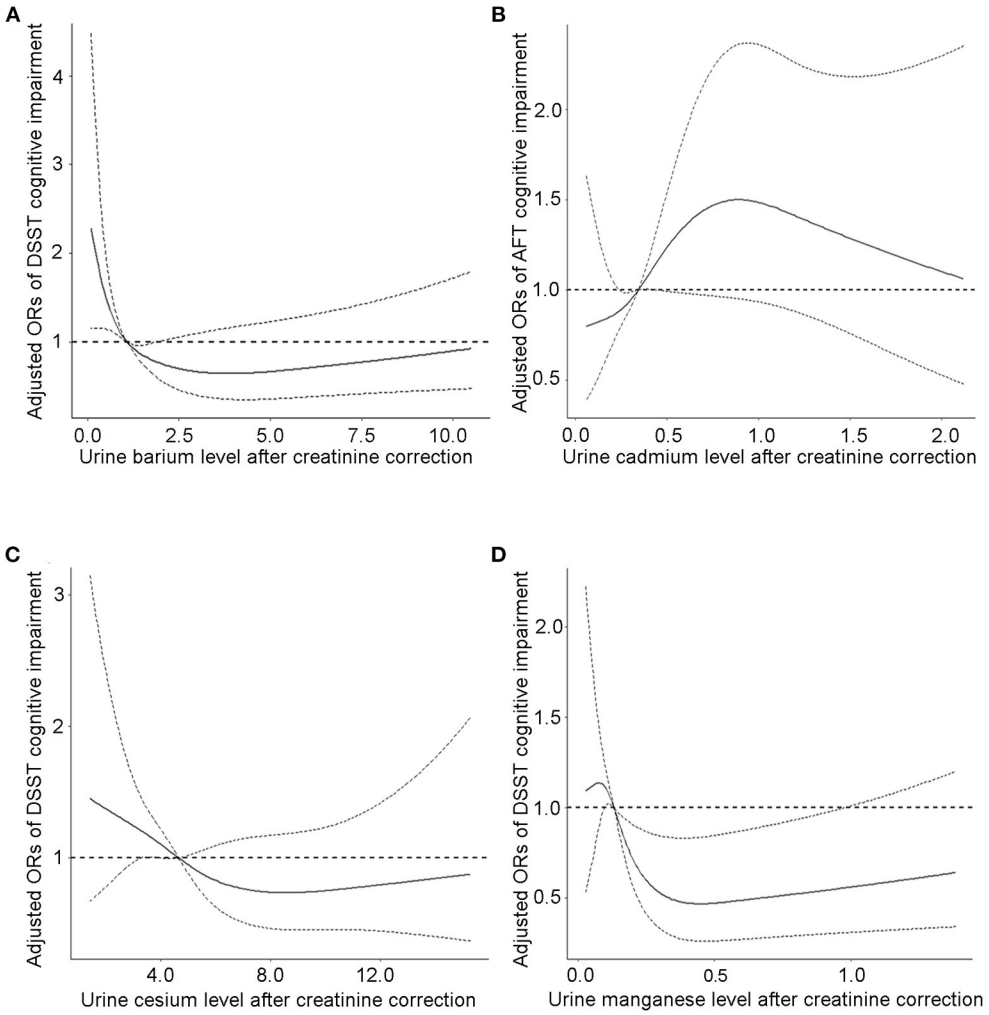

FIGURE 2
The continuous relationship between urinary **(A)** barium levels, **(C)** cesium levels, **(D)** manganese levels and DSST cognitive test scores based on a restricted cubic spline regression model. The continuous relationship between **(B)** cadmium levels and AFT cognitive test scores based on a restricted cubic spline regression model. Adjusted for covariates (age, sex, educational level, BMI, and PIR). The solid lines represent the ORs, and dashed lines represent the 95% CIs.

Potential limitations of this study are, first, that this is a cross-sectional design that cannot determine the temporal sequence of urinary metal exposure and cognitive function, is not suitable for examining the prospective relationship between urinary metal exposure and cognitive function. There are many unmeasured confounders from diet, environment, and lifestyle influenced the findings, so we were unable to assess causality for the association between urinary metal concentrations and low cognitive performance. Second, single-examination urinary metal concentrations may not be ideal biomarkers of exposure and adjusted creatinine concentrations may lead to variability and unexpected bias in the population, as some urinary metals reflect only short-term exposure, thus our findings should be carefully considered. Finally, since our subjects were required to be 60 years old and above, NHANES had data for cognitive tests only in 2011–2014, and the numerical values of the covariates were missing, ultimately including only 840 subjects, which may lead to biased research results.

Conclusion

We utilized logistic regression and restricted cubic spline models to perform statistical inference on NHANES data to assess the relationship between urinary metal levels and cognitive function in healthy older persons. U-Cd showed positive associations with performance on DSST modules. Concentrations of Cesium, Manganese and Barium had negative

associations with cognitive function, and the association of manganese with cognitive function remained significant even when the model was adjusted for covariates. These findings imply that Cs, Mn, Ba, and Cd may be involved in MCI pathogenesis, such as by interfering with potassium channels or protecting neurons.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: the datasets for this study can be found in the NHANES repository. Please see the https://www.cdc.gov/nchs/nhanes/index.htm for more details.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Review Board (ERB) of the US National Center for Healthcare Statistics (NCHS) authorized the 2011–2014 NHANES (Protocol Number: protocol#2011-17 and continuation of protocol #2011-17). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XW and PX: conceptualization, methodology, software, writing—original draft, and writing—review and editing. RW, CL, and ZZ: software, visualization, data curation, and formal analysis. SY and QW: writing—review and editing. YL, HZ, and XZ: conceptualization, supervision, project administration, and writing—review and editing. YZ: revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.985127/full#supplementary-material

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Association between urinary metals and leukocyte telomere length involving an artificial neural network prediction: Findings based on NHANES 1999–2002

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Objective: Leukocytes telomere length (LTL) was reported to be associated with cellular aging and aging related disease. Urine metal also might accelerate the development of aging related disease. We aimed to analyze the association between LTL and urinary metals.

Methods: In this research, we screened all cycles of National Health and Nutrition Examination Survey (NHANES) dataset, and download the eligible dataset in NHANES 1999–2002 containing demographic, disease history, eight urine metal, and LTL. The analysis in this research had three steps including baseline difference comparison, multiple linear regression (MLR) for hazardous urine metals, and artificial neural network (ANN, based on Tensorflow framework) to make LTL prediction.

Results: The MLR results showed that urinary cadmium (Cd) was negatively correlated with LTL in the USA population [third quantile: −9.36, 95% confidential interval (CI) = (−19.7, −2.32)], and in the elderly urinary molybdenum (Mo) was positively associated with LTL [third quantile: 24.37, 95%CI = (5.42, 63.55)]. An ANN model was constructed, which had 24 neurons, 0.375 exit rate in the first layer, 15 neurons with 0.53 exit rate in the second layer, and 7 neurons with 0.86 exit rate in the third layer. The squared error loss (LOSS) and mean absolute error (MAE) in the ANN model were 0.054 and 0.181, respectively, which showed a low error rate.

Conclusion: In conclusion, in adults especially the elderly, the relationships between urinary Cd and Mo might be worthy of further research. An accurate prediction model based on ANN could be further analyzed.

KEYWORDS

leukocytes telomere length, urinary metals, NHANES, ANN, aging people

Introduction

As far as we know, toxic metals had cumulative biological effects in human, and essential metals supported normal physiological body functions. However, metal binding proteins lack specificity, which were responsible for absorption and transportation of essential metals and, final control of their homeostasis (1). These metallothioneins could conduct molecular simulations so that nutritious essential metal could be replaced by toxic metal. Deficiency or excess of essential metals would cause damage to biological processes, and non-essential metals might have toxic effects (2). Toxic metals entered the human body in many ways, such as food, drinking water, and air. It was reported that exposure to heavy metals would result in varying degrees of lipid peroxidation, DNA damage, and protein modification. Epidemiological surveys suggested that accumulated heavy metals lead to damage of organs, and further resulted in chronic kidney disease, neurological development disorders, cardiovascular disease (CVD), neuronal damage, diabetes, and cancer (3, 4).

Telomeres were DNA protein complexes that protected the ends of eukaryotic chromosomes. Telomeres shortened each time a cell divided, partly because the ends of telomeric DNA could not replicate. Oxidative stress promoted telomere shortening, while telomerase could prolong telomere. However, the expression of telomerase was low in most human cells, making telomeres vulnerable to oxidative stress (5). When telomeres were severely shortened, cell senescence was triggered. Cell senescence led to functional defects and the secretion of inflammatory factors. Telomere shortening was not only a key mechanism of cell senescence, but also contribute to body's senescence. In epidemiological studies, researchers reported that the shortening of leukocytes telomere length (LTL) was associated with aging and several diseases including CVD, type 2 diabetes, dementia, and cancer. Although a twin study showed that the LTL was partly heritable, the heritability of twins decreased with age growth and lead to their differences in LTL, indicating that environmental factors played a role in LTL (6). Leukocytes telomere length was also associated with behavioral risk factors, such as smoking, alcohol, and socioeconomic status.

Chronic diseases and tumors caused by toxic heavy metals were consistent with LTL-related diseases. Telomere attrition might be an important mechanism of metal accelerating telomere shortening. Harmful heavy metals aggravated oxidative stress and cytokines production (7). Therefore, analyzing the relationship between heavy metals and LTL was an important direction to elaborate the mechanism of heavy metals and diseases. Urinary heavy metals were excreted by the body after absorbing, which could reflect the metal accumulated in kidney and other tissues (8). Therefore, this analysis would focus on the relationship between urinary heavy metals and LTL.

Deep learning was an important part of artificial intelligence. It became the main solution in image recognition, language recognition, and natural language processing (9). Deep learning algorithm was based on the traditional algorithm, the deep convolution neural network was invented to meet the requirements of feature extraction and learning with a big data (10, 11). In terms of hardware configuration, people proposed distributed computing and cloud computing to meet the high requirements for training environment, so that more people can participate in the research of deep learning. Many of the world's top high-tech companies set up laboratories to find a more convenient and rapid development mode for deep learning (12, 13). Tensorflow was a symbolic mathematical system, which was originally developed by Google brain group for deep neural networks in mechanical learning. It was an open-source software platform that uses data flow graphs to calculate numerical values (10–13). Tensorflow was a complete toolkit that could realize the training, testing, parameter adjustment and prediction of convolutional neural networks, and make the modularization deep learning. The principle of modularization made it easy to modify and expand the model network layer and loss function. Consequently, we made the prediction of LTL based on Tensorflow framework.

Previous studies focused on the risk factors exploration on LTL with limited methods to make prediction. We firstly screened the possible hazardous urinary metal for LTL. Since the prediction of LTL was also important, we tried to use the popular ANN platform Tensorflow.

Methods

Dataset

National Health and Nutrition Examination Survey (NHANES) was a nationally representative cross-sectional survey of the nutritional and health status of non-hospitalized civilians in the United States, conducted annually by the National Centers for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC). All the data could be obtained in the official website of American Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes).

Abbreviations: CVD, cardiovascular disease; LTL, leukocytes telomere length; NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; PIR, poverty income ratio; Ba, barium; Cd, cadmium; Co, cobalt; Cs, cesium; Mo, molybdenum; Pb, lead; Sb, antimony; Tl, thallium; NCHS, National Center for Health Statistics; CDC, Centers for Disease Control and Prevention; PCR, polymerase chain reaction; ICP-MS, Inductively coupled plasma mass spectrometry; GM, geometric mean; CI, confidential interval; LOD, limit of detection; ANN, artificial neural network; ReLU, logical and rectified linear unit; MAE, mean absolute error; MLR, multiple linear regression; GSSG/GSH, redox glutathione ratio; ROS, reactive oxygen species.

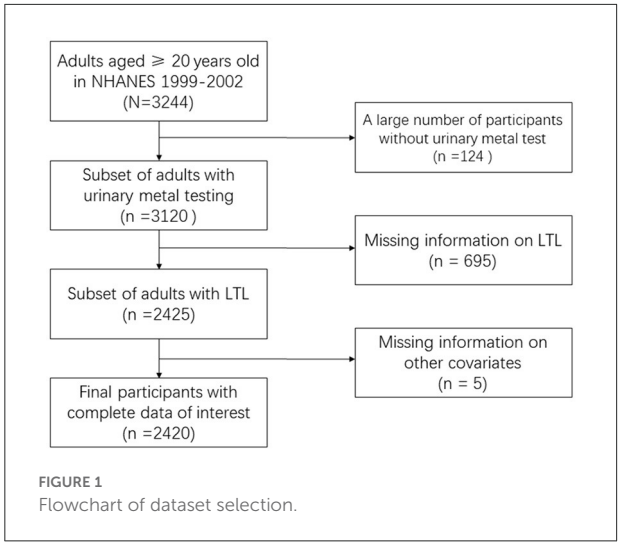

FIGURE 1
Flowchart of dataset selection.

In this research, the NHANES in 1999–2002 containing demographic, disease history, urine metal, and leukocyte telomere length (LTL) was achieved.

The demographic data included age, gender, race, education level, marital status, alcohol, smoking, body mass index (BMI), poverty income ratio (PIR), diabetes mellitus, and hypertension. Urine metal contained barium (Ba), cadmium (Cd), cobalt (Co), cesium (Cs), molybdenum (Mo), lead (Pb), antimony (Sb), and thallium (Tl). The outcome of LTL was skew continuous variable.

To screen LTL and related datasets, we searched related data in NHANES 1999–2002. In the raw data, there were 5,352 participants, 5,157 respondents having lab data, and 2,555 with OA status data. Finally, 2,420 participants having demographic, disease history, eight urine metal, and outcome of LTL were included (Figure 1).

Evaluation of LTL

From description of LTL detection in NHANES website, the telomere length test was carried out in Dr. Elizabeth Blackburn at the University of California, San Francisco, using the quantitative polymerase chain reaction (PCR) method to measure telomere length relative to standard reference DNA (T/S ratio) (14). Each sample was tested three times in three different days. Samples were tested in duplicate wells, resulting in six data points. The sample plates were tested in groups of three plates. Each test plate contained 96 control wells with eight control DNA samples. Tests with eight or more invalid control wells were excluded from further analysis. The control DNA values were used to normalize the variability between the series. Executions with more than four control DNA values less than 2.5 standard deviations from the mean of all test were excluded from the additional analysis. For each sample, any potential outliers were identified and excluded from the calculations. The mean and standard deviation of the T/S ratio were then calculated normally.

Assessment of urine metals

Urinary metal was used as an exposure assessment in this research, because it was a substitute for cumulative exposure and reflected the metal accumulated in the kidney and other tissues. Inductively coupled plasma mass spectrometry (ICP-MS) was a multi-element analysis technology (15). The liquid sample was introduced into the ICP through a nebulizer and a spray chamber carried by a flowing argon stream. By coupling RF power to flowing argon, a plasma was produced, in which the main components were positive argon ions and electrons. The sample passed through a plasma region with a temperature of 6,000–8,000 K. Heat atomized the sample and then ionized the atoms. Ions and argon entered the mass spectrometer through the interface, which separated the ICP working at atmospheric pressure from the mass spectrometer working at 10^{-6} Torr pressure. The mass spectrometer allowed the detection of ions in a rapid sequence to determine the individual isotopes of the elements. The electrical signal generated by the ion detection processed into digital information to indicate the strength of the ion and the subsequent element concentration. Seven elements in urine, including barium (Ba), cobalt (Co), cesium (Cs), molybdenum (Mo), lead (Pb), antimony (Sb), and thallium (Tl), were measured by ICP-MS according to the method of Mulligan et al. Urine samples were diluted 1 + 9 with 2% v/V double distilled concentrated nitric acid (GFS chemicals Inc., Columbus, OH), which contained iridium and rhodium for multiple internal standardization. In addition, Urine cadmium (Cd) levels were corrected for interference from molybdenum oxide. Corrected cadmium levels = original value for the cadmium – [(0.00175* Molybdenum) – 0.0136].

Covariates

Information on demography and disease history was collected by questionnaires. Demographic data were age (continuous), BMI (continuous), PIR (continuous), gender (male, female), race (non-Hispanic white, non-Hispanic black, other Hispanic, Mexican American, others), education (more than high school, high school or equivalent, and less than school), marital status (married, widowed/divorced/separated, and never married), smoking status (yes and no), alcohol status (yes and no), hypertension (yes and no), diabetes (yes, no, and borderline). The BMI (kg/m^2) was classified as normal weight <25, overweight 25 to <30, and obesity ≥30. The Department of Health and Human Services' poverty guidelines

were used as the poverty measure to calculate PIR. Diabetes was defined as reaching a fasting glucose level of ≥126 mg/dl or reporting a previous diagnosis (16). Hypertension was defined as resting blood pressure persistent at 140/90 mmHg or reporting a previous diagnosis (17).

Statistical analysis

To analyze the association between LTL and 8 urine metals including barium (Ba), cadmium (Cd), cobalt (Co), cesium (Cs), molybdenum (Mo), lead (Pb), antimony (Sb), and thallium (Tl) in the two groups (whole and aging population ≥60 years old), we conducted a three-step analysis.

We firstly describe the demographic and disease history data in overall and aging groups. Meanwhile, we analyzed the geometric mean (GM), LOD, and four quantiles of eight urine metals. Based on these results, chi-squared test, Cochran-Mantel-Haenszel test, and *t*-test were used to analyze the difference of demographic data in overall and aging population groups. Secondly, we conducted multiple linear regression (MLR) to find association between natural log-transformed LTL and quantiles of urine metals. Moreover, subgroup MLRs adjusted gradually for demographic and disease history were carried out to identify meaningful hazardous urine metals associated with changes of LTL. Thirdly, to make an accurate prediction of LTL, artificial neural network (ANN) was trained. All the variables in MLRs were put into the ANN model and three hidden layers were established to make a reliable prediction. All the analysis above were conducted in R software 4.1.2 (The R Foundation for Statistical Computing, USA). Two-sided $P < 0.05$ was considered statistically significant.

Artificial neural network prediction

In this research, an ANN framework: Tensorflow (developed by Google brain team based on the idea of a dataflow graph for building models) was adapted. Artificial neural network had three main components: (1) A group of synapses or connections was characterized by "weight," in which the input signal was connected to the neuron through connection weight; (2) An adder would add all weighted signal contributions; (3) The activation function (transfer function) affected neurons, which limited the amplitude of the network output and provided a permissible range for the output signal of finite value (18, 19). The common activation functions included linear, quadratic, geometric, logical, and rectified linear unit (ReLU).

The input layer and dense hidden layer used the activation function ReLU, which included specifying the value of neurons <0 as 0, and respecting the value of neurons ≥0 when its value is 0, as shown in the equation

$$ReLU(x) = \begin{cases} x, & x \geq 0 \\ 0, & x < 0 \end{cases}$$

Finally, in order to verify the results of ANN, three indicators were generated, including LOSS function (Squared error loss), MAE (mean absolute error), and scatter plot of actual and predicted values. Artificial neural network was mainly trained by reducing the iterations of LOSS function using gradient method. The commonly used techniques for calculating the LOSS function included mean square error, MAE, binary cross entropy, and Poisson.

In this study, after analyzing the relationship between urinary metal and telomere length, we carried out further prediction analysis. Artificial neural network became a popular prediction algorithm in recent years. In this study, "keras" (a high-level ANN application programming interface written in python) and "neuralnet" package (flexible ANN training program) were used to deploy the "Tensorflow" framework, setting hidden layers, and calculating with logistic function in each layer. The data was divided into training set and test set according to 8:2, 2,420 participants were divided into 1,936 in the training set and 404 in test set. Then the data sets were normalized, respectively. Firstly, the preliminary model was constructed, 25 variables were input (demographic, behavioral, disease, and urinary metal data included in this study), one hidden layer with five neurons and one output result were set, and the model compilation indicators were reported including LOSS function and MAE. Then we carried out model fitting and set the number of iterations to 100. Finally, we put the test set data into the trained model for prediction and verification. Based on the above steps, we also optimized the model parameters to reconstructed the model, changing one hidden layer to three hidden layers (100 neurons and 0.76 dropout rate in the first layer, 15 neurons and 0.5 dropout rate in the second layer, and 7 neurons and 0.2 dropout rate in the third layer). All layers adopted ReLU, and finally got an output. The whole process was conducted using R 4.1.2 (The R Foundation for Statistical Computing, USA).

Results

Characteristics of participants

The characteristic distribution of the study population (n = 2,420) in the total sample and aging sample (n = 821) was shown in Table 1. In overall group, the sample was mainly composed of the middle aged (49.5 ± 18.7), middle income (PIR 2.66 ± 1.64), overweight (37.36%), female (51.53%), White, Non-Hispanic (50%), more than high School (41.78%), married (59.01%),

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TABLE 1 Comparison between overall and aging population in weighted characteristics of the NHANES 1999–2002.

	Overall ($N = 2,420$)	Weighted	Aging ($N = 821$)	Weighted	t or chi-squared value
Age					
	49.5 ± 18.7		71.4 ± 7.93		−46.58*
PIR					
	2.66 ± 1.64		2.63 ± 1.57		0.47
BMI					
	747	30.87%	226	27.53%	7.23*
	904	37.36%	349	42.51%	
	769	31.78%	245	29.84%	
Gender					
Male	1,173	48.47%	437	53.23%	5.36*
Female	1,247	51.53%	384	46.77%	
Ethnicity					
Mexican American	609	25.17%	182	22.17%	12.85*
Other Hispanic	122	5.04%	31	3.78%	
White, Non-Hispanic	1,210	50.00%	465	56.64%	
Black, Non-Hispanic	409	16.90%	128	15.59%	
Other	70	2.89%	15	1.83%	
Education					
Less than high school	815	33.68%	347	42.27%	24.88*
High school diploma	594	24.55%	204	24.85%	
More than high school	1,011	41.78%	270	32.89%	
Marital status					
Married	1,428	59.01%	527	64.19%	228.26*
Widowed	208	8.60%	187	22.78%	
Divorced	207	8.55%	66	8.04%	
Separated	79	3.26%	17	2.07%	
Never married	350	14.46%	14	1.71%	
Living with partner	144	5.95%	8	0.97%	
Alcohol					
Yes	1,631	67.40%	506	61.63%	8.67*
No	788	32.56%	314	38.25%	
Smoking					
Yes	1,189	49.13%	434	52.86%	3.35
No	1,224	50.58%	384	46.77%	
Hypertension					
Yes	714	29.50%	403	49.09%	102.9*
No	1,704	70.41%	418	50.91%	
Diabetes					
Yes	238	9.83%	146	17.78%	42.32*
No	2,141	88.47%	652	79.42%	
Borderline	41	1.69%	23	2.80%	

*$p < 0.05$.

alcoholic (67.4%), non-smoking (50.58%), non-hypertension (70.41%), and non-diabetes (88.47%). In aging group, the main compositions included the elderly (71.4 ± 7.93), middle income (PIR 2.63 ± 1.57), overweight (42.51%), male (53.23%), Non-Hispanic White (56.64%), less than high school (42.27%), married (64.19%), alcoholic (61.63%), smokers (52.86%), non-hypertension (50.91%), and non-diabetes (79.42%). Between overall and aging groups, several characteristics had significant difference including BMI distribution, gender, race, education, marital status, alcohol, hypertension, and diabetes.

Distribution of urine metals

Table 2 showed the limit of detection (LOD), GM, 95% confidential interval (CI), and four quantiles of the

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TABLE 2 Urine metals (ng/ml) in overall and aging population of the NHANES 1999–2002.

Overall ($N = 2420$)	≥LOD (%)	GM (95%CI)	Quartile 1	Quartile 2	Quartile 3	Quartile 4
LTL		0.99(0.99, 1.01)	≤0.84	0.84–0.99	0.99–1.17	>1.17
Barium	0.084	1.29(1.24, 1.35)	≤0.66	0.66–1.39	1.39–2.65	>2.65
Cadmium	0.055	0.31(0.3, 0.33)	≤0.17	0.17–0.32	0.32–0.62	>0.62
Cobalt	0.024	0.36(0.35, 0.37)	≤0.22	0.22–0.38	0.38–0.59	>0.59
Cesium	0.13	4.46(4.33, 4.6)	≤3.01	3.01–4.96	4.96–7.26	>7.26
Molybdenum	0.8	42.46(40.97, 44)	≤25.4	25.4–47.4	47.4–77.2	>77.2
Lead	0.03	0.82(0.79, 0.85)	≤0.5	0.5–0.9	0.9–1.5	>1.5
Antimony	0.022	0.13(0.12, 0.13)	≤0.09	0.09–0.13	0.13–0.19	>0.19
Thallium	0.018	0.16(0.15, 0.16)	≤0.11	0.11–0.18	0.18–0.26	>0.26
Aging ($N = 821$)	**≥LOD (%)**	**GM (95%CI)**	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
LTL		0.88(0.87, 0.90)	≤0.75	0.75–0.88	0.88–1.02	>1.02
Barium	0.084	1.1(1.02, 1.18)	≤0.59	0.59–1.1	1.1–2.2	>2.2
Cadmium	0.055	0.41(0.38, 0.43)	≤0.24	0.24–0.44	0.44–0.75	>0.75
Cobalt	0.024	0.31(0.29, 0.33)	≤0.2	0.2–0.32	0.32–0.5	>0.5
Cesium	0.13	4.16(3.97, 4.37)	≤2.9	2.9–4.55	4.55–6.65	>6.65
Molybdenum	0.8	39.17(36.85, 41.63)	≤23.2	23.2–41.1	41.1–71.1	>71.1
Lead	0.03	0.87(0.82, 0.93)	≤0.5	0.5–0.9	0.9–1.6	>1.6
Antimony	0.022	0.11(0.11, 0.12)	≤0.08	0.08–0.11	0.11–0.16	>0.16
Thallium	0.018	0.14(0.13, 0.14)	≤0.09	0.09–0.14	0.14–0.22	>0.22

eight urine metals among total and aging participants in our study. All eight urinary metals were recorded using ng/ml. Besides, we analyzed the correlation among all the variables in the regression model. Supplementary Figure 1 showed that all urine metals and creatinine had some correlations.

Associations of urine metal metabolites with LTL

In this section, we fitted MLR in steps to validate the stability of result. The dependent variable LTL was log transformed and normalized, but the normality analysis showed that all variables did not obey normality. In Model 3 of overall group included all covariates and only Cd was found significant in association with shortening LTL (third quantile: −9.36, 95%CI = [−19.7, −2.32)]. In aging group, Mo was associated with prolonging LTL in model 3 [third quantile: 24.37, 95%CI = (5.42, 63.55)] (Table 3).

Artificial neural network for predicting mean T/S ratio

As shown in Figure 2, based on the risk factors analysis using MLR, we developed an ANN algorithm taking 25 items as the input parameters (data about demography, behavior, disease, and urinary metal). In the hidden layer setting, there were 24 neurons with 0.375 exit rate in the first layer, 15 neurons with 0.53 exit rate in the second layer, and 7 neurons with 0.86 exit rate in the third layer. Logical and rectified linear unit was used in all layers, and finally an output result was obtained. After the model was fitted, we evaluated the importance of the input variables on the model. From Figure 3, it could be seen that the greatest negative impact was urinary cadmium and the greatest positive impact was urinary molybdenum, which were consistent with the significant heavy metals analyzed by MLR.

In the process of model fitting, the relationship between the iterations and MAE was conducted in Figure 4. It could be seen that when the iterations reached 10, the minimum values of LOSS and MAE were 0.054 and 0.181, respectively. Since then, MSE would not change with the increase of iteration times, so 10 times iteration was selected as the parameter of model fitting. Finally, we took put test dataset into the model to get the predicted mean T/S ratio. Then scatter plot of predicted value with the original value with trend line was made. Supplementary Figure 2 showed that the scatter points had obvious linearity, indicating that the predicted value was reliable.

Discussion

The MLR results of the total population showed that there was a negative correlation between urinary Cd and LTL in model 1 (adjusted for urine creatinine), model 2 (adjusted for creatinine

TABLE 3 Percent difference (95% CI) in leukocyte telomere length (T/S ratio) by urine metals (ng/mL) in overall and aging population of the NHANES 1999–2002.

	Overall			Aging		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
Urinary barium						
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	−0.32 (−10.8, 11.4)	−1.85 (−11.42, 8.75)	−1.67 (−11.3, 8.99)	7.36 (−12.7, 32.02)	8.33 (−11.46, 32.55)	4.46 (−10.58, 22.04)
Quartile 3	1.79 (−9.35, 14.31)	3.32 (−7.1, 14.91)	3.37 (−7.05, 14.97)	0.93 (−15.46, 20.49)	1.19 (−14.47, 19.71)	2.97 (−17.83, 29.05)
Quartile 4	0.02 (−3.51, 3.68)	−0.06 (−3.26, 3.25)	−0.17 (−3.38, 3.15)	−0.89 (−6.1, 4.61)	−1.88 (−6.92, 3.45)	−2.76 (−8.23, 3.03)
p trend	0.74	0.17	0.23	0.62	0.65	0.67
Urinary cadmium						
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	−7.51 (−18.16, 4.52)	−3.55 (−14.27, 8.52)	−3.46 (−14.24, 8.67)	−10.67 (−25.92, 7.72)	−8.88 (−24.09, 9.37)	1.41 (−18.43, 26.08)
Quartile 3	**−18.47 (−27.89, −7.83)***	**−8.99 (−19.38, −2.73)***	**−9.36 (−19.7, −2.32)***	−5.6 (−24.64, 18.26)	−9.48 (28.1, 13.97)	−5.67 (−21.95, 14)
Quartile 4	**−4.09 (−8.59, −0.63)***	**3.05 (−1.52, −7.83)***	2.68 (−1.93, 7.5)	1.94 (−6.96, 11.68)	5.25 (−3.92, 15.29)	0.74 (−6.76, 8.85)
p trend	**<0.0001***	0.4	0.31	**0.01***	**0.03***	**0.04***
Urinary cobalt						
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	7.37 (−6.42, 23.19)	**8.56 (−4.43, 23.3)***	8.61 (−4.39, 23.39)	2.08 (−22.4, 34.29)	−3.21 (−26.21, 26.96)	6.53 (−13.02, 30.48)
Quartile 3	−1.53 (−17.24, 17.16)	−6.87 (−20.57, 9.18)	−7.97 (−21.49, 7.88)	−8.46 (−30.3, 20.23)	−10.54 (−31.89, 17.5)	−15.5 (−37.78, 14.76)
Quartile 4	2.4 (−2.44, 7.48)	−0.9 (−5.13, 3.53)	−0.87 (−5.11, 3.55)	**−6.35 (−12.69, 0.44)***	−3.65 (10.1, 3.27)	−4.17 (−11.59, 3.88)
p trend	0.29	0.89	0.83	0.15	0.6	0.66
Urinary cesium						
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	−0.91 (−17, 18.3)	−0.03 (−14.94, 17.49)	0.33 (−14.67, 17.96)	−13.33 (−34.44, 14.57)	−9.24 (−30.95, 13.92)	−3.71 (−24.93, 23.51)
Quartile 3	−9.47 (−25.13, 9.48)	−8.72 (−23.54, 8.98)	−10.07 (−24.71, 7.43)	1.64 (−26.39, 40.33)	−6.55 (−32.05, 28.52)	−8.01 (−34.48, 29.16)
Quartile 4	−1.91 (−7.95, 4.53)	**3.5 (2.17, 8.86)***	−3.87 (−9.21, 1.78)	−6.16 (−18.7, 8.31)	−7.16 (−19.4, 6.95)	−1.25 (−16.15, 16.3)
p trend	**0.03***	0.69	0.71	0.38	0.45	0.47
Urinary molybdenum						
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	−6.31 (−16.66, 5.33)	**7.91 (−2.53, 17.29)***	−5.13 (−14.89, 5.76)	−5.09 (−24.14, 18.74)	−2.05 (−21.65, 22.47)	−1.2 (−17.77, 18.72)
Quartile 3	**14.22 (−1.89, 32.98)***	**11.02 (−3.32, 27.48)***	10.23 (−3.98, 26.55)	3.15 (−17.79, 29.42)	11.51 (−10.97, 39.68)	**24.37 (5.42, 63.55)***
Quartile 4	−0.9 (−7.1, 5.71)	2.23 (−3.48, 8.28)	2.09 (−3.61, 8.12)	−0.09 (−9.02, 9.73)	0.17 (−8.53, 9.69)	1.2 (−8.4, 11.8)

(Continued)

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TABLE 3 (Continued)

	Overall			Aging		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
p trend	0.11	**0.03***	**0.03***	0.08	0.09	0.12
Urinary lead						
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	0 (−18.7, 23)	7.23 (−11.67, 30.17)	5.67 (−13.01, 28.36)	1.1 (−30.53, 47.12)	−2.5 (−30.4, 36.57)	−1.58 (−30.13, 38.63)
Quartile 3	−0.28 (−16.76, 19.46)	15.67 (−2.13, 36.7)	15.29 (−2.5, 36.33)	30.57 (−1.02, 72.24)	32.62 (0.5, 75.01)	31.18 (−0.81, 73.49)
Quartile 4	−0.59 (−5.08, 4.1)	2.22 (−2.05, 6.67)	1.97 (−2.31, 6.43)	−0.48 (−7.52, 7.1)	2.71 (−4.71, 10.71)	1.54 (−5.23, 8.79)
p trend	**0.0001***	0.12	0.13	0.22	0.73	0.69
Urinary antimony						
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	0.67 (−20.16, 26.94)	−3.01 (−20.81, 18.8)	−0.03 (−21.18, 18.5)	**−23.31 (−42.59, 2.43)***	−22.4 (−41.52, 2.97)	8.1 (−22.1, 50.01)
Quartile 3	−11.03(−28.76. 11.12)	−14.12(−30.08, 5.48)	−0.15(−30.06, 5.63)	−13.41(−46.52, 40.2)	−18.12(−48.69, 30.67)	−15.3 (−44.6, 29.48)
Quartile 4	0.11(−4.86, 5.35)	0.77(−3.87, 5.64)	0.005(−4.17, 5.34)	1.75(−5.15, 9.15)	1.25(−5.48, 8.46)	2.112 (−5.41, 10.24)
p trend	0.13	0.7	0.71	**0.04***	**0.04***	**0.04***
Urinary thallium						
Quartile 1	Reference	Reference	Reference	Reference	Reference	Reference
Quartile 2	1.89 (−14.26, 21.08)	−1.75 (−16.15, 15.13)	−1.3 (−15.82, 15.72)	7.87 (−13.47, 34.48)	7.43 (−13.3, 33.12)	2.58 (−17.4, 27.4)
Quartile 3	13.44 (−14.02, 49.67)	12.85 (−12.7, 45.86)	13.75 (−12.08, 47.16)	6.34 (−20.24, 41.77)	−3.32 (−27.19, 28.38)	−0.58 (−40.94, 67.39)
Quartile 4	1.46 (−6.19, 9.73)	4.16 (−3.42, 12.34)	3.6 (−3.93, 11.72)	−3.59 (13.14, 7.01)	−3.29 (−12.96, 7.46)	−4.3 (−16.76, 10.03)
p trend	**0.04***	0.53	0.41	**0.04***	0.19	0.16

Bold values were statistically significant with P value < 0.05. *$p < 0.05$.

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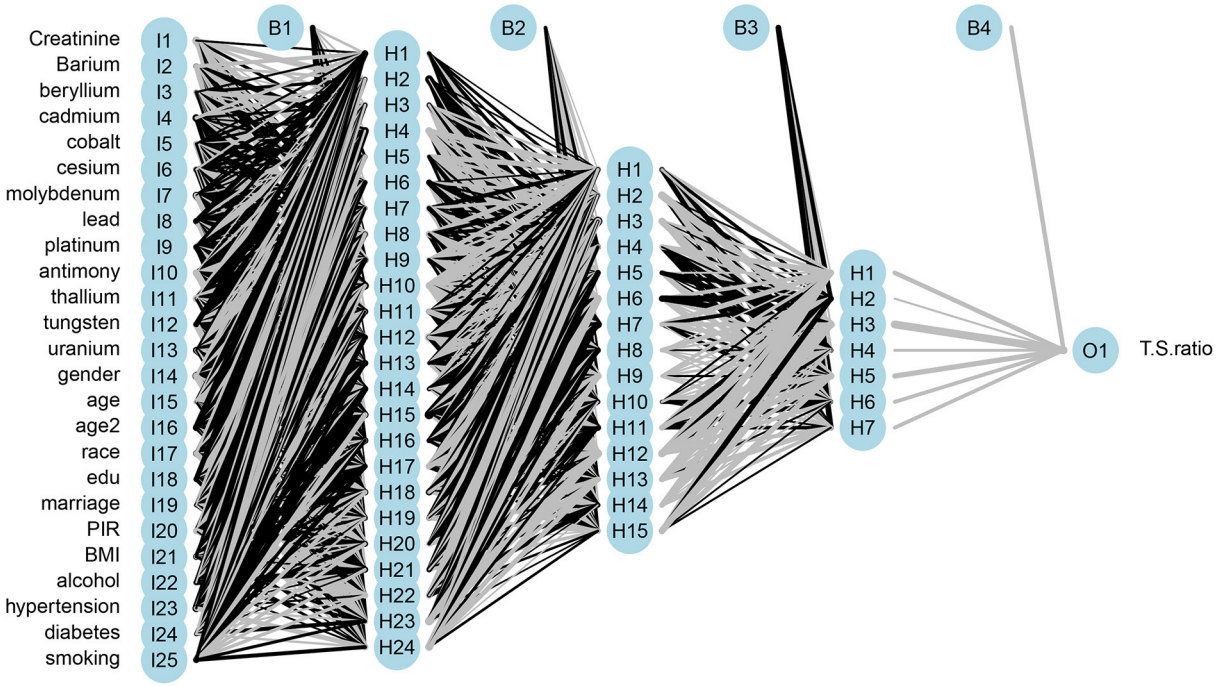

FIGURE 2
Architecture of multilayer artificial neural network of urinary metal for LTL prediction.

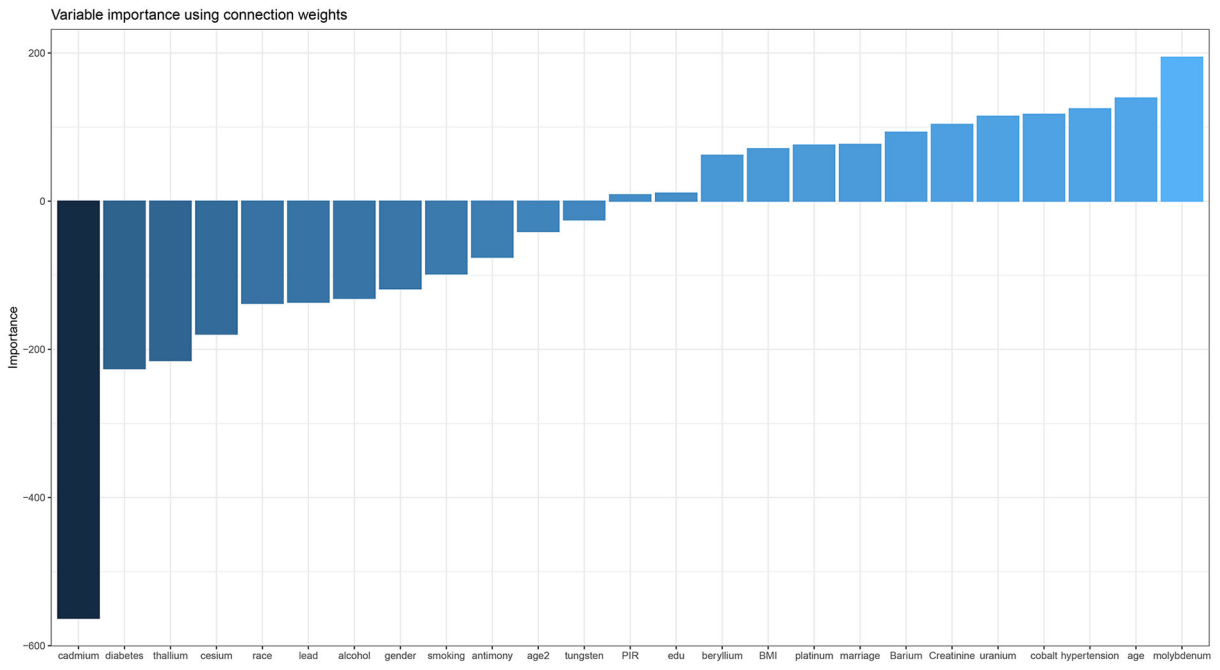

FIGURE 3
Variable importance plot of ANN.

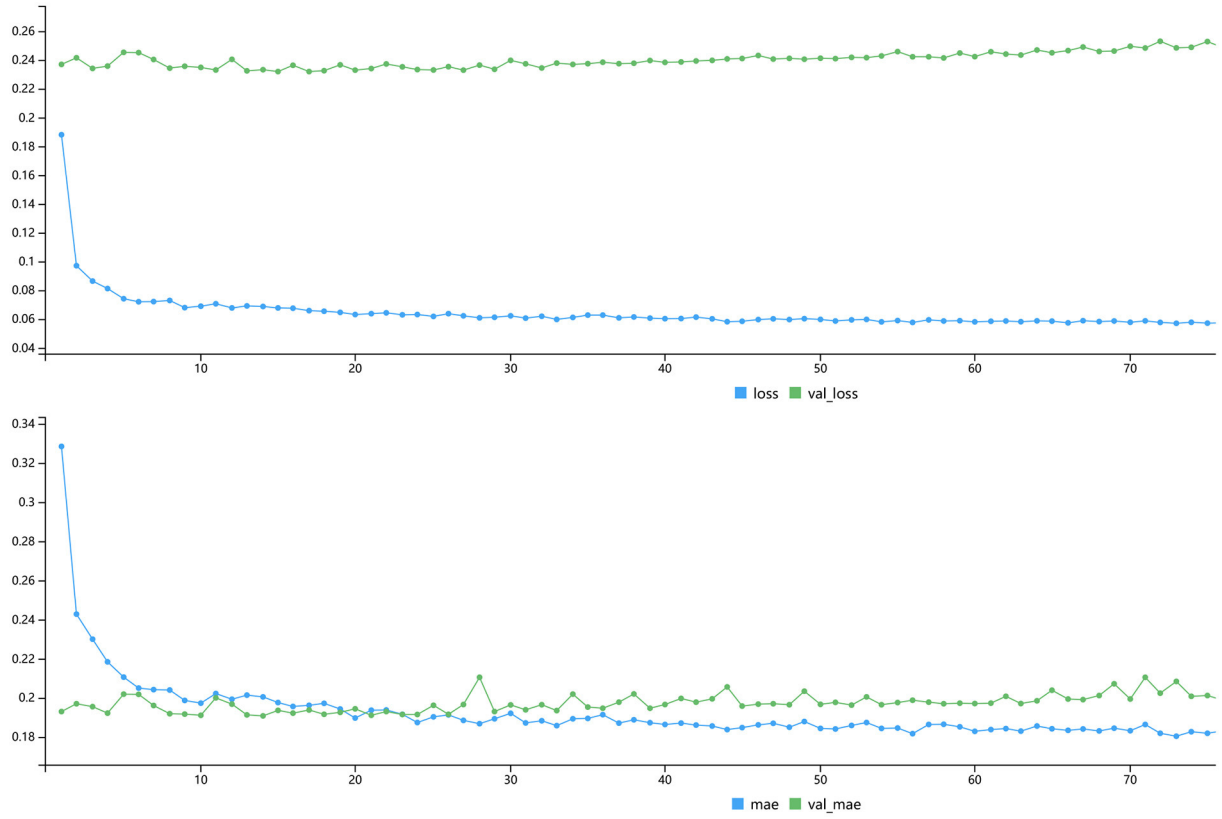

FIGURE 4
Plot of LOSS and MAE with iterations.

and demographic factors), and model 3 (adjusted for creatinine, demographic, and disease factors), indicating the higher the urinary Cd, the shorter the LTL. This result was biologically reasonable because Cd was associated with mechanisms that promoted telomere shortening, including oxidative stress, inhibition of DNA repair, and inflammation. Due to the high level of guanine, telomere was particularly sensitive to oxidative stress. At the same time, telomere might have defects in repairing single strand breaks. Inflammation might accelerate leukocyte telomere shortening by promoting cell renewal, replicative aging, and inducing oxidative stress. Cadmium could stimulate the inflammatory cytokines. Cadmium was a recognized human carcinogen and had been proved to interfere in DNA repair system. Zota et al. analyzed the NHANES 1999–2002 data set and reported the highest quartile of Cd in blood and urine was correlated with shorter LTL, and there was evidence of dose-response relationship ($P < 0.05$) (20).

In the elderly population, model 3 showed a high positive correlation between Mo and LTL [24.37, 95%CI = (5.42, 63.55)]. Domingo Raloso et al. found that the increase of urinary Mo level was related to the increase of redox glutathione ratio (GSSG/GSH), indicating that Mo might reduce the effect of metal oxidative stress. Nakadaira et al. investigated the levels of Mo and Se in sediments and the cancer mortality in 19 areas of Niigata Prefecture, Japan. It was found that Mo could inhibit gastrointestinal cancer (21). Meanwhile, Mo compounds could be used as drugs for detecting and treating tumors. Dhas et al. reviewed MoS2 nanocomposites had attracted extensive attention in the fields of optics, catalysis, electrochemistry, and cancer treatment (22). According to the literature search results, there was little research on association between Mo and LTL, which might be a direction worthy of exploration.

There was no correlation between urinary Co, Cs, Pb, and LTL in overall population and the elderly population, respectively. This was consistent with the research of Zota et al. (20). However, Herlin et al. believe that urinary Pb would affect telomere shortening in children, especially boys (23).

There was no correlation between urinary Sb, Tl, Ba, and LTL in the total population. There was no correlation between urinary Tl, Ba, and LTL in the overall and elderly population. It was reported that ANN could be used for age prediction based on DNA methylation (18). Leukocytes telomere length was closely related to human aging. Perhaps it was meaningful to put urinary metal, demographic data, behavior, and disease history

to predict LTL, since the close correlation between LTL and life expectancy. Compared with MLR, ANN especially Tensorflow framework is a brand new technique to make prediction. But, in exploration of risk factors, MLR had good performance which ANN is not good at. Artificial neural network might have better performance than MLR in prediction, since it could include all possible variables and large sample size (10–13).

To our knowledge, this was the first ANN analysis for LTL prediction based on urinary metal. Based on the analysis of the correlations between urinary metal and LTL above in this study, it was suitable for deep learning model. Artificial neural network was a classical algorithm framework of deep learning. It was widely used in categorical variable classifying, continuous variable regression, and time-series data prediction (24–27). Because ANN had the ability to introduce non-linearity in high-dimensional space, large scale factors could be considered to improve the prediction sensitivity and specificity (28, 29).

In the process of model setting, it was found that three hidden layers had good accuracy. The hidden nodes of three layers were reduced from 25 to 24, 24 to 15, and 15 to 7, and the final output result was obtained (Figure 2). This was the best setting after many comparisons in parameters. The training result on the variable importance was also in line with the expectation that Cd had the strongest negative correlation and Mo had the strongest positive correlation (Figure 3). After 10 iterations, LOSS and MAE reach stable minimum values of 0.054 and 0.181, respectively (Figure 4). Finally, the ANN prediction model was obtained. Based on the model, we put the test set into the model and got the scatter diagram of the real value and predicted value. From the diagram, it could be seen that the scatter has good linearity and had a reliable prediction (Supplementary Figure 2).

However, there were several limitations of our search. First, the data used in this study were cross-sectional design, which was impossible to infer the causal relationship between urinary metals and LTL. Secondly, the participants' urine samples were collected and detected at one time, and the single point of metal might not reflect the participants' continuous exposure. Thirdly, although we adjusted some demographic, medical history, and lifestyle factors in linear regression, there were still some confounding variables that affected the results. Fourthly, the lack of information among participants might lead to the exclusion of results. Finally, for the over fitting problem of ANN, it was difficult for us to find the parameters to get high accuracy without over fitting, so we could only choose the relatively best parameters.

Conclusion

Overall, the main findings in our study were as follows: urinary Cd was negatively correlated with LTL in the total population and urinary Mo was positively correlated with LTL. No correlations were found between urinary Co, Pb, Sb, Cs, Tl, Ba, and LTL. Therefore, in adults especially the elderly, the relationships between urinary Cd, Mo, and LTL might be worthy of further research. In addition, we also constructed an ANN model to make predictions of LTL based on urinary metals, demography, behavior, and disease history, which might help to make prediction of people involving the aging. This could be used in primary prevention of people especially the elderly.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

JW wrote the manuscript and analyzed the date in R language. QL and XL collected the data and screen it. FX designed and reviewed the research. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.963138/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Correlation matrix of included variables.

SUPPLEMENTARY FIGURE 2
Scatter plot with line trend of test and prediction value.

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Developing a guideline for measuring workplace non-Gaussian noise exposure based on kurtosis adjustment of noise level in China

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Objective: There is no unified standard for measuring workplace non-Gaussian noise (known as complex noise) exposure. This study aimed to develop a draft guideline for measuring workplace non-Gaussian complex noise exposure based on noise temporal structure adjustment.

Methods: Noise exposure level, e.g., the A-weighted sound pressure level normalized to a nominal 8-h working day ($L_{EX,8h}$), was adjusted using the temporal structure (expressed by kurtosis) of noise. Noise waveform analysis or the instrument's direct reading was used.

Results: The framework of the draft guideline included measurement metrics, the protocol using kurtosis to adjust $L_{EX,8h}$, technical requirements for measuring instruments, measurement steps, data analysis, and measurement recording.

Conclusion: The draft guideline could provide a basis for accurately measuring workers' exposure to non-Gaussian noise.

KEYWORDS

non-Gaussian noise, complex noise, measurement, kurtosis, guideline

Introduction

Noise is one of the most common occupational hazardous factors in the occupational environment. Noise-induced hearing loss (NIHL), a type of progressive sensorineural hearing loss, has become a global public health problem. World Health Organization (WHO) estimated that 10% of the global population is exposed to noise pollution, and of those, 6.2% suffer from NIHL (1). Approximately 16% of adult hearing loss was related to occupational noise (2). The prevalence of occupational NIHL was estimated at 10% in developed countries and 18–67% in developing countries, respectively (3).

In China, occupational noise-induced deafness has become the second primary occupational disease after pneumoconiosis, with the number of reported cases increasing at an annual rate of 18.68% from 2010 to 2019 (4, 5).

Regarding its temporal structure, industrial noise can be divided into steady-state, continuous (Gaussian) noise, and non-Gaussian complex noise. Complex noise is composed of transient high-energy impulsive noise superimposed on Gaussian background noise, which is common in the occupational environment (6, 7). Existing noise exposure measurement standards (8) are suitable for steady-state noise to assess the noise exposure level. Because the complex noise contains impulsive components, it is challenging to measure the complex noise in industrial settings. Conventional noise measurement techniques, which only use the noise energy metric of sound pressure level (L_{eq}), are not suitable for complex noise measurement due to the peak clipping effect of impulse noise (9). Moreover, these conventional noise measurement instruments (e.g., dosimeters or sound level meters) cannot measure the temporal structure of the noise.

The existing noise measurement standard is based on the "equal energy theory (EEH)." The principle of "EEH" is that the hearing damage caused by noise is only proportional to the noise energy; that is, no matter what type of noise, as long as the energy of noise is equal, it should cause the same damage to the hearing. A large number of animal experiments (10, 11) and epidemiological investigations (−19) have proved that exposure to complex noise leads to more severe hearing damage than steady noise, indicating that the "EEH" may underestimate the hearing loss induced by non-Gaussian complex noise. The problem with the existing standards is that the temporal structure of non-Gaussian noise is not considered in assessing the impact on hearing and only uses noise energy to characterize noise exposure. Therefore, it cannot fully reflect the hearing loss caused by complex noise. The measurement and evaluation of complex noise exposure should be combined with the energy metric of noise and the temporal structure metric, that is, the use of kurtosis to adjust the noise energy introduced in this paper.

Kurtosis is an indirect metric reflecting noise temporal structure (12). Animal experiments (10, 11) and epidemiological studies (12–19) suggest that kurtosis, a significant risk factor for NIHL, can adjust the noise energy metric into a combined metric. These kurtosis-adjusted noise energy metrics can accurately measure complex noise exposure and effectively assess the hearing loss caused by non-Gaussian noise. Although the measurement method of non-Gaussian noise based on kurtosis adjustment has been defined in human studies (12, 17, 18), there is no comprehensive measurement guideline for non-Gaussian noise exposure.

Based on our previous studies and literature reviews, we propose a draft guideline for China to measure workplace non-Gaussian complex noise exposure using kurtosis adjustment of the noise level. This draft guideline will stipulate a measurement standard and technical benchmarks for measuring non-Gaussian exposure in the workplace and provide a basis for protecting the hearing of noise-exposed workers, including vulnerable groups such as the elderly and women.

Methods

Terms and definitions

Relevant terms and their definitions in this guideline are shown in Table 1.

Measurement metrics

Noise energy metrics

The energy metric in existing noise measurement and evaluation criteria is the noise intensity, usually expressed by the A-weighted sound pressure level normalized to a nominal 8-h working day ($L_{EX,8h}$).

TABLE 1 Relevant terms and their definitions.

Terms	Definitions
Steady-state noise	Noise with sound level fluctuation <3dBA, also known as Gaussian noise
Non-Gaussian noise	The noise is composed of transient high-energy impulsive noise superimposed on Gaussian background noise, including classic impulsive noise, also known as complex noise
Kurtosis (β)	The ratio of the fourth-order central moment to the squared second-order central moment of a distribution, defines how heavily the tails of a distribution differ from the tails of a Gaussian distribution
Nominal day	Working day over which it is chosen to determine the noise exposure
Daily noise exposure level ($L_{EX,8h}$)	A-weighted sound pressure level normalized to a nominal 8-h working day
Week noise exposure level ($L_{EX,40h}$)	A daily noise exposure level normalized to a nominal week of five 8h working days
Task	A distinct part of workers' occupational activity
Job	Overall occupational activity that is carried out by a worker, consisting of all the tasks performed by the worker during the entire working day or shift
Homogeneous noise exposure group	A group of workers that are performing the same job and are expected to have similar noise exposure during a working day

$L_{EX,8h}$ can be calculated by the formula (8):

$$LEX, 8h = LAeq, Te + 10 * lg(Te/T0) \quad (1)$$

where T_e is the effective duration of the working day in hours; T_0 is the reference duration (8 h); $L_{Aeq,Te}$ is the L_{Aeq} for T_e.

If a normalized exposure level over a week is desired, it can be calculated as follows (20):

$$L_{EX,40h} = 10 * \lg\left[\frac{1}{5}\sum_{i=1}^{5}\left(10^{0.1*(L_{EX,8h})_i}\right)\right] \quad (2)$$

$L_{EX,40h}$ is $L_{EX,8h}$ normalized to a nominal week of five 8 h working days.

Noise temporal structure metrics

For a complex noise, noise temporal structure variables affecting hearing include the peak value, peak duration, and inter-peak distribution. In the actual measurement activity, it is not feasible to quantitatively analyze each of these variables to characterize the temporal structure for a shift-long noise exposure. Kurtosis, incorporating these time-domain variables into a simple metric, can quantify the impulsiveness of complex noise and is much more practical as a specific metric for the temporal structure of complex noise (12, 21). Kurtosis is a statistic that describes the normal distribution of probability distributions of random variables. The calculation formula is following:

$$\beta = \frac{\frac{1}{n}\sum_{i=1}^{n}(xi - \bar{x})^4}{\left[\frac{1}{n}\sum_{i=1}^{n}(xi - \mathrm{x})^2\right]^2} \quad (3)$$

Where β is the kurtosis; x_i is the i^{th} value of noise amplitude, and $\bar{x}$ is the sample mean. Kurtosis is a statistical measure of extreme values (or outliers) in data in either tail relative to a Gaussian distribution. Therefore, kurtosis is sensitive to the number of outliers. Put another way, kurtosis describes the tendency for a sound to have high amplitude events that depart substantially from the underlying, continuous, steady-state noise. Kurtosis can differentiate the degree of hearing loss caused by noise with different temporal structures at the same noise exposure level.

Kurtosis has some disadvantages: e.g., the length of intervals over which kurtosis is determined can affect the outcome and kurtosis has high sampling variability. Therefore, noise exposures can be clearly and effectively characterized by kurtosis only when the window length and the noise sampling rate are fixed or standardized. Based on the results of previous studies (17, 18, 22), the following protocol was established for kurtosis application in the evaluation of NIHL in industrial settings: The kurtosis of the recorded noise signal is computed over consecutive 60-s time windows without overlap over the shift-long noise record or whole measurement duration using a sampling rate of 48 kHz for noise recording. The mean of the measured kurtosis values, β_j, at every 60 s is calculated and used as the kurtosis of noise exposure (β_N):

$$\beta N = \frac{1}{N}\sum_{j=1}^{N}\beta j \quad (4)$$

Theoretically, the kurtosis value of steady-state (Gaussian) noise is 3. However, the steady-state noise environment is rare in industrial production, and the quasi-Gaussian noise environment (kurtosis ranging from 3 to 10) often occurs with its energy distribution close to a normal distribution (Gaussian distribution).

The adjustment protocol of noise level using kurtosis

The adjustment protocol applies kurtosis to adjust the noise intensity based on Goley's protocol from animal data (23). The calculation formula is as follows:

$$L_{EX,8h}\text{−K} = L_{EX,8h} + \lambda * \lg(\beta_N/3) \quad (5)$$

In the formula, β is the kurtosis value of the noise measured; $L_{EX,8h}$-K is kurtosis-adjusted $L_{EX,8h}$; λ is the adjustment coefficient obtained from the dose-effect relationship between noise exposure and human hearing loss among a large sample of populations. In Goley's study, the λ value is 4.02 based on animal data. According to the multiple linear regression results from human data (18), the λ value is 6.5. The $L_{Aeq,8h}$-K can be calculated as follows:

$$L_{EX,8h} - \mathrm{K} = L_{EX,8h} + 6.5 * lg(\beta_N/3) \quad (6)$$

where β_N is the average kurtosis value of noise during measurement duration. For example, when the average kurtosis of the noise is 30, the $L_{EX,8h}$ increases by 6.5 dB(A) according to Formula 6. The calculation of $L_{EX,40h}$-K can be performed according to Formula 6.

Requirement of measuring instruments

L_{Aeq} measurement can follow an occupational health standard in China, i.e., "Measurement of Physical Agents in the workplace-Part 8: noise (GBZ/T 189.8)," which is based on the ISO 9612 (2009) "Acoustics-Determination of occupational noise exposure-engineering method." The L_{Aeq} measurement can be made using either integrating-averaging sound level

meters or personal sound exposure meters. The two kinds of instruments shall meet the requirements of IEC 61672-1:2002.

Measurement of kurtosis (β) needs a dedicated personal sound exposure meter (or noise dosimeter) with a recording or direct reading function. This kind of personal sound exposure meter can also measure the L_{Aeq} and $L_{EX,8h.}$ The digital instrument has at least one of the following functions: (1) sound recording for further analysis of kurtosis or L_{Aeq}; (2) Automatic calculation of kurtosis, $L_{EX,8H}$, or $L_{EX,8h}$-K for direct reading. The primary technical requirements for the dosimeter are as follows (12–19): (1) a ¼" pre-polarized condenser microphone with a broad response frequency (20 Hz to 20 kHz) and high sensitivity level (2.24 mV/Pa); (2) The L_{Aeq} measurement ranges from 40 to 141 dB(A); (3) can work continuously for at least 16 h under full charge; (4) has an at least 32-GB memory card inside; (5) can record the noise continuously with a 32-bit resolution and at a sampling rate of 48 kHz.

Results

Measurement procedures

Field investigation

A field investigation is needed before noise measurement, which shall be carried out under normal production conditions and cover all workplaces involving noise exposure. The investigation includes the followings: (1) General information of enterprise, product, production process, and its zoning; (2) Source of noise, layout of noisy equipment, significant noise exposure event; (3) Work analysis. The field investigation aims to: (a) identify noise-related jobs; (b) define homogeneous noise exposure groups based on job title, function, and work area; (c) identify tasks that make up each job.

In the work analysis, workers' working-day recording of each noise-related job is needed as the original recording material in the noise measurement process. The contents shall include as follows: job title, the number of exposed workers, noise type, exposure time, exposure frequency, work shift, work sites and their change during the working day, task description, significant noise exposure events, and use of hearing protection devices. One or two representative workers per job or homogeneous noise exposure group are selected for the recording.

After finishing the field investigation, a noise measurement plan must be established, and a schematic diagram set with field sampling/measuring point must be drawn.

Preparation of instruments

Before measurement, the personal sound exposure dosimeter or sound level meter shall be fully charged, and a wind-proof cap of the microphone is prepared for use in a place where the wind speed is >3 m/s. Calibration of the instruments, including filed calibration, should be finished according to relevant calibration requirements.

Determination of sampling subjects

Kurtosis and $L_{EX,8h}$-K are obtained from personal noise recording. Each subject shall confirm that this is the noise they are typically exposed to on an average working day.

The number of subjects for sampling is determined based on an occupational health standard in China (i.e., Specifications of air sampling for hazardous substance monitoring in the workplace): if the number of each job (or homogeneous noise exposure group) is <3 workers, all workers are selected; if the number of each job is 3–5 workers, two workers shall be selected; if the number of each job is 6–10, three workers shall be selected; if the number of each job is >10, four workers shall be selected.

Measurement of noise

Suppose the noise is determined as steady-state noise through the field investigation, the measurement for steady-state noise follows the conventional noise measurement standard, the "Measurement of Physical Agents in the workplace-Part 8: noise (GBZ/T 189.8)" in China, which is based on the "Acoustics-Determination of occupational noise exposure-engineering method (20)."

Dosimeter wearing

Non-Gaussian noise measurement requires an appropriate way to wear the dosimeter. The dosimeter is clipped to the worker's collar, then mounted on the top of the shoulder at a distance of at least 0.1 m from the entrance of the external ear canal at the side of the most exposed ear and should be ∼0.04 m above the shoulder. When recording, the microphone stands up to avoid the mechanical influence or clothing covering. The participants are trained to wear the dosimeter properly. The microphone should wear a wind-proof cap if the wind speed exceeds 3 m/s. The interference from electromagnetic fields shall be avoided as far as possible.

Measurement methods

Measuring non-Gaussian noise has two methods based on the instrument's availability, i.e., noise waveform analysis and direct reading of the instrument.

Noise waveform analysis uses the specific noise dosimeter to record sound waves. Whole-shift sampling is preferred for recording the noise waveform. In order to facilitate practical operation, a long-time sampling with at least 1 h can be selected. The sampling period shall represent the whole-shift

activity of each job, covering typical tasks that produce the cyclic fluctuating or randomly fluctuating noise. The recording is transferred to a computer for subsequent analysis. The noise waveforms are analyzed using a particular software (e.g., MATLAB) to calculate $L_{EX,8h}$ and kurtosis value; Then, the $L_{EX,8h}$-K is calculated.

The direct reading method uses the specific noise dosimeter with the automatic calculation of kurtosis and $L_{EX,8h}$-K. The placement and measuring steps of the instrument is the same as the method of "Noise waveform analysis." The kurtosis, $L_{EX,8h}$, and $L_{EX,8h}$-K values obtained from whole-shift measurement or long-time sampling with at least 1 h can be read directly and downloaded to the computer.

Data analysis

Conduct the exposure assessment of non-Gaussian noise in workplaces based on a comparison between the $L_{EX,8h}$-K and the occupational exposure limit for noise (i.e., 85dB(A)); Prioritize the noise impulsiveness among different jobs or tasks by comparing kurtosis levels of various jobs or tasks.

Measurement records

Measurement records shall include the following: Measurement date, time, weather conditions (temperature, relative humidity, wind speed), field calibration of dosimeter, dosimeter, measurement location, job or task, significant noise exposure event, measuring duration, noise data, calculation formula and process, and signature of surveyor and accompanying personnel from the enterprise.

Notes of non-Gaussian noise measurement

Because kurtosis is an adjunct metric to energy, it has been shown that kurtosis had an impact on NIHL evaluation only when $L_{EX,8h}$ is $\geq$70 dB(A) (18). Therefore, the condition of using kurtosis adjustment (Equation 6) in assessment of NIHL is that $L_{EX,8h}$ $\geq$70 dB (A). On the other hand, the optimal application range of Equation 6 is $L_{EX,8h}$ between 70 and 95 dB (A), because Equation 6 was based on worker data at this noise level range. Workers exposed to this range of noise levels were not using hearing protection device at the time of data collection, so the data provide a reliable dose-response relationship. For $L_{EX,8h}$ higher than 95 dB (A), Equation 6 provided a reasonable interpolation (18).

Measurement personnel shall pay attention to their hearing protection during the filed measurement and investigation. Measuring the C-weighted equivalent sound pressure level is recommended to select effective hearing protectors for measurement personnel and noise-exposed workers based on a standard in China (i.e. Guideline for selection of hearing protectors, GB/T 23466).

Discussion

Studies have validated the adjustment methods for noise energy using kurtosis (12, 14, 15, 17, 19). Based on the definition of cumulative noise exposure (CNE) containing exposure duration and exposure level, there are two adjustment protocols; one is to adjust the exposure duration in CNE, and another is to adjust the noise exposure level, $L_{EX,8h}$ or $L_{EX,40h}$. This guideline does not include the adjustment of CNE. Although CNE is related to the prevalence of occupational hearing loss, its relationship with a specific degree of hearing loss, such as noise-induced permanent threshold shift (NIPTS), is unclear. In addition, the exposure duration (T) in CNE is calculated by years, and it is difficult to accurately investigate the exposure duration due to the frequent changes in workers' jobs and tasks.

This draft guideline must address several critical issues based on previous studies and literature reviews. (1) The validity of kurtosis to reflect noise's temporal structure: evidence shows that kurtosis can quantify the impulsiveness of complex noise and is much more practical as a specific metric for the temporal structure of complex noise (12, 21); (2) The validity of the adjustment protocol applies kurtosis to adjust the noise intensity: Formula 6 regarding the calculation of $L_{EX,8h}$-K is developed based on our human study results (18) and Goley's protocol from animal data (23). The λ value of 4.02 proposed by Goley is adjusted to 6.5, obtained from the multiple linear regression results from human data. After the adjustment of $L_{EX,8h}$ by kurtosis, we found that the underestimation of NIPTS346 by ISO 1999 improved. (3) The basis of the measurement procedures for non-Gaussian noise. The measurement procedures regarding field investigation, determination of sampling subjects, and dosimeter wearing were developed based on the "Measurement of Physical Agents in the workplace-Part 8: noise (GBZ/T 189.8)" in China, which is based on the "Acoustics-Determination of occupational noise exposure-engineering method (20)." In addition, measurement methods of non-Gaussian noise using individual sampling were developed based on our previous studies (12–19). The direct reading method of kurtosis and $L_{EX,8h}$-K values is the preferred method in the future if the dosimeter with kurtosis function becomes commercially available. The prototype of the dosimeter with kurtosis function has been developed successfully in China.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

MZ: conceptualization, funding acquisition, and writing–original draft. YH: methodology and visualization. WQ: methodology. XG: funding acquisition. AZ, ZS, and JX: literature retrieval. SB and XS: conceptualization, writing–review & editing, and supervision. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Risk of functional disability associated with solid fuel use and population impact of reducing indoor air pollution in China: A national cohort study

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Background: In China, numerous people still rely on solid fuel for household use. To date, the association between household solid fuel use and functional disability, and what benefit reducing household solid fuel usage could bring at the population level to China remain unclear.

Method: Data were from the China Health and Retirement Longitudinal Study. Household fuel was classified as clean or solid for cooking or heating. Functional disability was defined as difficulties in any item of activities of daily living (ADL) or instrumental activities of daily living (IADL). The associations of household fuel use in 2011 and its transitions between 2011 and 2013 with subsequent ADL or IADL disability were assessed with Cox proportional-hazards models. The number of events prevented in a population (NEPP) was generated to estimate how many functionally disabled patients could be prevented by reducing solid fuel usage.

Results: A total of 6,216 and 9,716 participants without prior ADL or IADL disability in 2011 were included. Solid (vs. clean) fuel users were more likely to develop ADL and IADL disability, with hazard ratios (HRs) and 95% confidence intervals (CIs) of 1.37 (1.28~1.45) and 1.38 (1.31~1.46) for using both solid cooking and heating fuel. Furthermore, participants that switched heating fuel from solid to clean (vs. keep solid) were about 20% less likely to develop functional disability. Cooking fuel use switching from solid to clean (vs. keep solid) was also negatively associated with IADL disability (HR = 0.84, 95% CI 0.74~0.96). Over the next 7 years, raising clean fuel usage to 80% could prevent about 4.9 million ADL disability and 2.6 million IADL disability among Chinese aged 45 and older.

Conclusion: Household solid fuel use was a risk factor for functional disability. Reducing solid fuel usage could help reduce the burden of functional disability in the current aging society of China.

KEYWORDS

household fuel, solid fuel, indoor air pollution, functional disability, activity of daily living, instrumental activity of daily living

Introduction

Population aging is now a significant global public health concern (1). Functional disability (FD), defined as limitations in activities of daily living (ADL) or instrumental activities of daily living (IADL), is significantly associated with aging and has reached a staggering proportion these years, with around 110 million individuals experiencing significant difficulties in functioning according to the World Health Survey (2–5). In recent years, it has also been discovered that air pollution can speed up aging and lead to FD (6, 7).

Indoor air pollution from the burning of household solid fuel for cooking and heating has received increasing attention recently (8–10). Although the Sustainable Development Goals (SDGs) seven issued by the United Nations calls for universal access to clean energy (11), there are still around 450 million people heavily relying on solid fuel for household requirements in China, especially the elderly and rural residents (12–14). Given the elderly typically spend the majority of their time indoors, their health is more likely to be impaired by prolonged exposure to indoor air pollution (15, 16).

Previous studies have found significant associations of solid fuel use with cognitive decline, visual impairment, and depression, all of which are risk factors for FD (17–19). Once functionally disabled, the elderly may spend more time indoors and be exposed to air pollution for longer, which may in turn aggravate their FD. Two cross-sectional studies have demonstrated associations of solid cooking fuel use with FD (20, 21). Wang et al. (22) also conducted a longitudinal study and found that using solid heating fuel was a risk factor for FD. However, limited studies have comprehensively investigated the longitudinal associations of household solid fuel use and its transition to cleaner with the occurrence and aggravation of FD.

To address this research gap, we hypothesize that long-term solid household fuel use is a risk factor for new-onset FD and that switching from solid to clean fuel can help prevent FD in middle-aged and elderly Chinese and conducted this study. Furthermore, we estimated how many potential FD cases could be prevented by abating indoor air pollution from household solid fuel.

Method

Study population

This study used data from the 2011–2018 China Health and Retirement Longitudinal Study (CHARLS), a nationally representative survey of adults aged 45 years and older from 450 villages/urban communities across China using a multistage probability sampling method (23). The national baseline survey of the CHARLS was conducted in 2011, with follow-ups in 2013, 2015, and 2018. Information on sociodemographic characteristics and health status were collected in each wave. Ethical approval was granted by the Institutional Review Board at Peking University. Each respondent has signed the written informed consent.

We enrolled participants with complete information on household cooking and heating fuel use, ADL/IADL at baseline, and at least two observations of ADL/IADL in the 2013, 2015, and 2018 waves for trajectory analyses. To investigate the long-term association between household fuel use in 2011 and new-onset ADL/IADL disability between 2011 and 2018, participants aged 45 years or older, with complete data on cooking and heating fuel use and covariates, and free of ADL/IADL disability at baseline were enrolled. To investigate the association of fuel use transition from 2011 to 2013 with subsequent new-onset ADL/IADL disability, we further excluded participants with incomplete information on cooking and heating fuel in 2013 or who had ADL/IADL disability before 2013 (Figure 1).

FD assessment

In CHARLS, FD was assessed by ADL and IADL, which was derived from the participants' self-reported difficulty in the six ADL items (dressing, bathing, eating, getting into/out of bed, toileting, and controlling urination and defecation) and the five IADL items (meal preparation, shopping, doing housework, taking medicines and managing money) (2, 3). Each item had four answers, including "have no difficulty," "have difficulty but can still do," "have difficulty and need help," and "cannot do." Participants who reported difficulty in any of the six ADL items (or five IADL items) were defined as ADL/IADL disability.

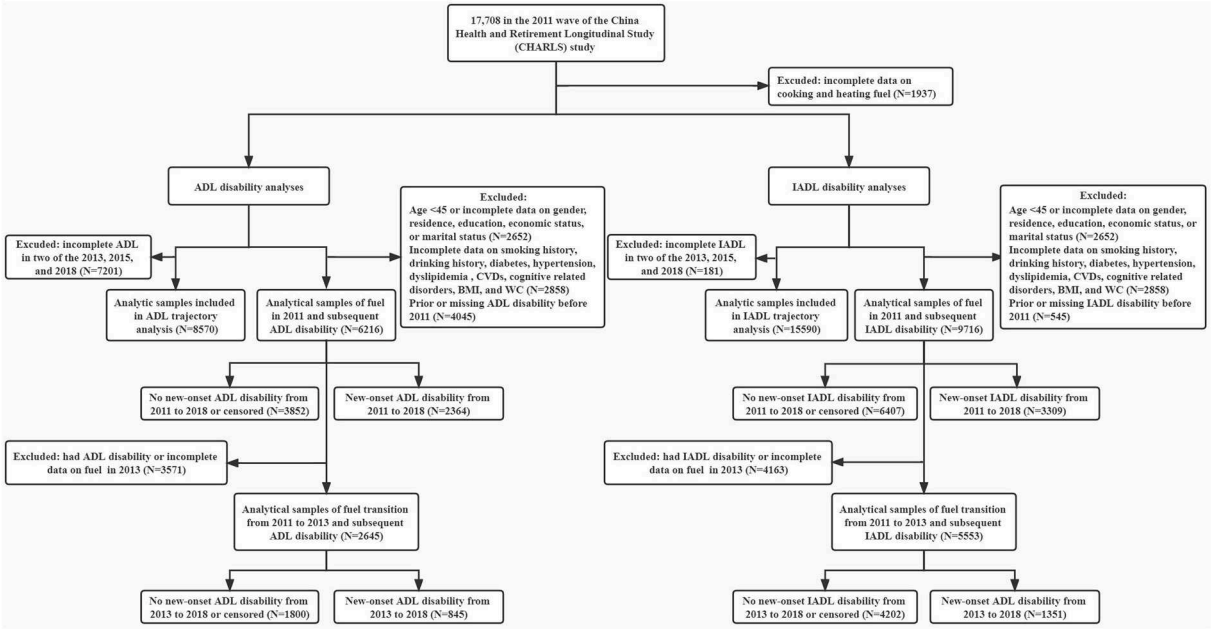

FIGURE 1
Flow chart. ADL, activity of daily living; IADL, instrumental activity of daily living; CVD, cardiovascular disease; BMI, body mass index; WC, waist circumference.

Furthermore, ADL/IADL disability were scored at each wave corresponding to the number of ADL/IADL items participants reported difficulty in. Accordingly, the sum of scores ranges from 0 to 6 and 0 to 5 for ADL/IADL disability.

Household fuel usage

The CHARLS asked participants "What is the main source of cooking fuel/ heating energy?" Cooking and heating fuel was classified into clean fuel (i.e., solar, natural gas, marsh gas, liquefied petroleum gas, or electric) and solid fuel (i.e., coal, crop residue, and wood) in 2011 and 2013 (12, 19). The cooking and heating fuel use was denoted as "Both clean," "Cooking clean and heating solid," "Cooking solid and heating clean," and "Both solid." We further named the cooking and heating fuel use as "Both clean," "1 solid," and "Both solid" in analysis on household fuel use transition from 2011 to 2013.

Covariates

Information on age, sex (male, female), residence (urban, rural), education (less than primary school, primary school, middle school, high school or above), marital status (married or cohabiting, single; "single" included participants who were separated from spouses, divorced, widowed, or unmarried), smoking history (never smoking, ever smoking), drinking history (never drinking, ever drinking), and cognitive-related disorders (no, yes) was collected through face-to-face interviews at baseline. Household economic status was assessed by the natural logarithm of per capita expenditures [ln (PCE)] and was categorized as bottom, middle, and top tertilec (24, 25).

Physical measurements, medical history, and blood biomarkers were recorded at baseline. Body mass index (BMI) status was divided into normal weight (BMI < 24.0 kg/m^2), overweight (24 kg/m^2 $\leq$ BMI < 28.0 kg/m^2), and obesity (BMI ≥ 28.0 kg/m^2). Waist circumference (WC) was defined as continuous. Hypertension was defined as blood pressure$\geq$ 140/90 mmHg and/or self-reported diagnosis or treatment (26). Diabetes was defined as fasting plasma glucose $\geq$7.0 mmol/L, and/or random plasma glucose $\geq$11.1 mmol/L, and/or HbA1c $\geq$ 6.5%, and/or self-reported diagnosis or treatment (27). Dyslipidemia was defined as self-reported diagnosis or treatment, and/or total cholesterol (TC) $\geq$ 240 mg/dL, and/or low-density lipoprotein cholesterol (LDL-C) $\geq$ 160 mg/dL, and/or high-density lipoprotein cholesterol (HDL-C) $\leq$ 40 mg/dL, and/or triglycerides (TG) $\geq$ 200 mg/dL (28). Cardiovascular diseases (CVDs) and cognitive-related diseases were defined by self-reported diagnoses.

Statistical analysis

The developmental trajectories of ADL/IADL disability scores from 2011 to 2018 were conducted by group-based trajectory modeling (GBTM), which can identify distinct groups of individuals with similar trajectories of a specific feature

(29–31). Models were estimated with two to five groups and the best fitting model was selected with the lowest values of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (Supplementary Table 1). The Chi-square test was further adopted to compare the household fuel among different trajectory groups.

The baseline characteristics of included participants were described as medians and interquartile ranges (IQRs) for continuous variables, and frequency and percent (%) for categorical variables. Wilcoxon rank sum tests for continuous variables and Chi-square tests for categorical variables were utilized to calculate *P*-values.

The Cox proportional-hazards model was used to investigate the association [hazard ratio (HR) and 95% confidence interval (CI)] of the cooking and heating fuel use in 2011 with new-onset ADL/IADL disability between 2011 and 2018 after adjusting for age, sex, residence, education, economic status, marital status, smoking history, drinking history, BMI status, WC, diabetes, hypertension, dyslipidemia, CVDs, and cognitive-related diseases in participants without ADL/IADL disability in 2011. The time to event was calculated as the intervals from the baseline survey dates (2011 to 2012) to the dates of the interview reporting an incident FD, death, loss of follow-up, or the end of follow-up (2013, 2015, or 2018), whichever came first. Mixed cooking and heating fuel use was further estimated using the floating absolute risk, which allows comparisons between any two exposure groups and can decrease undesired correlation between coefficients (32–34). Given the high usage of solid household fuel in rural areas, sex differences in exposure to solid fuel, and the pronounced hazards in the elderly, age- (<65 and ≥ 65), sex- (male and female), and residence-stratified (urban and rural) Cox proportional-hazards models were also conducted. To ensure the robustness of our results, sensitivity analysis was further conducted in individuals with no main chronic diseases. Considering that the time scales we used were not exact to a specific date, we also conducted a sensitivity analysis using logistic regression to verify the robustness of our conclusion. Furthermore, fully adjusted Cox proportional-hazard models and the floating absolute risk were also used to investigate the association of transition of household fuel use from 2011 to 2013 with subsequent new-onset ADL/IADL disability in participants without ADL/IADL disability in 2013, with time to event from the 2013 survey dates to the dates of the interview reporting an incident FD, death, loss of follow-up, or the end of follow-up (2015 or 2018), whichever came first.

Finally, we used the number of events prevented in a population (NEPP) to estimate the number of ADL/IADL disability cases that could be prevented over the next 7 years among the population aged 45 and above by reducing solid fuel. The NEPP describes the impact of interventions and can be used to estimate the incremental impact of moving from current to best practice (35, 36). The calculation formula is $NEPP = n \times Id \times Pe \times r_u \times HRR$, where $n =$ population size of aged 45 years and above, Id = incidence density of FD from 2011 to 2018, Pe = the proportion eligible for intervention, r_u = the risk of FD in the group using solid fuel, and HRR = the hazard ratio reduction associated with the intervention, which was calculated as $(r_u - 1)/r_u$. In order to reflect the incremental effect of changing from current to 'best' practice and to adjust for levels of compliance in the proportion eligible for intervention, Pe was calculated as $(Pb - Pt) \times Pc$, where Pt = the proportion currently intervened, Pb = the proportion that would be intervened if best practice was adopted, and Pc = the proportion of the population who are adherent to their intervention. The data on population size of those aged 45 years and above (n) in 2020 were obtained from China Statistical Yearbook 2021 (37). Best practice intervention goals (Pb) were taken as 80% for clean fuel usage according to China's clean energy policy (38), and compliance with each intervention of clean fuel usage (Pc) was assumed to be 50%. Other indicators originated from our own study.

Reporting of this study was done in accordance with Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. Analyses were performed using R statistical software version 4.1.2 (R Project for Statistical Computing) and STATA statistical software (version 15.0, STATA Corp). All analyses were two-sided, and a *P*-value of <0.05 or a 95% CI that did not cross 1.00 was considered statistically significant.

Results

Eight thousand five hundred and seventy and 15,590 participants were included to identify the developmental trajectories of ADL/IADL disability scores between 2011 and 2018. The two distinct trajectories that best characterized the developmental courses of FD scores were finally selected and labeled as "Maintained low ADL/IADL score" and "Increasing ADL/IADL score" (Supplementary Figures 1, 2). Supplementary Tables 2, 3 show that solid fuel (vs. Clean) users were more likely to develop FD (all *P* Value < 0.001).

A total of 6,216 and 9,716 participants without prior ADL/IADL disability before 2011 were included, of whom 2,364 (38.0%) and 3,309 (34.1%) developed new-onset ADL/IADL disability during 2011 and 2018. The geographic distributions of the included participants are shown in Supplementary Figures 3, 4. The baseline characteristics of the included participants categorized by new-onset FD status are described in Supplementary Tables 4, 5.

The associations of household fuel used in 2011 with new-onset FD between 2011 and 2018 are shown in Tables 1, 2. Solid (vs. clean) cooking fuel users were more likely to develop incident ADL/IADL disability, with fully adjusted HRs (95% CIs) of 1.14 (1.04∼1.26) and 1.27 (1.17∼1.38). Participants who used solid heating fuel (vs. clean) were also 1.28 and

TABLE 1 HR (95% CI) of fuel usage with new-onset ADL disability: Cox proportional-hazards model.

	Total population ($N = 6,216$)	Age-stratified			Sex-stratified			Residence-stratified		
		Age < 65 ($N = 4,417$)	Age ≥ 65 ($N = 1,799$)	P for interaction	Male ($N = 2,714$)	Female ($N = 3,502$)	P for interaction	Rural ($N = 4,316$)	Urban ($N = 1,900$)	P for interaction
Cooking fuel				0.806			0.365			0.126
Clean	Reference	Reference	Reference		Reference	Reference		Reference	Reference	
Solid	1.14 (1.04∼1.26)	1.12 (1.00∼1.25)	1.16 (0.98∼1.37)		1.20 (1.03∼1.40)	1.10 (0.98∼1.25)		1.09 (0.97∼1.22)	1.24 (1.06∼1.45)	
Heating fuel				0.378			0.061			0.048
Clean	Reference	Reference	Reference		Reference	Reference		Reference	Reference	
Solid	1.28 (1.14∼1.45)	1.26 (1.09∼1.46)	1.26 (1.03∼1.56)		1.50 (1.23∼1.84)	1.17 (1.01∼1.36)		1.16 (0.99∼1.37)	1.42 (1.19∼1.70)	
Cooking and heating fuel				0.749			0.055			0.158
Both clean	1.00 (0.88∼1.14)	1.00 (0.86∼1.17)	1.00 (0.80∼1.25)		1.00 (0.81∼1.23)	1.00 (0.85∼1.18)		1.00 (0.83∼1.21)	1.00 (0.85∼1.18)	
Cooking clean and heating solid	1.25 (1.14∼1.36)	1.27 (1.14∼1.41)	1.15 (0.98∼1.34)		1.29 (1.12∼1.49)	1.22 (1.10∼1.37)		1.07 (0.95∼1.20)	1.36 (1.19∼1.55)	
Cooking solid and heating clean	1.04 (0.83∼1.29)	1.08 (0.82∼1.41)	0.92 (0.64∼1.33)		0.68 (0.43∼1.07)	1.22 (0.95∼1.57)		0.91 (0.70∼1.18)	1.01 (0.68∼1.51)	
Both solid	1.37 (1.28∼1.45)	1.33 (1.24∼1.44)	1.33 (1.20∼1.49)		1.50 (1.37∼1.65)	1.29 (1.19∼1.39)		1.16 (1.10∼1.23)	1.57 (1.39∼1.77)	

ADL, activities of daily living; HR, hazard ratio; CI, confidence interval; HR was adjusted for age, sex (male or female), residence (urban or rural), education (less than primary school, primary school, middle school, or high school or above), economic status (poor, middle, or rich), marital status (married or cohabiting, or single), smoking history (never smoking or ever smoking), drinking history (never drinking or ever drinking), body mass index status (normal weight, overweight, or obesity), waist circumference, diabetes (yes or no), hypertension (yes or no), dyslipidemia (yes or no), cardiovascular diseases (yes or no), and cognitive-related disorders (yes or no).

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TABLE 2 HR (95% CI) of fuel usage with new-onset IADL disability: Cox proportional-hazards model.

	Total population ($N = 9716$)	Age-stratified			Sex-stratified			Residence-stratified		
		Age < 65 ($N = 7495$)	Age ≥ 65 ($N = 2221$)	P for interaction	Male ($N = 5043$)	Female ($N = 4673$)	P for interaction	Rural ($N = 6441$)	Urban ($N = 3275$)	P for interaction
Cooking fuel				0.021			0.338			0.079
Clean	Reference	Reference	Reference		Reference	Reference		Reference	Reference	
Solid	1.27 (1.17∼1.38)	1.32 (1.20∼1.45)	1.15 (0.99∼1.34)		1.30 (1.15∼1.46)	1.25 (1.13∼1.39)		1.22 (1.10∼1.34)	1.37 (1.19∼1.56)	
Heating fuel				0.394			0.005			0.827
Clean	Reference	Reference	Reference		Reference	Reference		Reference	Reference	
Solid	1.21 (1.10∼1.33)	1.23 (1.10∼1.39)	1.17 (0.98∼1.40)		1.41 (1.21∼1.65)	1.08 (0.95∼1.23)		1.21 (1.06∼1.38)	1.20 (1.03∼1.39)	
Cooking and heating fuel				0.154			0.005			0.337
Both clean	1.00 (0.90∼1.11)	1.00 (0.88∼1.13)	1.00 (0.82∼1.22)		1.00 (0.85∼1.18)	1.00 (0.87∼1.15)		1.00 (0.85∼1.17)	1.00 (0.87∼1.15)	
Cooking clean and heating solid	1.08 (1.00∼1.16)	1.08 (0.99∼1.18)	1.09 (0.95∼1.25)		1.17 (1.04∼1.31)	1.01 (0.92∼1.12)		1.10 (1.00∼1.22)	1.03 (0.91∼1.16)	
Cooking solid and heating clean	1.15 (0.98∼1.35)	1.18 (0.97∼1.44)	1.05 (0.79∼1.39)		0.89 (0.67∼1.18)	1.33 (1.09∼1.62)		1.13 (0.93∼1.37)	1.16 (0.87∼1.55)	
Both solid	1.38 (1.31∼1.46)	1.43 (1.35∼1.52)	1.26 (1.14∼1.39)		1.52 (1.40∼1.64)	1.28 (1.20∼1.37)		1.34 (1.27∼1.41)	1.46 (1.31∼1.62)	

ADL, activities of daily living; IADL, instrumental activities of daily living; HR, hazard ratio; CI, confidence interval. HR was adjusted for age, sex (male or female), residence (urban or rural), education (less than primary school, primary school, middle school, or high school or above), economic status (poor, middle, or rich), marital status (married or cohabiting, or single), smoking history (never smoking or ever smoking), drinking history (never drinking or ever drinking), body mass index status (normal weight, overweight, or obesity), waist circumference, diabetes (yes or no), hypertension (yes or no), dyslipidemia (yes or no), cardiovascular diseases (yes or no), and cognitive-related disorders (yes or no).

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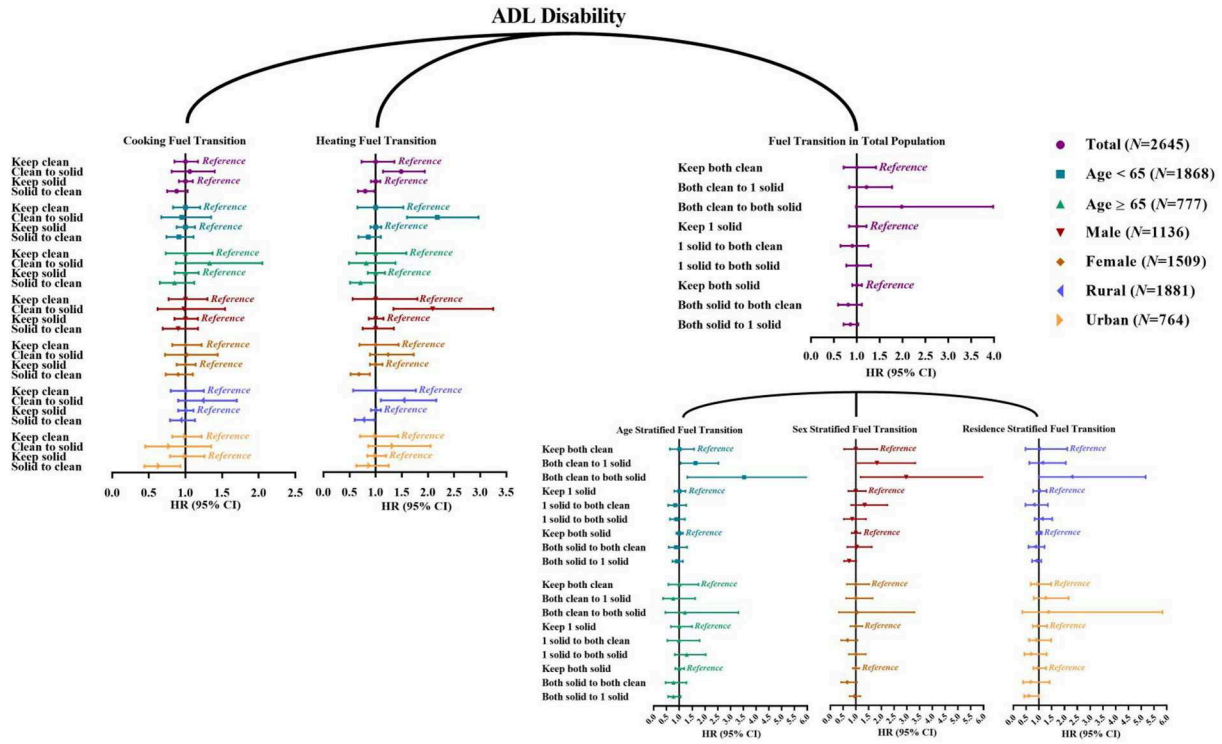

FIGURE 2
Hazard ratio (95% confidence interval) of fuel usage transitions with new-onset ADL disability: Cox proportional-hazards model. ADL, activities of daily living. The reference of "Clean to solid" is "Keep clean;" the reference of "Solid to clean" is "Keep solid;" the reference of "Both clean to 1 solid" and "Both clean to both solid" is "Keep both clean;" the reference of "1 solid to both clean" and "1 solid to both solid" is "Keep 1 solid;" the reference of "Both solid to both clean" and "Both solid to 1 solid" is "Keep both solid".

1.21 times more likely to develop new-onset ADL and IADL, respectively. For those using clean cooking fuel but solid heating fuel, the risks of ADL/IADL disability were elevated by 25% (HR = 1.25, 95% CI 1.14∼1.36) and 8% (HR = 1.08, 95% CI 1.00∼1.16). Furthermore, individuals who used both solid fuel (vs. both clean) demonstrated approximate 1.4 times higher risks of incident FD. In the age-, sex-, residence-stratified analyses, we found that the associations of fuel use with ADL were not modified by age and sex, while a stronger association between using solid heating fuel and ADL was observed among those who lived in urban area than that in rural area. We also found the associations of fuel use with IADL were not modified by residence, while stronger associations of using solid cooking fuel with IADL were observed among those who <65 than ≥65 and of using solid heating fuel with IADL among males than females. In the sensitivity analysis where we restricted to those without previous main chronic diseases (Supplementary Table 6), the associations were generally attenuated and turn to be non-statistically significant compared to the results from primary analysis. In Supplementary Table 7, the logistic regression of fuel usage in 2011 with new-onset ADL and IADL disability from 2011 to 2018 showed similar results in line with our primary analysis.

Supplementary Figures 5, 6 presented the household fuel use transition from 2011 to 2013 in participants without ADL/IADL disability before 2013 and their follow-up status between 2013 and 2018. Baseline characteristics of these participants were also described in Supplementary Tables 8, 9. We found that heating fuel use switching from clean to solid (vs. keep clean) was significantly associated with incident ADL disability (HR = 1.49, 95% CI 1.14∼1.94). In contrast, individuals with the transition from heating solid to clean (vs. keep solid) were less likely to develop ADL disability (HR = 0.80, 95% CI 0.66∼0.98). For cooking fuel usage, significant association was found of transition from solid to clean (vs. keep solid) with a decreased risk of new-onset ADL disability among urban residents (Figure 2; Supplementary Table 10). We also observed a significant association of household fuel usage switching from both clean to 1 solid and to both solid (vs. keep both clean) with new-onset ADL disability among those aged <65 years, with HRs (95%CIs) of 1.63 (1.05∼2.53) and 3.53 (1.31∼9.53). In terms of IADL, cooking fuel use switching from clean to solid (vs. keep clean), heating fuel usage switching from clean to solid (vs. keep clean), transition from both clean to 1 solid (vs. keep both clean), and from 1 solid to both solid (vs. keep 1 solid) were positively associated with incident IADL disability,

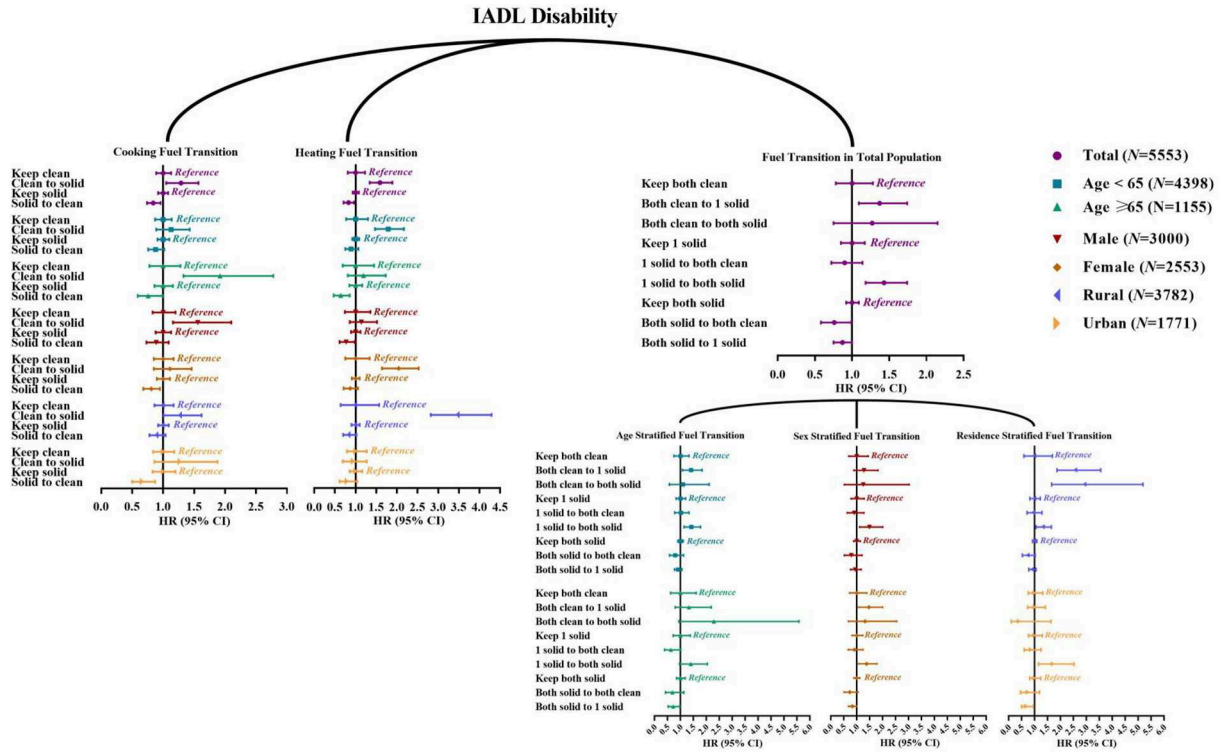

FIGURE 3
Hazard ratio (95% confidence interval) of fuel usage transitions with new-onset IADL disability: Cox proportional-hazards model. IADL, instrumental activities of daily living. The reference of "Clean to solid" is "Keep clean;" the reference of "Solid to clean" is "Keep solid;" the reference of "Both clean to 1 solid" and "Both clean to both solid" is "Keep both clean;" the reference of "1 solid to both clean" and "1 solid to both solid" is "Keep 1 solid;" the reference of "Both solid to both clean" and "Both solid to 1 solid" is "Keep both solid".

while cooking fuel usage switching from solid to clean (vs. keep solid), heating fuel usage switching from solid to clean (vs. keep solid), transition from both solid to 1 solid (vs. keep both solid), and from both solid to both clean (vs. keep both solid) were negatively associated with incident IADL disability (Figure 3; Supplementary Table 11).

Finally, the NEPP for incident FD are shown in Table 3. By increasing clean cooking fuel usage up to 80%, about 0.9 million aged <65, 0.9 million aged ≥65, 1.3 million males, 0.6 million females, 0.4 million urban residents, 1.4 million rural residents, and a total of 1.8 million people aged 45 and older could be prevented from ADL disability over the next 7 years. In terms of heating fuel usage, up to 4.9 million cases of ADL disability would be prevented. Moreover, 2.2 million and 2.6 million patients with IADL disability could be prevented under the same goal for cooking and heating fuel usage. Even if the compliance with the intervention was reduced to 50%, the number of individuals able to be prevented could reach half of the ideal goal.

Discussion

In this longitudinal population-based study, we found that exposure to solid cooking fuel, solid heating fuel, and both of them were positively associated with incident FD. We also found that cooking and heating fuel use switching from clean to solid was a risk factor for incident FD while switching from solid to clean was associated with decreased risks of FD. Additionally, our results showed that reducing solid cooking fuel usage could prevent about 1.8 million and 2.2 million patients aged 45 and older with ADL/IADL disability in the 7-year follow-up. As for reducing solid heating fuel usage, 4.9 million ADL disability and 2.6 million IADL disability could be prevented.

Our findings are in accordance with and extend results from previous studies of household solid fuel use in association with FD. Though several studies have investigated the association between solid fuel use and FD (20–22), their findings were limited by the cross-sectional study design or the incomplete definition of household fuel.

In households with little access to clean fuels, solid fuels are usually burned in inefficient combustion devices like traditional stoves, in which solid fuels are hard to fully burn (39). The incomplete combustion emits kinds of hazardous pollutants such as nitrogen dioxide, carbon monoxide, and volatile organic compounds (40, 41). Long-term exposure to these toxic pollutants, however, may increase inflammatory cytokines in systemic circulation and affect the central nervous system, leading to cognitive decline and depression (42, 43).

TABLE 3 Number of cases of ADL or IADL that could be prevented when prevalence levels of "clean fuel usage for up to 80%" in a Chinese population.

Outcome	Stratified population	N /10^5	Id /10^5	Pb	Pt	Pc	Pe	ru	HRR	NEPP
ADL	**Cooking fuel**									
	Age-stratified									
	<65	4101.72907	8473.824	0.80	0.361	0.50	0.219	1.12	0.107	914765.837
	≥65	1906.3528	11634.349	0.80	0.313	0.50	0.243	1.16	0.138	863817.863
	ALL	6008.082	9377.475	0.80	0.347	0.50	0.226	1.14	0.123	1784928.598
	Sex-stratified									
	Male	2974.94668	9000.188	0.80	0.328	0.50	0.236	1.20	0.167	1264942.695
	Female	3033.13519	9651.401	0.80	0.363	0.50	0.219	1.10	0.091	639956.940
	All	6008.082	9377.475	0.80	0.347	0.50	0.226	1.14	0.123	1784928.598
	Residence-stratified									
	Rural	2517.21544	22013.898	0.80	0.242	0.50	0.279	1.09	0.083	1390380.709
	Urban	3490.8664	3909.220	0.80	0.586	0.50	0.107	1.24	0.194	350579.734
	All	6008.082	9377.475	0.80	0.347	0.50	0.226	1.14	0.123	1784928.589
	Heating fuel									
	Age-stratified									
	<65	4101.72907	8473.824	0.80	0.177	0.50	0.311	1.26	0.206	2813183.793
	≥65	1906.3528	11634.349	0.80	0.170	0.50	0.315	1.26	0.206	1816746.498
	All	6008.082	9377.475	0.80	0.175	0.50	0.312	1.28	0.219	4927968.813
	Sex-stratified									
	Male	2974.94668	9000.188	0.80	0.164	0.50	0.318	1.50	0.333	4258686.396
	Female	3033.13519	9651.401	0.80	0.184	0.50	0.308	1.17	0.145	1532542.950
	All	6008.082	9377.475	0.80	0.175	0.50	0.312	1.28	0.219	4927968.813
	Residence-stratified									
	Rural	2517.21544	22013.898	0.80	0.114	0.50	0.343	1.16	0.138	3039897.168
	Urban	3490.8664	3909.220	0.80	0.314	0.50	0.243	1.42	0.296	1393584.560
	All	6008.082	9377.475	0.80	0.175	0.50	0.312	1.28	0.219	4927968.789
IADL	**Cooking fuel**									
	Age-stratified									
	<65	4101.72907	6015.909	0.80	0.421	0.50	0.189	1.32	0.242	1495817.808
	≥65	1906.3528	10035.143	0.80	0.330	0.50	0.235	1.15	0.130	674944.430
	All	6008.082	6869.944	0.80	0.400	0.50	0.200	1.27	0.213	2227714.687
	Sex-stratified									
	Male	2974.94668	5687.722	0.80	0.398	0.50	0.201	1.30	0.231	1021574.153
	Female	3033.13519	8208.394	0.80	0.403	0.50	0.198	1.25	0.200	1235151.699
	All	6008.082	6869.944	0.80	0.400	0.50	0.200	1.27	0.213	2227714.687
	Residence-stratified									
	Rural	2517.21544	7481.164	0.80	0.286	0.50	0.257	1.22	0.180	1065519.839
	Urban	3490.8664	5664.797	0.80	0.625	0.50	0.087	1.37	0.270	638684.062
	All	6008.082	6869.944	0.80	0.400	0.50	0.200	1.27	0.213	2227714.676
	Heating fuel									
	Age-stratified									
	<65	4101.72907	6015.909	0.80	0.214	0.50	0.293	1.23	0.187	1662241.873
	≥65	1906.3528	10035.143	0.80	0.184	0.50	0.308	1.17	0.145	1001832.064
	All	6008.082	6869.944	0.80	0.207	0.50	0.296	1.21	0.174	2568712.203

(Continued)

TABLE 3 (Continued)

Outcome	Stratified population	N /10^5	Id /10^5	Pb	Pt	Pc	Pe	ru	HRR	NEPP
	Sex-stratified									
	Male	2974.94668	5687.722	0.80	0.202	0.50	0.299	1.43	0.301	2173976.019
	Female	3033.13519	8208.394	0.80	0.213	0.50	0.294	1.12	0.107	877533.463
	All	6008.082	6869.944	0.80	0.207	0.50	0.296	1.21	0.174	2568712.203
	Residence-stratified									
	Rural	2517.21544	7481.164	0.80	0.136	0.50	0.332	1.20	0.167	1251319.736
	Urban	3490.8664	5664.797	0.80	0.348	0.50	0.226	1.21	0.174	937756.818
	All	6008.082	6869.944	0.80	0.207	0.50	0.296	1.21	0.174	2568712.190

N, population size of Chinese aged 45 years and above in 2020; Id, incidence density of functional disability in the population from 2011 to 2018; Pb, proportion be intervened when best practice adopted; Pt, proportion of those with the disability currently receiving intervention; Pc, compliance with intervention; Pe, proportion eligible for intervention; ru, risk of functional disability in the solid fuel usage group; HRR, hazard ratio reduction; NEPP, number of events prevented in the population.

These nervous impairments will subsequently cause a loss of hand-grip strength (44) and accelerate frailty (45). All of these disorders, if not treated well, can finally lead to FD, especially in older adults (46–48).

Noteworthy, switching from solid to clean household fuel was negatively associated with new-onset FD, implying that reducing solid household fuel use may effectively prevent FD. In March 2022, the Chinese government introduced a 5-year plan on elderly care, emphasizing the importance of preventing FD in older adults (49). This study provides population-based evidence for policymakers and highlights the benefits of reducing household solid fuel for FD prevention. In other words, we urge the government to elevate the usage of clean fuel to 80% in houses to prevent potential FD.

To the best of our knowledge, we are the first to investigate the longitudinal associations of household fuel use and its transition with new-onset FD in China. We employed GBTM, Cox proportional-hazards models, floating absolute risk, and sensitivity analysis to conclude that solid cooking and heating fuel use was positively associated with the onset and exacerbation of FD. These statistical methods ensure the accuracy and comprehensiveness of our conclusions. Furthermore, we found that reducing solid household fuel can effectively prevent FD, which may provide valuable evidence for the reduction of the FD burden and the implementation of relevant policies.

Limitations

Our study has several limitations. Firstly, we excluded a considerable proportion of participants at baseline due to missing data, which might have caused selection bias and affected the representativeness of our findings. Furthermore, indoor air pollution in this study was only assessed by the use of solid cooking and heating fuel, there might be other indoor pollutants that possess adverse health effects. Given that the ascertainments of fuel usage and FD were self-reported, potential misclassification might result in either an overestimation or an underestimation of the association between the two. For instance, the HR (95% CI) would be underestimated if participants with new-onset FD incorrectly reported being healthy. Some potential risk factors that may contribute to FD, such as cognitive function and trauma, were not included in this study owing to limited sample size or data constraints. Finally, due to data limitations, we only considered the fuel transition from 2011 to 2013, the subsequent transition between 2013 and 2018 was not assessed.

Conclusion

In this cohort study, we found that solid cooking and heating fuel use was positively associated with the occurrence and exacerbation of FD. Switching from solid to clean household fuel, on the other hand, could significantly prevent FD, which emphasized the importance of universal access to clean energy advocated by the SDGs 7 and provided a viable direction for the development of healthy aging.

Data availability statement

Publicly available datasets were analyzed in this study. This can be found here: http://charls.pku.edu.cn.

Ethics statement

Ethical review was approved by the Institutional Review Board at Peking University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PS and JL designed the study. ZR, LH, and SZ managed and analyzed the data. ZR and SS prepared the first draft. WS and ZR reviewed and edited the manuscript, with comments from PS, JL, CG, YW, and QY. PS had full access to the data and gave final approval of the submitted versions. All authors were involved in revising the paper, contributed to the article, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.976614/full#supplementary-material

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Prevalence status and associated factors of wrist postural injury in the Chinese occupational population

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Objective: This study investigated the prevalence of wrist injuries in 15 industries and different types of work in China. Study on the associated factors of wrist injuries provides a scientific basis for prevention and treatment of wrist diseases in occupational workers.

Methods: A cross-sectional study of musculoskeletal symptoms of related practitioners in 15 industries, including automobile manufacturing, was conducted to retrieve worker demographic information, working wrist posture, and pain conditions. Multivariable binary logistic regression analyses were performed to identify factors associated with work-related musculoskeletal disorders (WMSDs).

Results: The prevalence of wrist injuries among the study population was 13.2%. Toy manufacturing, animal husbandry, automobile manufacturing, shoe manufacturing, and biopharmaceutical manufacturing had the highest wrist injury rates at 29.1, 19.1, 14.9, 14.9, and 14.0%, respectively. Among the types

of jobs, enamel workers (63.0%), butchers (43.6%), combers (32.5%), welders (31.3%), and scaffolders (26.5%) had the highest prevalence rates. Based on the final multivariate logistic regression analysis: female [odds ratios (OR) = 1.24; 95% confidence interval (CI), 1.15–1.35], 6–10 years of service (OR = 1.11; 95% CI, 1.03–1.18), >10 years of service (OR = 1.15; 95% CI, 1.06–1.25), frequent upward and downward flexion in wrist posture at work (OR = 1.81; 95% CI, 1.84–2.11), and frequent wrist placement on the edge of angular objects increased the OR of injury (OR = 1.52; 95% CI, 1.44–1.61). Need to squeeze objects tightly while working (OR = 1.72; 95% CI, 1.57–1.89), prolonged wrist flexion (OR = 1.86; 95% CI, 1.75–1.97), and work hand position above the shoulder for prolonged periods (OR = 1.11; 95% CI, 1.04–1.19) also suggested the relationship between these factors and the higher prevalence of wrist injury in the workers. The associated factor was physical activity (OR = 0.86; 95% CI, 0.80–0.94).

Conclusion: This study suggested the relationship between these factors and the higher prevalence of wrist injury in the toy manufacturing, animal husbandry, automobile manufacturing, and shoe-making industries, enamel workers, butchers, and combers. And are work types that require special attention. Females, working age, physical activity, and abnormal posture of the wrist were factors significantly associated with WMSDs.

KEYWORDS

Chinese worker, wrist posture, wrist injury, damage, associated factors

Introduction

Work-related musculoskeletal disorders (WMSDs) are injuries or diseases of the muscles, nerves, tendons, joints, cartilage, and discs caused by work-related factors (1). Musculoskeletal pain is a widespread and expensive healthcare issue worldwide (2). Physical injuries are related to gradual damage to tissues and organs in the body (3). Additionally, WMSDs affect the body organs. The spinal vertebrae and hands are the most sensitive organs with risk of WMSDs (4). Wrist pain is a type of musculoskeletal disorder with an annual consultation prevalence of 0.058% in the UK, making it the fourth most common upper extremity pain site after the shoulders, hands, and elbows. Wrist pain is very common in people who perform daily manual labor and sports, but is less common in the general population and non-manual workers. Although wrist pain is less frequent than back, shoulder, hip, or knee pain, it makes up a significant amount of total strain on the musculoskeletal system (5, 6). Walker-Bone et al. showed that 10% of the general population have non-specific hand and wrist pain (6).

The total number of cases of work-related musculoskeletal diseases published on the UK Labor Department official website between 2021 and 2021 was 470,000, with a prevalence rate of 1,420 per 100,000 workers. Construction, human health, and social work activities have significantly higher prevalence rates than the overall industry average. Compared to all occupational groups, the prevalence of work-related musculoskeletal disorders was significantly higher among skilled workers, nurses, leisure workers, factory workers, and machine operators over a 3-year period (2018–2021). According to a 2019 survey in China, the prevalence of WMSDs in the total working population was 42.9%, with wrist pain accounting for 13.4% of the total population. The three industries with the highest prevalence of wrist diseases were toy manufacturing, animal husbandry, and biopharmaceutical manufacturing (7).

Current research indicates that age and female sex are associated factors for musculoskeletal disorders (8, 9); however, smokers and overweight people are also at increased risk of developing WMSDs (10). Lower socioeconomic status, including reductions in education, income, and occupation is associated with WMSDs (11), and work-related factors, such as night shifts, years of service (12), and physical exposure in the work environment are also associated factors for WMSDs (13).

High repetition can cause WMSDs, with or without the use of force. There are a number of different tissue types, such as bones, tendons, muscles, and loose connective tissue. Early discrete tissue injury initiates an acute inflammatory response that can be controlled by tissue healing under conditions of flow repetition and low effort or by more tissue damage. The musculoskeletal system can become overloaded by repetitive

motion, bad posture, and continuous excessive force, which increases the risk of developing WMSDs (14). The wrist is linked with longest absenteeism, which means that compared to other anatomical locations, the wrist is linked to a larger loss of productivity and earnings. Epidemiological studies have associated repeated and powerful hand-intensive jobs with onset and severity of hand and wrist WMSDs. When performing such duties in conditions of awkward wrist and forearm posture, severe low temperature, or vibration, these disorders deteriorate more quickly (15). China, as an industrialized country, has a large number of occupational workers and large base of WMSDs; however, more studies are still required to understand the illness state and associated factors for local occupational groups.

Through a survey of enterprise workers in key industries in China, this study found the prevalence of musculoskeletal diseases of the wrists of occupational workers in different industries, clarified the associated factors affecting wrist injuries, and provided a scientific basis for formulating corresponding measures for occupational workers' health.

Methods

Research design and themes

The study runs from 2018 to June 2021.This study adopted the stratified cluster sampling method to select all workers who were on duty and met the inclusion criteria from representative enterprises in key industries (16) in seven regions: North China, East China, Central China, South China, South-West China, North-West China, and North-East China. Inclusion criteria for the study participants was working experience of more than 1 year. Exclusion criteria include the following: congenital spinal deformity, non-WMSDs due to trauma, infectious diseases, malignant tumors, etc. Selection of key industries was based on representative industries that are closely related to the occurrence of WMSDs. We selected automobile manufacturing, footwear manufacturing, biopharmaceutical manufacturing, electronic equipment manufacturing, shipbuilding and related device manufacturing, petrochemical industry, construction industry, furniture manufacturing, coal mining and washing, animal husbandry, medical personnel, automobile 4S shops, vegetable greenhouses, civil aviation crews, toy manufacturing, and other 15 industries or working groups with a total of 64,052 individuals. A total of 61,034 questionnaires were received with a questionnaire response rate of 94.6%, and 57,501 valid questionnaires were received with a questionnaire response rate of 94.2%. A one-on-one face-to-face survey was used. The significance level (α) was 0.05, the confidence level (1–α) was 0.95, the allowable error (δ) was 0.023, and the proportion (p) was 0.2324, and the calculated sample size was 1,321.The sample size calculation formula is:

$$N = \left(\frac{Z_{1-\alpha}}{\delta}\right)^2 \times \mathrm{P} \times (1\text{-P})$$

Survey design

The ergonomic evaluation and analysis system for WMSDs developed by the study group, Occupational Protection and Ergonomics Research Office, Institute of Occupational Hygiene and Poison Control, Chinese Center for Disease Control and Prevention were used in this survey. The tool is one of the built-in questionnaires in the system, namely the electronic questionnaire system of "Chinese Version of Musculoskeletal Disorders Questionnaire," which is based on the Nordic Musculoskeletal Questionnaire. The survey content includes:(1) general demographic characteristics, including Gender, age, education level, marital status, living habits, and work of this job age, etc.; (2) Disease of WMSDs in different body parts; (3) Work Composition, including type of work, labor organization, working posture, etc. It has good reliability and validity and can be used among the Chinese occupational population (17).

Musculoskeletal injury criteria

The US National Institute for Occupational Safety and Health criteria for musculoskeletal injuries are pain, stiffness, burning, numbness or tingling, and other uncomfortable symptoms, and at the same time satisfy (i) discomfort within the past 1 year; (ii) began to feel discomfort after engaging in the current job; (iii) no previous accident or sudden injury (affecting the local area of discomfort); and (iv) if discomfort occurs every month or lasts for more than 1 week, it is referred to a musculoskeletal disorder in this area (18).

Data analysis

Chi-square test and binary logistic regression statistical analysis were performed using SPSS 25.0. First, differences in the prevalence of wrist pain and injury under various conditions were compared, and logistic analysis was carried out on jobs with high prevalence in animal husbandry, toy manufacturing, biopharmaceutical manufacturing, and other industries. Odds ratio (OR) values were calculated, and various types of work were compared. Descriptive analysis was performed for dependent and independent variables, and a binary logistic regression model was used to determine the statistical association between different predictors and outcome

TABLE 1 Wrist injury rate under different characteristics.

Variable	Category	Number	Constituent Ratio (%)	Prevalence of hand injury (%)	*P*-value
Gender	Female	37,240	64.8	13	0.15
	Male	20,261	35.2	13.4	
strong hand	Right hand	53,095	92.3	13	<0.01
	Left hand	4,406	7.7	14.9	
Education	Junior high and below	15,369	26.7	14.1	<0.01
	High school and technical secondary school	21,900	38.1	14.3	
	Junior college	12,026	20.9	11.7	
	Bachelor and master degree or above	8,206	14.3	10.1	
Working age	≤5	35,432	61.6	13.4	0.03
	>5	22,096	38.4	12.8	
Smoking	No	36,530	63.5	13.1	0.01
	Occasionally	10,111	17.6	12.4	
	Frequently	9,903	17.2	14.1	
	Rimonabant	957	1.7	13	
Marriage	Spinsterhood	20,997	36.5	13.5	0.05
	Married	35,343	61.5	12.9	
	Married but living alone	1,161	2	14.8	
Monthly income	<3,000 rmb	11,220	19.5	16.8	<0.01
	3,001–5,000 rmb	28,371	49.3	13.6	
	>5,000 rmb	17,910	31.1	10	
Sporting	No	17,945	31.2	14.4	<0.01
	Occasionally	30,175	52.5	13	
	Frequently	9,381	16.3	11.1	

variables. We adjusted for factors, such as education level, industry, monthly income, marital status, and occupation. The models included sex, age, physical activity, and various wrist positions.

Results

A total of 57,501 individuals were surveyed after obtaining informed consent, most of whom were males (64.8%). Height was 167.03 ± 11.57 cm, weight was 64.1 ± 16.04 kg, age was 32.8 ± 9.1 years old, this category of service was 5.75 ± 6.14 years, and total length of service was 7.51 ± 7.18 years. A majority (92.3%) of the participants were right-handed, and there was no difference in wrist injury rate between the left and right hands ($p = 0.15$). Workers with high school and technical secondary school education accounted for the largest proportion (38.1%). Workers with working age of fewer than 5 years were the most common (61.6%), and there was a difference in the prevalence of wrist injuries between ≤5 and >10 years. With an increase in working years, the prevalence of wrist injuries also increased gradually. Most of the surveyed individuals were married (61.5%), and there was no difference in the injury rate between different marital statuses. In terms of monthly income, the proportion of people with a monthly income of 3,001–5,000 Yuan was the largest, and the wrist injury rate of different income groups was similar. Differences were observed between the groups (Table 1). Because the frequency of exercise increased, the prevalence of wrist injuries gradually decreased.

Industry sickness

The survey covered 15 industries: animal husbandry, ship building and related equipment manufacturing, electronic equipment manufacturing, furniture manufacturing, construction, coal mine washing industry, civil aviation flight attendants, automobile 4S shops, automobile manufacturing, biomedical manufacturing, petrochemical industry, petrochemical industry, vegetable greenhouses, toy manufacturing, medical staff, and shoe manufacturing ($p < 0.001$). The wrist injury rates were not similar in the different industries. Five industries with the most wrist injuries were toy manufacturing, animal husbandry, automobile manufacturing, and shoe manufacturing, and the biological drug manufacturing and wrist injury rates were 29.1, 19.1, 14.9, 14.9, and 14%,

TABLE 2 Wrist injury rate under different industry.

Industry	Number	Constituent ratio(%)	Prevalence of hand injury (%)	*P*-value
Animal husbandry	246	0.4	19.1	
Shipbuilding and related equipment	3,488	6.1	13	<0.01
Electronic equipment manufacturing	8,116	14.1	11	
Furniture manufacturing	4,471	7.8	12.4	
Construction industry	1,379	2.4	6.5	
Coal mining and cleaning	1,500	2.6	11.2	
Flight attendants	1,356	2.4	7.2	
4S automobile store	544	0.9	9.2	
Automobile manufacturing	21,560	37.5	14.9	
Biopharmaceutical manufacturing	243	0.4	14	
Petrochemical industry	150	0.3	4.7	
Vegetable greenhouse	243	0.4	6.6	
Toy manufacturing	333	0.6	29.1	
Medical staff	6,766	11.8	11.6	
Footwear industry	7,106	12.4	14.9	

TABLE 3 Prevalence of wrist injuries by industry by age of service and sex.

Industry	Wrist injury			
	Working age ≤5		Working age >5	
	Male	Female	Male	Female
Animal husbandry	56 (17.9)	35 (20.0)	102 (21.6)	53 (15.1)
Shipbuilding and related equipment	1,026 (11.1)	317 (16.1)	1,857 (12.9)	288 (16.7)
Electronic equipment manufacturing	3,155 (7.7)	2,844 (12.9)	761 (8.8)	1,396 (15.5)
Furniture manufacturing	2,897 (13.0)	1,177 (11.3)	289 (11.4)	108 (11.1)
Construction industry	542 (7.9)	78 (5.1)	717 (5.4)	42 (7.1)
Coal mining and cleaning	567 (11.5)	24 (0.0)	871 (11.4)	38 (10.5)
Flight attendants	191 (2.1)	612 (8.2)	109 (3.7)	444 (9.0)
4S automobile store	220 (6.4)	9 (11.1)	309 (11.0)	6 (16.7)
Automobile manufacturing	13,356 (16.3)	940 (15.2)	6,712 (12.0)	552 (14.9)
Biopharmaceutical manufacturing	72 (13.9)	58 (13.8)	37 (18.9)	76 (11.8)
Petrochemical industry	37 (0.0)	1 (0.0)	106 (5.7)	6 (16.7)
Vegetable greenhouse	10 (0.0)	16 (6.3)	144 (4.2)	73 (12.3)
Toy manufacturing	91 (35.2)	168 (28.6)	28 (28.6)	46 (19.6)
Medical staff	329 (6.7)	2,527 (9.8)	475 (9.7)	3,435 (13.6)
Footwear industry	1,423 (12.9)	11,500 (12.6)	791 (15.9)	2,198 (16.5)

respectively. Pairwise comparisons revealed differences in the prevalence of wrist injuries among the construction, automobile, toy, medical, and shoe industries (Table 2).

Grouping industries by length of service and gender showed that in the toy manufacturing industry with the highest prevalence, women with more than 5 years of service had a lower prevalence of wrist injury than those with <5 years of service (Table 3).

We performed a univariate logistic regression analysis of occupations in 11 industries to compare the prevalence among occupations. Jobs with the highest prevalence were glue-laying (63.0%), slaughter (43.6%), car-combing (32.5%), solder (31.3%), and bracket (26.5%) workers (Table 3). The jobs in each industry were car combers in the toy manufacturing industry, slaughter workers in the animal husbandry industry, polishers in the automobile manufacturing industry, gluing

workers in the shoe manufacturing industry, bottling workers in the biopharmaceutical manufacturing industry, ship building and related manufacturing industries, sanders and welders in the electronic equipment manufacturing industry, punchers in the construction industry, bracket workers in the coal mining industry, doctors in the medical industry, and furniture industry operators in the furniture manufacturing industry.

The number of people surveyed in the toy manufacturing industry was 333, and the ORs of wrist injury was 58.85 and 16.83 for rubber enamel and car comb workers, respectively. The total number of people surveyed in the livestock industry was 246, and the prevalence of milking workers was 4.3%, while the ORs of wrist injury was 3.93 times higher for feed workers and 17 times higher for slaughter workers. The number of people surveyed in the automobile manufacturing industry was 21,560, and the number of forklift workers was 2,860 with a wrist injury prevalence rate of 10.9%. The OR of wrist injury in glue coating workers was 0.73 times that of forklift workers. The ORs of illness were 1.26, 2.23, 1.63, and 1.93 for forklift workers. The number of people surveyed in the footwear industry was 7,106. The ORs of wrist injury was 1.67, 2.0 times higher for tailors and molding workers, and 2.07 times higher for gluing workers. The wrist injury rate of QC workers in biopharmaceutical manufacturing was 9.6%, and the OR of illness was 3.12 times higher for bottling workers than for QC workers (Table 4).

TABLE 4 Results of binary logistic regression analysis of different types of work in various industries.

Type of work	Number	Number of cases (%)	*P*-value	OR (95%CI)
Animal husbandry				
Milker	69	3 (4.3)		
Feeder	33	5 (15.2)	0.07	3.93 (0.88, 17.57)
Butcher	39	17 (43.6)	<0.01	17 (4.55, 63.56)
Shipbuilding and related equipment				
Coppersmith	164	12 (7.3)		
Craneman	339	43 (12.7)	0.07	1.84 (0.94, 3.59)
Electric welder	595	91 (15.3)	0.01	2.29 (1.22, 4.29)
Ship-fitter	824	126 (15.3)	0.01	2.29 (1.165, 2.58)
Polishing operator	202	52 (25.7)	<0.01	4.39 (2.25, 8.56)
Electronic equipment manufacturing				
Electric welder	223	16 (7.2)		
Packer	277	36 (13.0)	0.04	1.93 (1.04, 3.58)
Fitter	1,520	276 (18.2)	<0.01	2.87 (1.70, 4.85)
Automatic operator	105	21 (20.0)	<0.01	3.23 (1.61, 6.50)
Solder work	96	30 (31.3)	<0.01	5.88 (3.02, 4.45)
Construction industry				
Bar placer	206	12 (5.8)		
Woodworking	324	39 (12.0)	0.02	2.21 (1.13, 4.33)
Punching workers	19	3 (15.8)	0.11	3.03 (0.78, 11.86)
Coal mining and cleaning industry				
Drainage workers	55	2 (3.6)		
Punching workers	100	9 (9.0)	0.23	2.62 (0.55, 12.59)
Driver	324	48 (14.8)	0.04	4.61 (1.09, 19.54)
Timberer	34	9 (26.5)	0.01	9.54 (1.92, 47.45)
Automobile manufacturing				
Forklift worker	2,860	313 (10.9)		
Gluer	3,726	306 (8.2)	<0.01	0.73 (0.62, 0.86)
Auto Spray-Painter	909	122 (13.4)	<0.01	1.26 (1.01, 1.58)
Electric welder	2,658	443 (16.7)	<0.01	1.63 (1.39, 1.9)
Fitter	8,275	1,589 (19.2)	<0.01	1.93 (1.70, 2.20)
Polishing operator	298	64 (21.5)	<0.01	2.23 (1.65, 3.01)
Biopharmaceutical manufacturing				
Quality worker	114	11 (9.6)		
Formula work	50	9 (18.0)	0.14	2.06 (0.79, 5.33)
Filling work	28	7 (25.0)	0.04	3.12 (1.08, 8.98)
Toy manufacturing				
Packer	71	2 (2.8)		
Comber	114	37 (32.5)	<0.01	16.83 (3.93, 72.16)
Glue maker	46	29 (63.0)	<0.01	58.85 (12.77, 271.25)
Medical staff				
Carer	384	29 (7.6)		
Nurse	4,057	465 (11.5)	0.02	1.593 (1.07, 2.34)

(Continued)

Logistic regression analysis

After grouping according to the length of service and sex, we analyzed the logistic regression analysis of wrist posture and found that the wrist often bent upwards and downwards, needs to be pinched with hands, grasps some objects tightly, and women with more than 5 years of service above the shoulder are at the highest OR. Placing the hand on the edge of hard and angular objects (such as the edge of a table) was highest among women with <5 years of service. Prolonged wrist flexion had the highest relationship among men within 5 years of service (Table 5).

After adjusting for education level, monthly income, marital status, dominant hand, type of work, and industry, multivariate logistic analysis showed that the OR of wrist injury in women was higher than that in men (OR = 1.24). The OR of wrist injury also increases gradually. Exercise is an associated factor against injury, and the more frequent the exercise, the greater the protection. We found that wrist posture was a dominant factor with the greatest OR value for long-term flexion of the wrist (OR = 1.86; 95% CI, 1.75–1.97), followed by wrist posture requiring frequent upward and downward flexion during work for workers' OR of wrist injury was very high (OR = 1.81; 95% CI, 1.84–2.11), which also increased the OR of wrist injury when workers needed to pinch/grab at work (OR = 1.72; 95% CI, 1.57–1.89). The OR of wrist injury was also increased (OR = 1.52; 95%

TABLE 4 (Continued)

Type of work	Number	Number of cases (%)	*P*-value	OR (95%CI)
Doctor	1,782	239 (13.4)	<0.01	1.9 (1.27, 2.84)
Footwear industry				
Bottom-making	204	21 (10.3)		
Cropper	1,250	233 (18.6)	<0.01	1.67 (1.02, 2.75)
Shapers	634	102 (16.1)	<0.01	2.00 (1.24, 3.21)
Gluer	406	78 (19.2)	<0.01	2.07 (1.24, 3.47)
Furniture manufacturing				
Sanders	234	26 (11.1)		
Operator	447	80 (17.9)	0.02	1.74 (1.09, 2.80)
4S automobile store				
Reworkers	110	7 (6.4)		
Mechanic	235	27 (11.5)	0.142	1.91 (0.81, 4.53)
Painter	124	11 (8.9)	0.474	1.43 (0.54, 3.83)
Flight attendants				
Flight attendants	1,104	96 (8.7)		
Purser	73	2 (2.7)	0.093	0.30 (0.07, 1.23)
Petrochemical industry				
Plumber	42	2 (4.8)		
Cranes	13	1 (7.7)	0.687	1.67 (0.14, 20.01)
Welders	25	2 (8.0)	0.592	1.74 (0.23, 13.19)
Vegetable greenhouse				
Greenhouse worker	243	16 (6.6)		

CI, 1.44–1.61) when the hand was frequently placed on the edge of hard and angled objects (such as the edge of a table). People whose wrists were higher than the shoulders had a higher OR of wrist injury than those whose shoulders were below (OR = 1.11; 95% CI, 1.04–19) (Table 6).

Discussion

This study investigated the population of key industries in China to understand the prevalence and distribution of wrist injuries and to explore related epidemiological characteristics. Wrist injury is a common injury of the upper extremities. Our study found that female sex, working age, and poor wrist posture all increased the ORs of wrist injury. The ORs of some types of work is much higher than that of other work types in the same industry. The strengths of this study include the large sample size, specific case criteria, and detailed exposure to wrist posture, representing a broad range of industries, trade, and locations, adding to the generalizability of the findings.

Poor working posture can cause excessive muscle load on workers and cause the body to produce a physiological stress response. Under such stress conditions for a long time, it causes injury to muscles, nerves, and tendons. The results of this study show that among the 15 key related industries, toy manufacturing, animal husbandry, automobile manufacturing, shoe manufacturing, and biopharmaceutical manufacturing are the five industries with the greatest ORs of wrist injury. The prevalence rates of workers, including glue workers, solder workers, canners, and doctors are also higher than those of other types of workers in the same industry. The degree of mechanization in the toy manufacturing and production processes is not high. In monotonous and repetitive manual assembly line operation, the wrist requires frequent movements to complete the task (19). During work, they needed to bend over and turn around, keep their neck down for a long time, hold the tool in both hands, straighten their right hand, and keep their arms higher than their shoulders. This working method is more prone to wrist injuries than other jobs (20). In animal husbandry, for dairy farms with larger herds, the production cost is more inclined to milking in the milking room, which is equipped with modern milking equipment; therefore, the wrist injury rate is higher than that of traditional milkers. Feeders and slaughter workers still rely on manual operations to a certain extent; therefore, the ORs of musculoskeletal diseases is much greater than that of milkers. Workers in large livestock industries are exposed to factors, such as awkward postures, repetitive movements, high muscle loads, few opportunities for rest, and poor environmental conditions, which may increase the risk of WMSDs (21). Auto-manufacturing workers often need to carry heavy objects, such as auto parts and auxiliary tools for carrying out lifting operations, which will increase load on the wrist. Most auto-manufacturing workers perform assembly work, and the work content is similar every day. The body parts involved in the work of workers are impacted by the same load year after year. The prevalence rate of wrist injuries in country's footwear industry was 14.9%. An Indian survey of handmade shoes found that the prevalence of wrist pain was as high as 88.5%, and many factories in India make such handmade shoes. Sole cutting is a time-consuming, ineffective, and a physically labor-intensive job that requires manual operation and necessary skills and practice. Awkward postures, such as prolonged sitting and forward bending of the body increased the risk of WMSDs (22).

There are several notable findings regarding the association of personal and ergonomically associated factors with wrist injuries. First, our study found that the adjusted prevalence of wrist injuries differs from that of men among female workers, and that increasing working age also increased the ORs of wrist injuries, while physical activity reduces the ORs of wrist injuries. Studies have shown that the prevalence of WMSDs increases with the number of years of work, and there are differences between males and females (23). Differences in the health status of male and female workers may be due to differences in the exposure to different associated factors. Because of gender segregation in the labor market, men and women tend to work in different jobs; therefore, they face different ORs. Furthermore,

TABLE 5 Logistic regression was used to evaluate the effect of wrist posture on wrist injury by gender and length of service.

Variable	Wrist Injury OR (95% CI)*			
	Working age ≤5		Working age >5	
	Male	Female	Male	Female
Whether the wrist is often bent up/down at work	1.90 (1.69, 2.15)	1.92 (1.62, 2.27)	2.22 (1.87, 2.64)	1.89 (1.58, 2.25)
Whether the wrist is often placed on the edge of a hard, angular object	1.67 (1.54, 1.82)	1.43 (1.26, 1.62)	1.50 (1.32, 1.70)	1.40 (1.23, 1.61)
Do you need to pinch/grasp objects/tools with your hands during work	1.71 (1.46, 2.00)	1.62 (1.33, 1.98)	1.89 (1.53, 2.32)	1.68 (1.36, 2.06)
Above shoulder level	1.14 (1.03, 1.25)	1.18 (1.01, 1.39)	1.19 (1.03, 1.36)	0.92 (0.77.1.10)
Whether the wrist needs to be bent for a long time	1.89 (1.73, 2.07)	2.07 (1.80, 2.37)	1.8 (1.57, 2.06)	1.72 (1.48, 2.00)

*Is the OR value after adjusting smoking, industry, occupation.

TABLE 6 Results of binary logistic regression analysis of associated factors of wrist injury.

Variable	Category	Number		Injury OR (95% CI)	
		No injury	With injury	Crude	Adjusted*
Gender	Female	17,544	2,717		
	Male	32,404	4,836	1.07 (1.01, 1.12)	1.28 (1.18, 1.39)
Working age	≤5	30,693	4,739		
	>5	19,255	2,714	0.99 (0.94, 1.04)	1.09 (1.03, 1.15)
Sporting	No	15,361	2,584		
	Occasionally	26,249	3,926	0.94 (0.88, 0.99)	0.92 (0.87, 0.98)
	Frequently	8,338	1,043	0.83 (0.77, 0.90)	0.86 (0.80, 0.94)
Whether the wrist is often bent up/down at work	No	19,298	1,074		
	Yes	30,650	6,479	2.01 (1.87, 2.17)	1.97 (1.82, 2.12)
Whether the wrist is often placed on the edge of a hard,	No	33,997	3,478		
angular object	Yes	15,951	4,075	1.47 (1.40, 1.56)	1.54 (1.45, 1.62)
Do you need to pinch/grasp objects/tools with your hands	No	12,695	625		
during work	Yes	37,289	6,928	1.86 (1.70, 2.04)	1.73 (1.58, 1.90)
Hand position at work	Shoulder or below shoulder level	41,295	6,090		
	Above shoulder level	8,653	1,463	1.15 (1.08, 1.22)	1.16 (1.05, 1.19)
Whether the wrist needs to be bent for a long time	No	29,919	2,356		
	Yes	20,029	5,197	1.93 (1.82, 2.04)	1.87 (1.76, 2.00)

*Is the OR value after adjusting smoking, industry, occupation.

even though men and women have the same job, they may have different specific tasks, which may lead to different risk exposures (23, 24). Kihlberg and Hagberg demonstrated an OR of 1.4 for wrist pain with age (25), and Davatchi et al. showed that the prevalence of wrist pain in women was 14.7%, which was higher than that in men (5.6 %) (26). We found that the prevalence of wrist injuries increased with working age, but the difference was not statistically significant. One possible reason is the healthy worker selection effect; that is, healthy workers, even in physically demanding jobs, can also maintain longer working hours. Another possibility is that pain elsewhere is more prevalent and may occur earlier than pain in the distal upper extremities. Neck and shoulder pain may prevent workers from continuing to sew, while distal upper extremity pain may take longer to develop (27). This study also identified a significant association between exercise and lower prevalence of wrist injuries. Workers who exercised were less likely to develop wrist injuries than those who did not exercise, and the more frequent the exercise, the lower the OR of injury. Exercise can provide workers with an opportunity to break free from work to restore and strengthen their bodies, while also providing mental relaxation from the high psychosocial demands of work. These effects may help improve health and reduce the risk of musculoskeletal symptoms (28).

Poor working posture is an important factor for wrist injury. Regarding the effect of wrist posture on wrist injuries found at work, the wrist is often flexed up or down, the wrist is placed on the edge of a hard object, the need to hold objects tightly, the

wrist is above shoulder level, and prolonged flexion increases the OR of wrist injury. All work requires the use of the wrist, and some work also requires carrying and using tools, particularly vibrating tools. When the wrist is often bent up or down, it also increases the OR of wrist injury, and our study cannot reflect the effect of angular velocity of the wrist on wrist injury, but only the frequency of wrist movement. However, studies have shown that the risk of carpal tunnel syndrome (CTS) increases with increasing levels of wrist angular velocity (29). Many of our operations are performed on the work surface, and the wrist is often placed on the edge of hard and angular objects (such as the edge of a table), which increases the OR of wrist bumps and can easily lead to inflammation and fibers in the muscle tissue, resulting in wrist injury. The wrist tissue is also in a tense state when the hand needs to frequently pinch or grip objects or tools. Few studies have examined the position of the wrist across the body and above or below the shoulder. We found that maintaining a high working position for long periods also increased the OR of wrist injury and pain. This may be because the wrist is in a state of lifting above the shoulder, lacking certain support, and the pressure on the muscles and bones is high, resulting in injury. When the wrist is in a flexed state, the wrist muscles are in a tense state, and symptom, such as pain, is prone to occur when this state is maintained for a long time. One study also showed that when the wrist is extended more than 33° or flexed more than 49°, there is an increased risk of CTS (30). Studies have found a significant association between wrist injuries and lifting unsupported weights in each hand, grasping objects with force, and grasping objects with flexed wrists. There was also a significant association between wrist injuries and the use of hand tools, such as impact tools (e.g., jack and chisel hammers), impact wrenches, and chainsaws (31). Chronic flexion of the wrist, gripping objects with hands, upper limb or hand exertion, repetitive manipulations multiple times per minute (32), and the use of vibrating tools have been found to be associated factors for wrist pain. However, one study showed no significant increase in the frequency of CTS when the wrist repetition rate was considered independent of strength. In contrast, forceful hand repetition frequency (a measure of both exposure to forceful and repetitive hand force) was significantly associated with an increased OR of CTS, which is similar to the increased OR of wrist injury when we exert force, such as pinching objects with our hands, which shows that if there is no force, even if the wrist is often bent, it will not increase the injury. Therefore, our definition of posture has included strength because these postures require strength to complete the work, and the study also found that the prevalence of CTS appears to increase linearly with the number of hard hand repetitions up to 30/min (33).

Current research suggests that high repetition, force, awkward posture, and other sports can damage the musculoskeletal system and peripheral nerves (34, 35). A high value is closely related. Therefore, we recommend that individuals pay attention to adjusting their posture at work to prevent pain and achieve the purpose of skeletal muscle rest through reasonable work time allocation, reasonable physical exercise, warm-up, etc. to reduce the occurrence of injury.

Limitations

This study has several limitations. First, it was not possible to make causal inferences between risk factors and WMSDs due to the cross-sectional nature of the study. Because this study used a questionnaire, the resulting report and recall biases may have affected the results, and the number of years of work used in assessing the effect of length of service on wrist injuries only includes total years in current employment and not previous employment. Therefore, to make the research more in-depth, the survey industry can be expanded and cohort and intervention studies can be conducted.

Conclusions

Through cross-sectional surveys of 15 key industries in seven regions of China, we learned about the prevalence of wrist injuries in China's occupational population and related factors. This study provides a reference for the development of relevant measures to prevent and control the occupational population of WMSD. Toy manufacturing, automobile manufacturing, animal husbandry, and shoemaking have the highest ORs of wrist injury. Vinyl, slaughterers, car combers, solder workers, and bracket workers have the highest prevalence rates of wrist injury; therefore, there is a need to pay attention to them. Additionally, female sex and length of service increase the ORs of wrist injury, and abnormal posture of the wrist is the main cause of wrist injury. Physical exercise can reduce the OR of wrist injury, suggesting that the OR of wrist injury can be improved by adjusting working posture and performing reasonable physical exercise. Simultaneously, managers and workers in various industries need to raise health awareness, improve working conditions in a reasonable way, and protect their own health.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethical Review Committee National Institute for Occupation Health and Poison Control

Chinese Center for Disease Control and Prevention. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NC and GuL: article writing. XS, MZ, HuZ, RL, YiL, GaL, ZR, YY, HS, HeZ, JLi, BQ, DW, QZ, ZL, RW, JC, DZ, LM, YoL, JLiu, CZ, TL, and ZW: data handling. QC and NJ: provide topic selection and writing guidance. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cardiovascular consequences of aircraft noise exposure

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The results from epidemiological studies suggest that environmental noise including aircraft, railway, road traffic, wind turbine, and leisure-related noise is a growing public health concern. According to the WHO, at least 100 million people in the European Union are affected by traffic noise levels above the WHO-recommended thresholds. Environmental noise can adversely affect physical and mental health, as well as wellbeing. Chronic low-level noise exposure typical for most environmental sources is associated with psychophysiological stress causing non-auditory or indirect noise effects leading ultimately to cardiovascular diseases. Among all environmental noise sources, aircraft noise is considered the most annoying, and its leading mechanism of action is autonomic system activation such as increases in heart rate and blood pressure. Previously, we observed that long-term exposure to aircraft noise was associated with increased diastolic blood pressure, arterial stiffness (as assessed by pulse wave velocity), and impaired left ventricular diastolic function. All mentioned above effects are early, subclinical, and potentially reversible changes which preceded late noise effects in the cardiovascular system, that is, established cardiovascular diseases such as myocardial infarction, stroke, and heart failure. However, even a short-term reduction in aircraft noise exposure as observed during the COVID-19 lockdown may reverse these negative effects on arterial stiffness and blood pressure and may decrease the prevalence of insomnia. In this review, we aimed to critically discuss our obtained results considering recent studies on the influence of aircraft noise (and other traffic noises) on cardiovascular diseases in the context of the WHO Environmental Noise Guidelines for the European Region.

KEYWORDS

aircraft noise, environmental noise, noise exposure, cardiovascular diseases, hypertension

Introduction

Cardiovascular diseases (CVD) are still a leading cause of mortality and morbidity around the world. According to World Health Organization (WHO), in 2019 about 17.9 million people died from CVDs, which constitute 32% of all deaths (1). The etiology of CVD is heterogenous and arises from an interplay between genetic components (non-modifiable risk factors) and environmental/lifestyle determinants (usually modifiable) which can lead to deterioration of endothelial structure and function as well as atheromatous plaque formation as an early stage in the development of atherosclerotic CVD (2). Subsequent artery narrowing or occlusion remains the most crucial element of developing CVD, increasing the risk of cardiovascular events such as stroke, myocardial infarction, heart failure, and peripheral artery disease, as well as renal dysfunction, and cognitive impairment (3, 4).

Environmental noise in the spectrum of cardiovascular risk factors

To estimate a 10-year risk of fatal and non-fatal CVD events in European populations, the Systematic COronary Risk Evaluation (SCORE2) algorithm is widely used. However, this score includes only traditional risk factors, such as age, sex, blood pressure, plasma cholesterol, and cigarette smoking (5, 6). Other well-established risk factors like diabetes mellitus, unhealthy diet, sedentary lifestyle, obesity, and alcohol consumption are included (1). In addition, recent studies recognize many underlying determinants of CVDs that arise mostly from globalization and urbanization which include exposure to air and soil pollution as well as above-threshold noise levels (5, 7). Noise is defined as an unpleasant or harmful sound. The most common environmental noise sources studied are those produced by transportation (road traffic, railway, and aircraft) and industry (8, 9). It can affect human health depending on the characteristics of the sound and time of exposure, as well as subjective perception described as annoyance (10). The noise effect on the cardiovascular system is associated with chronic low-level exposure, which dysregulates homeostasis through autonomic nervous and endocrine system arousal (11). Recent animal studies, as well as observational studies on humans, show that especially nighttime noise is critical to endothelial dysfunction development, which indicates that sleep deprivation and fragmentation due to noise annoyance are important mechanisms of stress-related damage (12, 13). Noise activates the pituitary–adrenal–cortical axis and the sympathetic–adrenal–medullary axis. It also provokes fluctuations of stress-related hormones including epinephrine, norepinephrine, and cortisol (14). These stress responses induce cardiovascular and cerebral oxidative stress and inflammation (15). Sustained, chronic reaction to stress increases and accelerates the risk of developing CVD such as arteriosclerosis, hypertension, and ischemic heart disease (16).

Environmental noise regulations

The European noise policy has been developed and harmonized for over two decades. In 1996, the Commission of the European Communities enlightened the problem of increased noise exposure due to urbanization and recognized it as the main environmental problem in Europe (17). Noise emission limits have been successively laid down for most of the urban-related noise sources according to the Directive of the European Parliament and the Council published in 2002 (18). Especially aircraft noise had been taken into consideration, as this noise is characterized by the highest annoyance as compared with other transportation noise sources (19). Annoyance is a term used in order to describe subjective negative feelings such as displeasure or irritation caused by noise. It can be measured semi-quantitatively through dedicated questionnaires (20). There is a level-dependent relationship between noise and annoyance, however, it is different for different noise sources. Aircraft noise has been reported to be more annoying than other transportation noises at the same noise level, which was highlighted by European Agency Report (20, 21).

Sound exposure levels are expressed in decibels (dB), and to assess chronic exposure to noise, long-term indices are in use (22). The most commonly used are average sound pressure level over all day–evening–night periods in a year (Lden) and average sound level over all night periods in a year (Lnight) (22, 23). With these standardized indicators, it is possible to create acoustic maps containing noise levels to assess the number of people exposed to different levels of noise, which can be harmonized for all EU Member States (9). The WHO Guideline Development Group recommends reducing aircraft noise below 40 dB Lnight as the noise above this level is linked with health adverse effects (9). Noise effect on human health can be

Abbreviations: ABPM, 24-h ambulatory blood pressure monitoring; ACE2, glyoxalase I (GLO1) angiotensin-converting enzyme 2; AIS, Athens Insomnia Scale; BP, blood pressure; COVID-19, coronavirus disease 2019 caused by SARS-CoV-2; CVD, cardiovascular disease; dB, decibels; DBP, diastolic blood pressure; E/E', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; E', tissue Doppler-derived early diastolic mitral annulus velocity; EU, European Union; FMD, flow-mediated dilation; FS, follistatin; GLO1, glyoxalase I; HPA, hypothalamic–pituitary–adrenal axis; LA, A, HA, little annoyed, annoyed, highly annoyed; Lden, average sound pressure level over all day–evening–night periods in a year; Leq, equal average sound pressure level; Lnight, average sound level over all night periods in a year; PWV, pulse wave velocity; SCORE2, Systematic COronary Risk Evaluation; SNS, sympathetic nervous system; WHO, World Health Organization.

associated with auditory, or direct consequences, as well as non-auditory (indirect). CVDs develop as an indirect noise effect and result from chronic exposure (24).

In this mini-review, we aimed to discuss the results of our studies, focused on aircraft noise exposure consequences for CV systems, with other currently published study results in this field with regard to the WHO Environmental Noise Guidelines for the European Region.

Cardiovascular consequences of aircraft noise exposure

Rojek et al. conducted a cross-sectional study between 2015 and 2016, among participants exposed to high (above 60 dB Lden) and low (below 55 dB Lden) aircraft noise levels to assess the impact of long-term exposure to aircraft noise on blood pressure (BP), prevalence of arterial hypertension, and indices of asymptomatic organ damage (10). The authors revealed that long-term aircraft noise exposure was associated with higher blood pressure indices, that is, higher office and night-time diastolic blood pressure (DBP). Moreover, in the group exposed to higher aircraft noise levels, more advanced hypertension-related organ damages were observed, that is, increased pulse wave velocity (PWV), the measure of arterial stiffness, and lower values of tissue Doppler-derived early diastolic mitral annulus velocity (E')—representing an early stage of diastolic left ventricular dysfunction (10, 25, 26). Of note, higher office and night-time DBP, PWV, and E' values were explicitly observed in exposed normotensive participants. Moreover, PWV in aircraft noise-exposed normotensive participants was equal to that of two decades older unexposed normotensive participants and was significantly associated with noise annoyance. Numerous studies focused on the relation between environmental noise exposure and hypertension prevalence or BP increase (27, 28). While data on subclinical organ damage are scarce, Foraster et al. in the SAPALDIA study revealed that long-term railway noise exposure during the night and the number of night-time noise events related to road traffic were associated with arterial stiffness (29). In a human field study, Schmidt et al. (30) observed an increase in arterial stiffness assessed by the carotid–femoral transit time (a component used in the calculation of PWV) as a consequence of nocturnal exposition to aircraft noise in healthy individuals (30). They revealed also an increased release of catecholamines after noise exposure suggesting the involvement of sympathetic nervous system activation by stress mechanisms (30). Moreover, noise exposure impaired endothelial function in patients with or at high risk for coronary artery disease, which was pronounced in these patients compared to healthy subjects (31). Münzel et al. (16) extensively described the pathophysiological mechanisms connecting noise exposure with stress reaction neuro-humoral activation, and hemodynamic and metabolic consequences (16).

The importance of the SAPALDIA study resulted from a large sample size ($N = 2775$), while the strength of the Rojek study results from a very detailed and wide assessment of the blood pressure phenotype [including 24-h ambulatory blood pressure monitoring (ABPM)] and the analysis of three different indices of cardiovascular damage: intima–media thickness, arterial stiffness, and echocardiography. Measured parameters of organ damage have a crucial prognostic value to assess the risk of cardiovascular complications and mortality (16).

In a subsequent study from the same group of authors (8), the impact of chronic night-time exposure to aircraft noise on BP profile, sleep disturbances, and annoyance was assessed in individuals without hypertension (8). The participants were divided into two groups regarding their exposure to night-time aircraft noise. Exposed individuals were selected from an area exposed to noise exceeding 50 dB of Ln, while the unexposed group lived in the village exposed to noise below 45 dB. Insomnia was assessed by means of the Athens Insomnia Scale (AIS) and was defined as AIS above six points (32). Individuals living in the night noise-exposed area were characterized by a 2-fold higher insomnia prevalence than those living in the low noise-exposed area (33 vs. 16%, $p = 0.046$) and reached higher scores in AIS. As a consequence of sleep disturbances induced by noise, the authors observed higher diastolic BP at night and higher office DBP in exposed individuals compared to those living in a low noise exposure area (8).

A greater prevalence of insomnia and impaired sleep quality was also reported among individuals living near Orio al Serio International Airport by Carugno et al. (33). In contrast to the results obtained by Rojek et al. and Carugno et al. (8, 33) found no differences in BP between aircraft noise-exposed and unexposed subjects. A potential explanation may include the difference in the noise level threshold and type of indices between these studies (Lnight in Rojek study, Lden in Carugno study) which may result in a less pronounced contrast between exposed and unexposed subjects.

The results obtained by Rojek regarding the influence of aircraft noise on noise-exposed residents are largely in agreement with the results obtained by Schmidt et al. (34). In this experiment, 70 individuals with cardiovascular risk factors or established cardiovascular disease were subjected to three different scenarios. The control scenario comprised no noise exposure (regular background noise in the sleeping room of the participants), and the noise scenario nights comprised 60 and 120 noise events, respectively. In both noise scenario nights, subjects were exposed to similar equal average sound pressure levels (Leq). In all experimental conditions, polygraphy recordings, echocardiography, measurement of flow-mediated dilation (FMD), and blood sample analysis were performed. Questionnaires regarding sleep quality and annoyance were also collected (34). The study demonstrated a worsening of vascular function after noise-exposed nights compared to control nights. Furthermore, worsening of left ventricular diastolic function

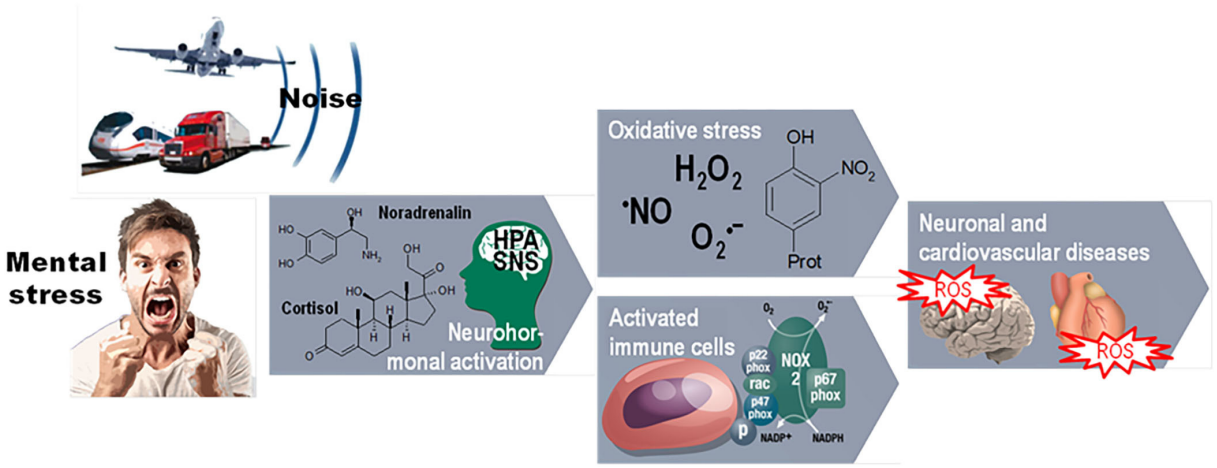

FIGURE 1
Pathways of environmental noise action on cardiovascular disorders through mental stress and neurohormonal, immune, and oxidative stress mechanisms. The environmental risk factors noise exposure and mental stress cause a primary stress reaction, mediated either by the hypothalamic–pituitary–adrenal (HPA) axis with subsequent cortisol release or by activation of the sympathetic nervous system (SNS) with subsequent catecholamine formation. These stress reactions activate inflammatory or oxidative stress pathways which can stimulate each other and, together with stress hormones, vasoconstrictors, and alterations of gene expression, contribute to the classical risk factors such as hypertension and atherosclerosis leading to neuronal, cardiovascular, and metabolic diseases. Reused from Daiber A, Kröller-Schön S, Frenis K, Oelze M, Kalinovic S, Vujacic-Mirski K, et al. Environmental noise induces the release of stress hormones and inflammatory signaling molecules leading to oxidative stress and vascular dysfunction-Signatures of the internal exposome. Biofactors. 2019 Jul;45(4):495–506. doi: 10.1002/biof.1506 with permission.

($p = 0.043$) displayed by an increased ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/E') was observed in both night noise scenarios. Plasma analysis after noise exposure (120 events) revealed a decrease in follistatin (FS) ($p = 0.016$), glyoxalase I (GLO1) ($p = 0.044$), and angiotensin-converting enzyme 2 (ACE2) ($p = 0.032$). These findings prove that night-time noise is a factor in deteriorating endothelial function, increasing the risk of developing fibrosis, and increasing metabolic stress through impaired detoxification of reactive aldehydes. There were significant ($p<0.001$) differences in FMD between scenarios with noise events (7.27 ± 3.21% for Noise 60 and 7.21 ± 3.58% for Noise 120) and the control night (10.02 ± 3.75%). This finding proved that short-time noise exposure leads to endothelial dysfunction. The study did not show any statistically significant differences in BP between observed individuals (34). However, the short-term exposure to noise led to numerous vascular and biochemical changes which may explain the long-term noise effects on BP changes as observed by Rojek et al. (8).

Cardiovascular consequences of noise reduction

Although the adverse effects of aircraft noise on the cardiovascular system are well-established, less is known about the potential reversibility of these changes after noise reduction, which is suggested by regulatory measures. Evidence on this issue came from Wojciechowska et al. by following up with the individual in 2020 from the Rojek et al. (35) study. After a follow-up of 5.5 years, the authors evaluated the impact of a sudden decline in air traffic for about 4 months which took place due to the COVID-19 lockdown. As a result, the average aircraft noise level decreased from 61.7 to 47 dB during the day and 55.4 to 43.4 dB during the night period in the region previously marked as exposed to aircraft noise in 2015. Therefore, both investigated groups were exposed to similar levels of aircraft noise. The study was conducted with the same protocol as the Rojek study in 2015. ABPM, PWV, and echocardiographic measurements were performed, and questionnaires regarding annoyance and insomnia were collected. The prevalence of hypertension in the exposed group increased in the follow-up. This is consistent with other studies, proving the long-lasting effects of aircraft noise exposure on hypertension risk (36, 37). Due to the aging of the cohort, an increase in arterial stiffness was expected in both the exposed and unexposed groups. In both groups, the decline in PWV was observed; however, the decrease in PWV during follow-up assessment was more pronounced in the exposed group (mean 10.2 vs. 8.8 m/s at follow-up, $p = 0.001$) as a result of noise level decline (35). A similar relationship was observed concerning noise-induced annoyance. In the exposed group, annoyance significantly decreased in this period ($p = 0.006$) but was still more pronounced compared to the unexposed group. During the follow-up visit, lower BP values

were observed in both groups regardless of their noise exposure, although a decrease in office, central BP, and night-time DBP was significantly dipper in the group of previously exposed individuals (35). Moreover, after calculating the estimated BP values at a 5.5-year follow-up and comparing it with actually measured BP values in the individuals from the exposed group without antihypertensive treatment, the observed office DBP was significantly ($p = 0.048$) lower than the expected DBP. There were no such differences in the unexposed group (35). Both reductions in noise-inducted annoyance and drop in BP during the follow-up visit are factors that could explain the decrease in arterial stiffness. The fact that reduction in noise exposure resulted in more pronounced PWV changes than BP changes is consistent with the results of the study by Schmidt et al. (30). The study by Wojciechowska et al. revealed that even the short-time reduction of aircraft noise can not only reverse the unfavorable long-term effect on BP and arterial stiffness. Another important finding is that the decline in aircraft noise during the pandemic restores the natural relation between PWV and age. This relation was previously blunted by the noise influence, that is, there was no increase in PWV with age (35).

Unlike other cardiovascular risk factors, such as tobacco intake or unhealthy lifestyle, noise exposure cannot be managed on the outpatient clinic level, but rather by guidelines followed by regulations on local and systemic levels. Hahad et al. (28) compared the publication of Wojciechowska et al. (35) with previous reports regarding the influence of noise on human health, raising the importance of treating noise as a psychosocial stressor leading to annoyance, which induces a cascade of neuroendocrine changes resulting in elevated blood pressure and increased stress hormone levels and heart rate (28). These processes contribute to the development of cardiovascular diseases, which was widely discussed in another manuscript by Hahad et al. (38). These results show the inter-relationship between noise, annoyance, and arterial stiffness and provide evidence that eliminating noise as the underlying cause also reduces annoyance and arterial stiffness (35). Consequently, long-term exposure to aircraft noise *via* different mechanisms with a leading role in endothelial dysfunction is accompanied by a higher prevalence of hypertension (15). The most important finding of the cohort study by Wojciechowska et al. (35) is the reversible character of noise effect on subclinical organ damage, even with the short-term decrease in air traffic. This shows the importance of noise level restriction implementations, consistent with WHO recommendations, as an important aspect of managing public health.

Discussion

Exposition to aircraft noise increases the prevalence of insomnia, evoked annoyance, sleep disorders, and subsequently early functional and structural changes in the endocrine and cardiovascular system such as an increase in stress hormones, oxidative stress, endothelial dysfunction, and arterial stiffness (Figure 1). At this stage, those changes are still reversible. However, the late consequences of long-lasting noise exposure, that is, established cardiovascular diseases, are not only indisputably confirmed by numerous epidemiological studies but also are irreversible. The only way of mitigating noise-induced health burden is to systematically reduce the noise level as recommended by the WHO (9). Even though environmental noise has been recognized as a burden of public health almost two decades ago, there is still an area for action to improve noise regulations in Europe.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between global biomarker of oxidative stress and quantitative ultrasound parameters in middle-aged and elderly adults: A cross-sectional study

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Introduction: With the population aging, osteoporosis has become a major public health concern. Elevated oxidative stress is a vital detrimental factor for bone health. Compared to common oxidative stress-related biomarkers, Fluorescent Oxidation Products (FlOPs) reflect the global levels of oxidation from proteins, lipids, and DNA. Nevertheless, whether plasma FlOP levels are related to bone health measured by Quantitative ultrasound (QUS) is unclear. Thus, the present study examined the association between FlOPs and QUS parameters in middle-aged and elderly adults.

Methods: This community-based cross-sectional study was conducted in Changchun, northeast China. Plasma FlOPs were determined by a fluorescent microplate reader at a wavelength of 320/420 nm (excitation/emission). QUS parameters [speed of sound (SOS) and broadband ultrasound attenuation (BUA)] of the calcaneus were assessed by an ultrasound bone densitometer. We used multivariable linear regression to examine the association between FlOPs and QUS parameters.

Results: A total of 491 subjects were included in this study. Their average age was 65.2 years (standard deviation [SD]: 9.7 years). FlOPs were inversely associated with SOS (β for an increase of logarithmic interquartile range = −10.64; P = 0.018). Higher FlOP levels were marginally associated with lower SOS in females (β for an increase of logarithmic interquartile range = −9.68, P = 0.066), but not in males (β for an increase of logarithmic interquartile range = −11.84, P = 0.131). No significant relationship between FlOPs and BUA was observed.

Conclusions: Plasma FlOP levels were inversely associated with SOS, but not with BUA in middle-aged and elderly adults.

KEYWORDS

oxidative stress, fluorescent oxidation products, quantitative ultrasound parameters, speed of sound, broadband ultrasound attenuation, middle-aged and elderly adults

Introduction

With the aging of the population, osteoporosis has become a major public health concern, leading to lower quality of life and imposing a huge disease burden on patients, their families, and society (1, 2). In China, the prevalence of osteoporosis was 19.2% for people aged 50 years or older, and 32.0% for those over 65 years of age (3). By 2050, it is estimated that the annual number of fragility fractures in China will increase to 5.99 million and the related medical cost will reach $25.43 billion (4). In communities, usage of the quantitative ultrasound device has become a relatively convenient tool for osteoporosis screening (5).

Oxidative stress occurs from the imbalance between the production of free radicals and the antioxidant defense system. The accumulation of excessive reactive oxygen species (ROS) induces oxidative damage to tissue and cellular macromolecules (e.g., protein, lipids, and DNA), leading to increased risk of many diseases such as cardiovascular disease, chronic kidney disease, and osteoporosis (6, 7).

In vivo and *in vitro* evidence suggests that ROS are involved in the pathogenesis of bone loss, increasing the level of bone resorption by stimulating the differentiation of osteoclasts and reducing bone formation *via* inhibiting the activity of osteoblasts (8–10). Previous studies on the relationship between oxidative stress and bone health are primarily based on the bone mineral density (BMD) determined by dual-energy X-ray absorptiometry (DXA) (11–13), only a few surveys are based on quantitative ultrasound (QUS) parameters (14, 15). Compared to DXA, QUS is less expensive, portable, and free from ionizing radiation. Several human studies have examined the relationship between traditional oxidative stress-related biomarkers [i.e., malondialdehyde (MDA)] and bone health assessed by BMD or QUS parameters, however, their results were inconsistent (11, 12, 14, 15). A recent study conducted in Iraq suggested that MDA is negatively associated with BMD in postmenopausal women (13). In contrast, Wu et al. observed an insignificant relationship between MDA and BMD in Chinese postmenopausal women (12). This inconsistency is likely due to the fact that traditional oxidative stress biomarkers only capture one specific aspect of oxidative damage. For example, MDA and 8-hydroxyguanosine (8-OHdG) were commonly used to assess the level of lipid peroxidation and DNA oxidation, respectively (16).

Fluorescent Oxidation Products (FlOPs) reflect oxidative damage in terms of protein, lipids, DNA, and carbohydrate, and have been used as a global biomarker of oxidative stress in epidemiologic studies (17, 18). Compared to specific oxidation measurements such as MDA assay *via* colorimetric thiobarbituric acid, the fluorescence method is 10–100 times more sensitive (19). In our previous study, higher FlOP levels were found to be associated with lower hip BMD in male veterans (20) and an increased risk of hip fracture in postmenopausal women (21). However, whether FlOPs are associated with bone health determined by QUS parameters is unclear. Given the above evidence, we hypothesized that FlOPs are negatively associated with QUS parameters. QUS measurements at the calcaneal could provide information on the structural and mechanical properties of the bone (22, 23). Knowing this relationship would expand our understanding of the impact of oxidative stress on the structural and mechanical properties of bone assessed by QUS.

Materials and methods

Study design and participants

This study is part of the national project entitled "The Comprehensive Demonstration Research Project of Major Chronic Disease Prevention and Control Technology in Northeast China (Health Northeast)" initiated by China Medical University. As one of the important participating units, Jilin University undertook the main work of the project in Jilin. The design and implementation of the study have been previously described (24). In brief, a community-based cross-sectional study was performed between January and December 2019 in Changchun, Jilin, China. We cooperated with more than 20 community health service centers distributed in 10 districts in Changchun. All participants were interviewed face-to-face at the community health service centers using a structured questionnaire. We collected data such as socio-demographic information, medical history, and lifestyle factors. We additionally measured data such as height, weight, fasting blood glucose, and blood pressure. Because we were limited to only one QUS device, we randomly selected two community health service centers from two urban districts in Changchun for the present study. All subjects provided written informed consent. This project was approved by the institutional review board (IRB) of China Medical University.

We included all individuals aged 40 years or older, with complete and valid information on QUS parameters, who also provided blood samples. Individuals who met any of the following criteria were excluded: (1) having osteoporosis-related medications, such as bisphosphonates, estrogen, and glucocorticoids; (2) having diseases that may contribute to secondary osteoporosis (e.g., thyroid/parathyroid disorders, type 1 diabetes mellitus, chronic liver/kidney disease, rheumatoid arthritis, or cancer); and (3) having missing data on covariates, such as age, sex, and body mass index (BMI).

Quantitative ultrasound measurement

QUS measurements of the calcaneus were performed using an ultrasound bone densitometer (Osteo KJ3000, Kejin Inc., Nanjing, Jiangsu, China). This device produces two key parameters: speed of sound (SOS, expressed as m/s) and broadband ultrasound attenuation (BUA, expressed as dB/MHz). SOS is the transmission time of sound waves divided by the length of the body part studied; BUA refers to the slope between the attenuation of sound signals and their frequency (23). The daily performed control spine phantom had a coefficient of variation (CV) of <5%. Participants with invalid QUS measurements (i.e., negative values) were excluded.

Blood collection

Fasting blood samples (≥8 h) were collected with anticoagulant tubes (BD, Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) from all subjects. Within 4 h, these samples were transported to the laboratory of Jilin University using ice boxes for processing and stored at −80°C until assay.

FlOP measurement

We measured FlOPs for all individuals with collected blood samples. Measurement of FlOPs was performed based on the method modified by Shimasaki (25) and Wu (26), and has been previously described (20). In brief, plasma was extracted with ethanol/ether (3:1, v/v) and centrifuged at 3,000 rpm for 10 min at 4°C. Then the supernatant was added to a black 96-well Microplate (Black Fat Bottom Polystyrene High Bind Microplate 3925, Corning) and measured by a fluorescent microplate reader (Cytation 3 Cell Imaging Multi-Mode Reader, BioTek, Vermont, USA) at a wavelength of 320/420 nm (excitation and emission wavelength). The fluorescence of FlOPs was presented as relative fluorescent intensity units per milliliter (FI/ml). The inter-assay and intra-assay CVs for FlOP measurement were 3.3 and 1.7%, respectively. We additionally tested the long-term stability of FlOPs among 16 participants in a pilot study. We found that FlOPs were stable at −80°C for at least 90 days. In the present study, all blood samples were collected between July and September 2019. Plasma FlOP levels were measured in October 2019. The storage duration of the blood samples and subsequent measurement of FlOP levels within 90 days in our study ensured the stability of FlOP levels.

Anthropometric assessment

Body weight and height, without shoes and heavy clothes, were measured using a full automatic ultrasonic height and weight measuring instrument (SK-CK90, SONKA, Shenzhen Shuangjia Electronic Technology Co., Ltd., Guangdong, China). Body weight and height were recorded to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as weight (kg) divided by height (meters) squared. Participants were categorized as non-obese (BMI < 28 kg/m^2) or obese (BMI ≥ 28 kg/m^2) according to the cut-points recommended by the Working Group on Obesity in China (27).

Ascertainment of other covariates

The covariates included in this study were socio-demographic data (e.g., age and sex), anthropometric variables (e.g., BMI), medical history (e.g., hypertension, type 2 diabetes mellitus status, and family history of kyphosis,), and lifestyle data (e.g., smoking and physical activity). Smoking was defined as the current or past use of tobacco. Frequent alcohol users were defined as a person who consumed an average of 3 or more units of alcohol per day. One unit is equivalent to half a pint (285 ml) of beer, one glass (125 ml) of wine, or a pub measure of spirits (8–10 g pure alcohol). Physical activity was computed using the frequency, duration, and intensity (light, moderate and heavy) of physical activity that was reported by participants and was subsequently expressed as metabolic equivalent hours per week (Met-hours/week) (28). Frequent users of calcium supplementation, dairy or soy products, and seafood were defined as an individual who ate these food items at least three times a week. Fasting blood glucose and blood pressure were obtained by physical examination. Diabetes mellitus was determined by either a fasting blood glucose ≥ 7.0 mmol/L, a self-reported diagnosis by a physician, or taking hypoglycaemic drugs (29). Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg, a self-reported diagnosis of hypertension by a physician, or the use of antihypertensive medication (30). Coronary heart disease, history of fracture, family history of osteoporosis diagnosis, and family history of kyphosis were self-reported.

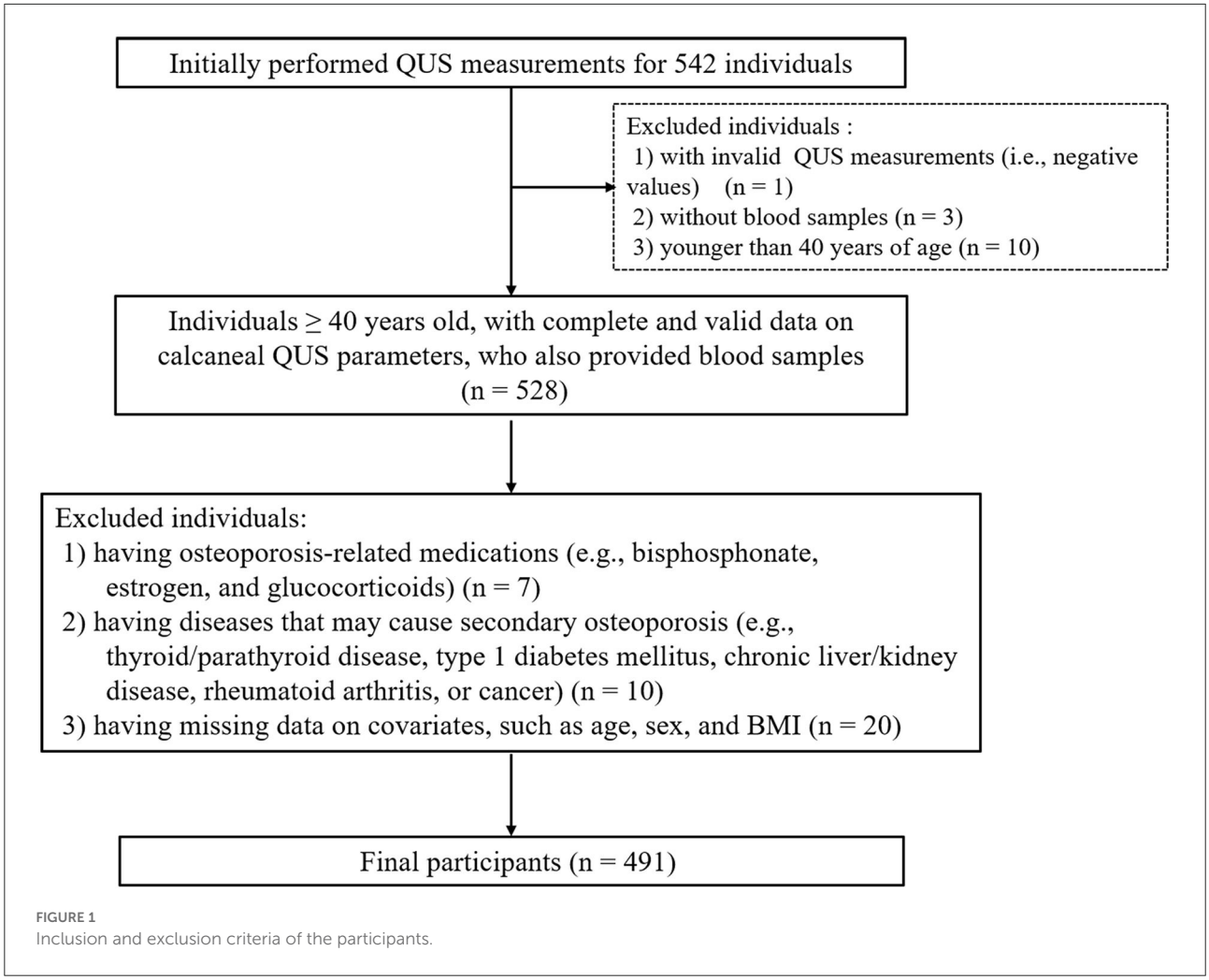

FIGURE 1
Inclusion and exclusion criteria of the participants.

Statistical analysis

Descriptive data for the total population as well as by sex are provided. Continuous variables with a normal distribution are reported as means and standard deviations (SDs). Categorical variables are reported as frequencies and percentages. Data with a skewed distribution are presented as medians and interquartile ranges. The characteristics of participants by sex were compared using Student's *t*-test or Wilcoxon non-parametric test for continuous variables or Chi-square test for categorical variables. To test whether there was potential selection bias, we compared the baseline characteristics (i.e., age, sex, and BMI) between the included individuals for this study with the overall population from the 10 districts.

As the effect of oxidative stress on bone homeostasis is regulated by sex hormones and QUS measures were different between sexes (31, 32), all the regression analyses were performed stratified by sex. We used multivariable linear regression models to evaluate the associations of FlOPs with SOS and BUA. To better compare a person with a typical "high" value of FlOPs to a person with a typical "low" value, we rescaled the values of FlOP levels using the interquartile range, defined by the distance between the 25th and the 75th percentiles (33). FlOPs were further transformed into the natural logarithmic scale due to its skewed distribution. The following covariates were considered in all the adjustment models: age, BMI, smoking, frequent alcohol users, physical activity, frequent dairy or soy products, and history of fracture; sex and menopausal status were additionally adjusted for in the analysis of all the participants and in the analysis of only female participants, respectively. We included the covariates for adjustment if they were associated with either SOS or BUA at alpha = 0.1 in the bivariate analysis or were well-known risk factors for bone health. We also examined the relationships between covariates and FlOPs using bivariate analysis. Subgroup linear regression analyses by age (<60 years and ≥60 years), sex (male/female), BMI (<28 kg/m^2 and ≥28 kg/m^2), smoking (yes/no), frequent dairy or soy products use (yes/no), frequent alcohol use (yes/no), type 2 diabetes mellitus (yes/no), and hypertension (yes/no) were

also performed. We conducted these subgroup analyses mainly because these stratified factors were related to FlOPs and/or QUS parameters (17, 32). To test whether there is interaction by these potential factors on FlOPs in relation to QUS parameters, we built the interaction terms (e.g., FlOPs* age, FlOPs*sex, FlOPs*BMI, FlOPs*smoking, FlOPs*frequent dairy or soy products use, FlOPs*frequent alcohol use, FlOPs*type 2 diabetes mellitus, and FlOPs*hypertension) in the linear regression models. All analyses were conducted with SPSS (version 24.0, IBM SPSS Inc., Chicago, IL) or R (version: 4.0.0; R Foundation for Statistical Computing, Vienna, Austria) statistical software.

Results

We measured QUS for all 542 participants. However, we excluded one participant who had a negative BUA measurement value and further excluded ineligible individuals, resulting in a final study sample of 491 eligible subjects for analysis (Figure 1). Our participants were younger than the overall population from the 10 districts (65.2 vs.70.0 years; $P < 0.05$). However, there was no significant difference in the proportion of females (59.6 vs. 59.1%; $P > 0.05$) nor BMI (24.9 vs. 24.9 kg/m^2) between the two populations. The characteristics of the included participants are shown in Table 1. The participants' median value of FlOPs was 143.0 FI/ml (IQR: 128.3–160.9 FI/ml; range: 97.6–478.8 FI/ml). Compared to males, females had a lower BMI and were less likely to be smokers and frequent alcohol users, and were more likely to consume seafood on a frequent basis (all $P < 0.05$). Females were also less likely to have type 2 diabetes mellitus, more likely to use calcium supplementation, and have a family history of kyphosis (all $P < 0.05$). Females also had a significantly lower median level of FlOPs compared to males ($P < 0.05$).

In the bivariate analyses, we observed significant positive associations between FlOPs with age, BMI, smoking, frequent alcohol use, type 2 diabetes mellitus, hypertension, and coronary heart disease; there was also a negative relationship between FlOPs and family history of kyphosis (all $P < 0.05$; Supplementary Table 1). As compared to males, females were associated with higher FlOPs. Hypertension and coronary heart disease were positively associated with FlOPs in males, whereas type 2 diabetes mellitus was positively associated with FlOPs in females (all $P < 0.05$).

In the bivariate analyses (Supplementary Tables 2, 3), SOS and BUA were inversely associated with age, while positively associated with frequent alcohol users. BMI had a positive relationship with SOS, but not with BUA. Frequent dairy or soy product users were only inversely associated with SOS. We only observed a positive association between smoking and BUA. Compared with males, females were associated with lower levels of SOS and BUA. In males, we only observed a statistically significant positive relationship between BMI and SOS. In females, age, coronary heart disease, and menopause were negatively associated with SOS, whereas age, hypertension, and menopause were negatively associated with BUA (all $P < 0.05$).

In the adjusted multivariable linear regression models (Table 2), we observed an inverse association between FlOPs and SOS (β for an increase of logarithmic interquartile range $= -10.64$; $P = 0.018$). Higher FlOP levels were marginally associated with lower SOS in females (β for an increase of

TABLE 1 Characteristics of the study participants.

Variables	Total ($n = 491$)	Male ($n = 201$)	Female ($n = 290$)
Age (years)	65.2 (9.7)	66.0 (9.1)	64.6 (10.1)
Body mass index (kg/m^2)	24.9 (3.7)	**25.5 (3.5)**	**24.6 (3.7)**
Smoking (n, %)	82 (16.7%)	**74 (36.8%)**	**8 (2.8%)**
Frequent alcohol users (n, %)	52 (10.6%)	**50 (24.9%)**	**2 (0.7%)**
Physical activity (MET-hours/week)[a]	32.6 (2.3,44.1)	32.6 (7.0, 44.1)	32.6 (2.1, 44.1)
Use of calcium supplementation (n, %)	153 (31.2%)	**48 (23.9%)**	**105 (36.2%)**
Frequent dairy or soy products users (n, %)	210 (42.5%)	76 (37.8%)	134 (46.2%)
Frequent seafood users (n, %)	45 (9.2%)	**9 (4.5%)**	**36 (12.4%)**
Sunlight expose ≥ 30 min per day (n, %)	405 (82.5%)	167 (83.1%)	238 (82.1%)
Type 2 diabetes mellitus (n, %)	150 (30.6%)	**76 (37.8%)**	**74 (25.5%)**
Hypertension (n, %)	270 (55.0%)	112 (55.7%)	158 (54.5%)
Coronary heart disease (n, %)	82 (16.7%)	32 (15.9%)	50 (17.2%)
History of fracture (n, %)	24 (4.9%)	6 (3.0%)	18 (6.2%)
Family history of osteoporosis diagnosis (n, %)	36 (7.3%)	12 (6.0%)	24 (8.3%)
Family history of kyphosis (n, %)	38 (7.7%)	**8 (4.0%)**	**30 (10.3%)**
Menopause (n, %)	NA	NA	260 (89.7%)
FlOPs (FI/ml)[a]	143.0 (128.3, 160.9)	**148.1 (133.7, 165.4)**	**140.0 (124.9, 155.7)**
Natural logarithmic-scaled FlOPs (FI/ml)	5.00 (0.24)	**5.04 (0.24)**	**4.98 (0.24)**

Variables with a normal distribution are presented as mean (standard deviation); [a]Variables with a skewed distribution are presented as median (interquartile range); categorical variables are presented as n (%). Bold-faced values indicate statistical significance at alpha = 0.05 between male and female. MET, metabolic equivalent Task; NA, Not applicable.

TABLE 2 Fluorescent oxidation products (FlOPs) and quantitative ultrasound (QUS) parameters: multivariable linear regression analysis.

Subjects	FlOPs (FI/ml, 75th vs. 25th percentile)	SOS (m/s)		BUA (dB/mHz)	
		β (95% CI)*	*P*	β (95% CI)*	*P*
Model 1^{+}: total ($n = 491$)	160.9 vs. 128.3	−10.64 (−19.40, −1.88)	0.018	−0.14 (−2.75, 2.47)	0.893
Model 2^{+}: male ($n = 201$)	165.4 vs. 133.7	−11.84 (−27.14, 3.47)	0.131	−1.59 (−6.61, 3.44)	0.537
Model 3$^{+:}$ female ($n = 209$)	155.8 vs. 124.9	−9.68 (−19.95, 0.59)	0.066	0.83 (−1.88, 3.53)	0.548

*Per increase of logarithmic interquartile range in FlOPs. $^{+}$Model 1 adjusted for age, sex, BMI, smoking, frequent alcohol use, physical activity, frequent dairy or soy products use, and history of fracture. $^{+}$Model 2 adjusted for age, BMI, smoking, frequent alcohol use, physical activity, frequent dairy or soy products use, and history of fracture. $^{+}$Model 3 adjusted for factors in model 2 + menopausal status.

logarithmic interquartile range = −9.68, $P = 0.066$), but not in males (β for an increase of logarithmic interquartile range = −11.84, $P = 0.131$). No significant association between FlOPs and BUA was noted (all $P > 0.05$; Table 2).

Subgroup analyses showed that the relationship between FlOPs and SOS was stronger in participants with type 2 diabetes mellitus (β = −24.700, $P = 0.003$) than in individuals without diabetes (β = −4.389, $P = 0.405$; P for interaction = 0.028; Table 3). The FlOP-SOS relationship was not modified by age, sex, BMI, smoking, frequent dairy or soy products, frequent alcohol users, or hypertension (all P for interaction > 0.05).

Discussion

In this community-based cross-sectional study, we observed that FlOPs were inversely associated with SOS in middle-aged and elderly adults. Higher FlOP levels were marginally associated with lower SOS in females, but not in males. No significant relationship between FlOPs and BUA was observed in the overall analysis nor by sex. The present findings expand our current knowledge of the relationship between FlOPs and QUS parameters.

As far as we know, this is the first study examining the relationship between FlOPs and QUS parameters. To some extent, our results were in agreement with two previous studies, in which higher FlOP levels are associated with lower BMD in male veterans (20) and an increased risk of hip fracture in postmenopausal women (21). Since QUS reflects the structural and mechanical properties of the bone (22, 23), the present study extended the evidence about the relationship between FlOPs and bone health in males and females. Moreover, among all the interaction terms, we observed that only type 2 diabetes mellitus status significantly modified the relationship between FlOPs and SOS. We did not find evidence to support smoking status as an effect modifier in the association between FlOPs and SOS. This is concordant with a previous study where smoking did not modify the relationship between FlOPs and BMD (20). Nevertheless, the possible explanation for the insignificant interaction terms between some subgroups (i.e., FlOPs*sex, FlOPs*smoking, and FlOPs*BMI) may be due to small sample size.

When compared our results with those of studies using other oxidative stress-related biomarkers, there are both consistencies and inconsistencies. For example, Basu et al. suggested that 8-iso-$PGF_{2\alpha}$, a lipid peroxidation marker, is negatively associated with SOS and BUA in Swedish adults (34). In the study of 868 Spanish men older than 50 years, Hernández et al. observed that higher levels of serum uric acid, a substance with antioxidant properties, are positively associated with all QUS parameters (14). In the present study, FlOPs were only associated with SOS, but not with BUA. This finding was partially consistent with the pooled results obtained by Enneman et al., which showed a statistically significant inverse association between homocysteine and SOS, but not BUA in older persons (15). Even though SOS and BUA are highly correlated (35), they reflect different aspects of bone properties and are influenced by various factors. SOS reflects the material property of the bone, such as the elastic modulus and compressive strength. BUA reflects bone microarchitecture and bone strength (23, 36). Previous *in vivo* study suggests that SOS has a stronger association with BMD than BUA as BUA failed to predict the mechanical properties of high-density trabecular bone (37). Further studies are warranted to elucidate this discrepancy.

Several potential mechanisms may explain the association between FlOPs and QUS parameters. Numerous lines of evidence suggest that oxidative stress is involved in the process of bone remodeling, inducing an imbalance between osteoclastic bone resorption and osteoblastic bone formation (7, 38, 39). Excessive ROS affects the differentiation and activity of osteoclasts by regulating mitogen-activated protein kinases (MAPKs), nuclear factor-kappa (NF-κB), and Ca^{2+}-mediated signaling cascades (40). Baek et al. found that the number and activity of osteoclasts, as well as the receptor activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) ratio, were increased when hydrogen peroxide (H_2O_2) was added to human marrow mononuclear cells (41). Higher levels of oxidative stress decrease osteoprogenitor differentiation to the osteoblast cell lineage and promote the apoptosis of osteoblasts (7, 42). Bai et al. reported that H_2O_2-induced oxidative stress

TABLE 3 Fluorescent oxidation products (FlOPs, Per increase of logarithmic interquartile range) and quantitative ultrasound (QUS) parameters: multivariable linear regression analysis stratified by age, sex, BMI, smoking, frequent alcohol users, frequent dairy or soy products users, type 2 diabetes mellitus, and hypertension[G].

Variables	Subgroup	Number	SOS (m/s)			BUA (dB/mHz)		
			β	*P*	*P* for interaction	β	*P*	*P* for interaction
Age (year)	<60	129	−4.760	0.590	0.489	1.335	0.612	0.842
	≥60	362	−12.676	0.016		−0.393	0.799	
Sex	Male[+]	201	−11.837	0.131	0.965	−1.585	0.537	0.566
	Female[‡]	290	−9.678	0.066		0.829	0.548	
BMI (kg/m^2)	<28	417	−7.541	0.093	0.150	0.117	0.928	0.756
	≥28	74	−24.931	0.126		−1.421	0.786	
Smoking	No	409	−10.231	0.026	0.388	0.216	0.877	0.880
	Yes	82	6.062	0.657		1.127	0.772	
Frequent alcohol users	No	439	−12.071	0.013	0.207	−0.478	0.736	0.294
	Yes	52	7.263	0.552		6.744	0.090	
Frequent dairy or soy products users	No	281	−13.216	0.045	0.603	−0.236	0.892	0.771
	Yes	210	−7.177	0.222		−0.231	0.912	
Type 2 diabetes mellitus	No	341	−4.389	0.405	0.028	0.286	0.849	0.637
	Yes	150	−24.700	0.003		−1.092	0.678	
Hypertension	No	221	−10.780	0.145	0.961	−0.134	0.943	0.985
	Yes	270	−11.447	0.051		−0.419	0.828	

[G]All models were adjusted for age, sex, BMI, smoking, frequent alcohol use, physical activity, frequent dairy or soy products use, and history of fracture, unless otherwise specified. [+]Adjusted for age, BMI, smoking, frequent alcohol use, physical activity, frequent dairy or soy products use, and history of fracture. [‡]Adjusted for age, BMI, smoking, frequent alcohol use, physical activity, frequent dairy or soy products use, history of fracture, and menopausal status.

suppresses the osteoblastic differentiation process, manifested by a reduction of bone formation markers including alkaline phosphatase (ALP) (43).

Most of the existing studies focused on the relationship between oxidative stress and BMD (11, 12, 20). Bone strength is not only captured by BMD, but also by bone microarchitecture, bone mechanical properties, mineralization degree, and quality of collagens (44–46). In some situations, measurement of DXA is not available due to its high cost, ionizing radiation, and non-portability. QUS measurement of the calcaneus is a suitable method for screening osteoporosis. Moreover, compared to other oxidative stress-related biomarkers (i.e., MDA) that only reflect one specific aspect of oxidative damage (i.e., lipid peroxidation), FlOPs reflect the global level of oxidative damage *in vivo*. Overall, the present study provided supporting evidence for the association between FlOPs and bone mechanical and structural properties determined by QUS parameters. If our findings are confirmed in further studies, FlOPs may be a better biomarker for assessing the impact of global oxidative damage on BMD at the calcaneus and evaluating the effects of antioxidant use on bone health.

Several limitations of the present study need to be mentioned. First, due to the nature of the cross-sectional design, the temporal association between FlOPs and SOS cannot be determined. Second, our study had a small sample size; this may negatively impact the reliability of our results. Third, the possibility of residual confounding cannot be completely excluded, because some risk factors (i.e., vitamin D intake) were not included in the analysis. However, this limitation is likely to be minor as vitamin D intake is highly correlated with calcium intake (47, 48). Lastly, due to the difference in age between the included individuals selected from two urban districts in Changchun and the overall participants from the 10 districts, the present study may suffer from potential selection bias.

Conclusions

In summary, plasma FlOP levels were inversely associated with SOS, but not with BUA in middle-aged and elderly adults. The present findings support the possibility of using FlOPs as a global biomarker to assess the impact of oxidative stress on the structural and mechanical properties of the bone. It would be worthwhile to conduct further studies to elucidate the roles of FlOPs in QUS parameters with a longitudinal study design.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) of China Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SY and YL designed the study. XS prepared the first draft of the paper. XS, QZ, BL, and YF contributed to the investigation and methodology of the present study. XS, MZ, and SY were responsible for the statistical analysis of the data. SY, MZ, AV, and HC reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1032550/full#supplementary-material

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Relationship of blood heavy metals and osteoporosis among the middle-aged and elderly adults: A secondary analysis from NHANES 2013 to 2014 and 2017 to 2018

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Objective: This study aimed to assess the relationship between blood heavy metals and a higher prevalence of osteoporosis in middle-aged and elderly US adults using the National Health and Nutritional Examination Surveys (NHANES).

Methods: The secondary data analysis was performed using the data of NHANES 2013–2014 and 2017–2018. We used the information, including physical examination, laboratory tests, questionnaires, and interviews, provided by participants in NHANES. Logistic regression and weighted quantile sum (WQS) regression models were used to explore the relationships between levels of blood heavy metals and a higher prevalence of osteoporosis.

Results: A total of 1,777 middle-aged and elderly participants were analyzed in this study, comprising 115 participants with osteoporosis and 1,662 without osteoporosis. Adjusted model 1 showed a significant positive relationship between cadmium (Cd) levels and a higher prevalence of osteoporosis (quartile 2, OR = 7.62; 95% CI, 2.01–29.03; $p = 0.003$; quartile 3, OR = 12.38; 95% CI, 3.88–39.60; $p < 0.001$; and quartile 4, OR = 15.64; 95% CI, 3.22–76.08; $p = 0.001$). The fourth quartile of selenium (Se) level (OR = 0.34; 95% CI, 0.14–0.39; $p < 0.001$) led to a lower prevalence of osteoporosis and exerted a protective effect on model 1. Other models produced similar results to those of model 1. A subgroup analysis showed that Cd levels were positively related to a higher prevalence of osteoporosis in all three models in women, while this relationship was not found in men. The fourth quartile of the Se level was related to a lower prevalence of osteoporosis in both male and female analyses. A significant positive relationship was found between the blood Cd level and a higher prevalence of osteoporosis in the non-smoking subgroup. Blood Se level showed a protective effect on the fourth quartile in both the smoking and non-smoking subgroups.

Conclusion: Blood Cd level aggravated the prevalence of osteoporosis, while blood Se level could be a protective factor in osteoporosis among the US middle-aged and older populations.

KEYWORDS

osteoporosis, heavy metals, NHANES, risk factors, middle-aged and older population

Introduction

Osteoporosis is a systemic metabolic disease and remains a global health problem, which is increasingly becoming common in both developing and developed countries (1). It is estimated that there were 10.2 million cases of osteoporosis among the US population aged over 50 years in 2010 and that this number will reach 13.5 million by 2030 (2, 3). Osteoporosis is characterized by a loss of bone mineral density (BMD), which leads to an increased risk of fragility fractures and thus an increased economic and medical burden on the patient (4). As the definition of osteoporosis either by experts or by an explanation based on histology did not prove to be practical for patient care, a panel of the World Health Organization (WHO) defined osteoporosis as BMD values of 2.5 standard deviations (SDs) or more below the mean of the young adult reference group (5). There are many risk factors for osteoporosis and BMD reduction, including older age and female gender (6). In recent years, it has been hypothesized that heavy metals may be associated with the risk of degenerative diseases and fractures (7).

Heavy metals have been demonstrated to be associated with adverse health effects. Moreover, exposure to heavy metals in the environment will affect genes and increase disease susceptibility (8). The accumulation of heavy metals in the human body will change hormone metabolism and lead to vasoconstriction, thus leading to adult diseases (7). Accordingly, a recent study revealed that the accumulation of blood heavy metals in bones increases bone resorption and changes bone mineral content, which will eventually lead to osteoporosis and bone fracture (9). Several studies indicated a negative correlation between daily or long-time exposure to cadmium (Cd), lead (Pb), mercury (Hg), and BMD (10). However, no significant correlation between dietary intake of these heavy metals and bone parameters was observed (11).

The relationship between blood heavy metals and the risk of osteoporosis has only been reported in observational studies involving small sample sizes (12). Moreover, several bodies of research determined the exposure to heavy metals based on the urinary or environmental levels of heavy metals (13–15). Nevertheless, it is unclear whether blood heavy metal levels are associated with osteoporosis in the general aging population. Therefore, this study aimed to assess the relationship of blood heavy metals with a higher prevalence of osteoporosis in a US population of middle-aged and elderly people using the National Health and Nutritional Examination Surveys (NHANES). Investigation of the correlation between blood heavy metals and osteoporosis is important as people may experience cumulative exposure in some circumstances and osteoporosis is a threat to the aging population. An analysis of the relationship between aging and osteoporosis could help prevent osteoporosis and reduce the exposure of the aging population to the risk factors.

Methods

Study subjects

This study was performed as a secondary analysis using the data collected in NHANES 2013–2014 and 2017–2018, and the data were collected by physical examination, laboratory tests, questionnaires, and interviews. Details of the NHANES can be found on the website of the American Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes). In the present study, we first enrolled all participants from NHANES 2013 to 2014 ($N = 10,175$) and 2017 to 2018 ($N = 9,254$). Then, we excluded participants with incomplete information on blood heavy metals ($N = 7,330$), BMD data ($N = 8,347$), and missing basic information as well as those aged below 40 years ($N = 1,975$). In the end, a total of 1,777 individuals were included in the final analysis (Figure 1).

Evaluation of osteoporosis

The BMD values at different sites (the total femur, the femur neck, the trochanter, and the trochanter intertrochanter) were measured using dual-energy x-ray absorptiometry (DXA) with Hologic QDR-4500A fan-beam bone densitometers (Hologic, Inc., Bedford, MA, USA). The regions of the proximal femur of the left hip were routinely examined. An examination of the left hip was replaced by the right hip on the condition that the participant reported having replacement or metal objects in the left leg. Any participant who was pregnant, who weighed over 300 pounds, or had a history of radiographic contrast material, fractures, replacements, or pins in both hips was excluded from the DXA examination.

Osteoporosis was defined as BMD values of 2.5 standard deviations (SDs) or more below the mean of the young adult reference group according to the guidelines of the World Health Organization (WHO) (5). This study assessed osteoporosis in four regions of the femur: the total femur, the femur neck, the trochanter, and the intertrochanter, and the thresholds were 0.67 g/cm^2, 0.56 g/cm^2, 0.46 g/cm^2, and 0.79 g/cm^2, respectively (16). Osteoporosis in any femoral region was defined as overall osteoporosis.

Assessment of heavy metals

After performing the step involving a simple dilution sample preparation, blood heavy metals, such as Pb, Cd, total Hg, selenium (Se), and manganese (Mn), were directly measured in whole blood samples by mass spectrometry. To carry out a uniform distribution of cellular components, a small amount of whole blood was extracted from a larger sample of whole blood after mixing during the dilution phase. Dilution of blood includes simple dilution of 1 part sample + 1 part water + 48 parts diluent during sample preparation before analysis. Liquid samples were introduced into the mass spectrometer through the inductively coupled plasma ionization ion source (17).

Ascertainment of covariates

Information on demography and lifestyle factors was collected by trained personnel, according to the statement mentioned on the NHANES website. Demographic characteristics included age

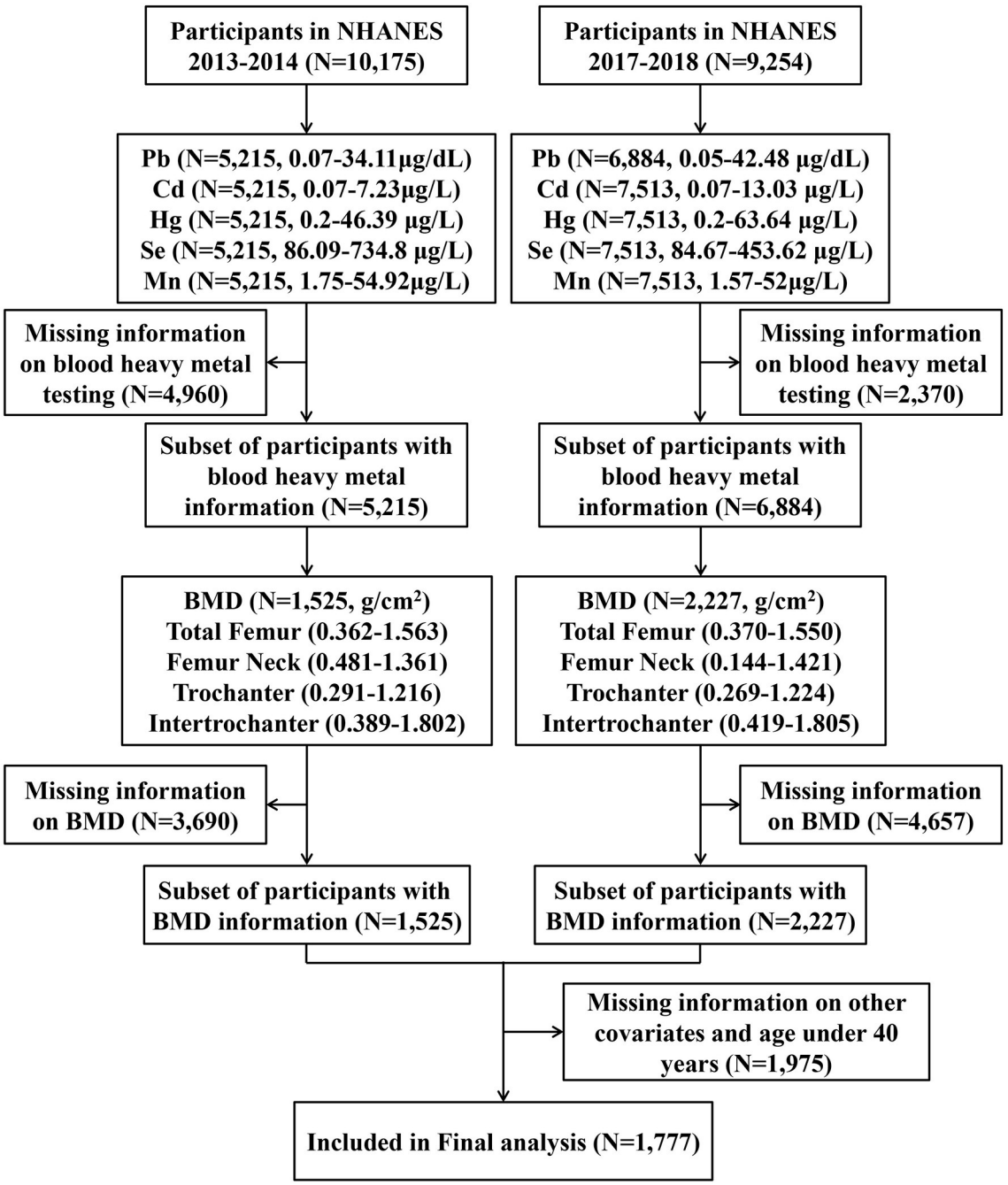

FIGURE 1
Flowchart of the study population selection.

(years), gender (male or female), race/ethnicity (Mexican, non-Hispanic white, non-Hispanic black, Mexican American, and other races), educational level (less than 9th grade, 9–11th grades, high school, some college, or college graduate), and physical activity (Yes and No). Alcohol consumption was defined as <12 or ≥12 alcoholic drinks per year. Smoking status was categorized into never smokers or current smokers. Exposure to secondhand smoke was indicated as no one in the household is a smoker or ≥1 one member in the household is a smoker. Sedentary behavior was defined as sitting for more than 6 h a day, which does not include time spent sleeping. The medical examinations were carried out in mobile centers. Body mass index (BMI, kg/m^2) was classified as <25, 25–30, or >30. Diabetes was defined as reporting a previous diagnosis or reaching a fasting glucose level of ≥126 mg/dl. Hypertension status was defined as reporting a previous diagnosis (yes or no). Arthritis was defined as a doctor ever diagnosing one to have had arthritis. A thyroid problem was defined as a doctor ever diagnosing one to have had a thyroid problem. Hypercholesterolemia was defined as total cholesterol values ≥240 mg/dl. The estimated glomerular filtration rate (GFR) was

calculated based on age, gender, and serum creatinine according to the Chronic Kidney Disease Epidemiology Collaboration equation (18). The annual household income was classified as <$20,000, $20,000–$34,999, $34,999–$74,999, or ≥$75,000.

Statistical analysis

All analyses considered complex survey design factors, including sample weights, clustering, and stratification, with instructions for using NHANES data. Four-year sampling weights were calculated by multiplying the sampling weights provided by NHANES for 2-year cycles by two. Data were expressed as mean ± standard derivation (SD) for continuous variables and numbers (percentages) for categorical variables. We used Student's *t*-test for continuous variables and the Chi-square test for categorical variables. As the blood heavy metals displayed non-normal distribution, categorical groups rather than continuous values were used in statistical analysis. The levels of blood heavy metals (Pb, Cd, Hg, Mn, and Se) were categorized into one of the four groups based on quartiles (quartile 1: <25th percentile, quartile 2: 25th−50th percentile, quartile 3: 50th−75th percentile, and quartile 4: >75th percentile). Categorical groups and continuous analysis of blood heavy metals of logistic regressions with weights were used to estimate the odds ratio (ORs) with 95% confidence intervals (95% CIs) for the relationships between blood heavy metals and the prevalence of osteoporosis. Model 1 was adjusted for gender, age, and race, and model 2 was further adjusted for all the covariates. Blood heavy metals were evaluated by using quartile 1 as the reference. We further used weighted quantile sum regression (WQS) models with positive and negative directionality modes for the mixed effects. A two-sided value of P of <0.05 was considered statistically significant. All the analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software version 4.2.2 (Vienna, Austria).

Results

Characteristics of participants

The present study included a total of 1,777 participants, involving 115 of them with osteoporosis and 1,662 without osteoporosis. The weighted average age was 58.9 ± 0.4 years and 50.4% of them were men. Table 1 shows the basic characteristics of the study participants. Compared with the non-osteoporosis group, participants with osteoporosis were older and were more likely to be women. These participants also had a higher prevalence of normal BMI, arthritis, thyroid problems, a lower GFR, and a lower annual household income. There were no significant differences in race, education, smoking status, exposure to secondhand smoke, alcohol consumption, physical activity, sedentary behavior, hypercholesterolemia, or history of diabetes or hypertension between the osteoporosis group and the non-osteoporosis group (Table 1). Characteristics of participants based on the levels of heavy metals in their blood are listed in Supplementary Tables S1–S5. The weighted geometric mean (GM) and quartiles of concentrations of blood heavy metals are listed in Table 2.

Relationships of blood heavy metals with osteoporosis

Tables 3, 4 show the relationships between levels of blood heavy metals and osteoporosis using univariate logistic regression and multivariate logistic regression, respectively. Cd levels had a positive relationship with osteoporosis. Moreover, there is a negative relationship between Se levels and osteoporosis. The adjusted model 1 (adjusted by age, gender, and race) showed a significant positive relationship between Cd levels and osteoporosis (quartile 2, OR = 7.62; 95% CI, 2.01–29.03; $p = 0.003$; quartile 3, OR = 12.38; 95% CI, 3.88–39.60; $p < 0.001$; and quartile 4, OR = 15.64; 95% CI, 3.22–76.08; $p = 0.001$). In Se element analysis, taking the first quartile as a reference, the fourth quartile (OR = 0.34; 95% CI, 0.14–0.39; $p < 0.001$) led to a lower prevalence of osteoporosis and exerted a protective effect on model 1. However, the second (OR = 0.52; 95% CI, 0.27–1.02; $p = 0.056$) and third quartiles (OR = 0.46; 95% CI, 0.21–1.03; $p = 0.059$) were associated with a numerically decreased prevalence of osteoporosis with borderline significance. The third quartile of the Mn level showed a borderline negative significant relationship with osteoporosis (OR = 0.47; 95% CI, 0.22–0.99; $p = 0.049$) in model 1. Pb and Hg have no relationship with osteoporosis. Model 2 (adjusted by age, gender, race, education, BMI, arthritis, thyroid problems, GFR, and annual household income) and model 3 (adjusted by age, gender, race, education, smoke, diabetes, hypertension, physical activity, BMI, alcohol consumption, exposure to secondhand smoke, sedentary behavior, arthritis, thyroid problems, hypercholesterolemia, GFR, and annual household income) produced similar results to those of model 1 for the relationship between blood heavy metals and the prevalence of osteoporosis.

Blood heavy metals that make a major contribution to the whole relationship of the mixture (Pb, Cd, Hg, Se and Mn) were analyzed using the WQS models. The ranking of blood heavy metals was based on the probability of the maximum weight of blood heavy metals in the mixture. WQS with a positive directional mode showed that Cd was positively related to a higher prevalence of osteoporosis, while Se was negatively related to the higher prevalence of osteoporosis (Figure 2).

Subgroup analysis

In the subgroup analysis stratified by gender, logistic regression analysis revealed that the third and fourth quartiles of the Se level were associated with a lower prevalence of osteoporosis (OR = 0.31; 95% CI, 0.10–0.92; $p = 0.035$, OR = 0.16; 95% CI, 0.04–0.63; $p = 0.009$, respectively) in model 3 in men. There was no relationship between Cd levels and the prevalence of osteoporosis in men (Supplementary Table S6). However, in women, Cd levels were shown to be positively related to a higher prevalence of osteoporosis (quartile 2, OR = 14.11; 95% CI, 2.12–94.13; $p = 0.006$; quartile 3, OR = 30.55; 95% CI, 5.90–158.11; $p < 0.001$; and quartile 4, OR = 27.00; 95% CI, 3.34–218.29; $p = 0.002$) in model 3. The fourth quartile of the Se level was related to a lower prevalence of osteoporosis (OR =

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TABLE 1 Characteristics of participants with and without osteoporosis in the enrolled population of NHANES.

Characteristic	Total ($N = 1,777$)	No osteoporosis ($N = 1,662$)	Osteoporosis ($N = 115$)	T/χ^2	*P*-value
Age (weighted years, mean ± SD)	58.9 ± 0.4	58.4 ± 0.4	66.9 ± 1.5	32.75	<0.001
Gender, no. (weighted %)[a]				28.24	<0.001
Men	903 (50.4)	865 (52.0)	38 (25.2)		
Women	874 (49.6)	797 (48.0)	77 (74.8)		
Race, no. (weighted %)[a]				7.54	0.342
Mexican	218 (8.8)	209 (9.2)	9 (3.5)		
Other Hispanic	165 (6.0)	154 (5.8)	11 (9.7)		
Non-Hispanic white	788 (61.8)	728 (62.0)	60 (59.3)		
Non-Hispanic Black	351 (13.4)	333 (13.3)	18 (14.0)		
Other Race	255 (10.0)	238 (9.7)	17 (13.5)		
Education, no. (weighted %)[a]				7.53	0.217
Less than 9th grade	209 (9.5)	187 (9.3)	22 (12.3)		
9–11 grade	503 (25.1)	470 (24.7)	33 (31.5)		
High school graduate or equivalent	423 (24.0)	398 (23.8)	25 (27.2)		
Some college or AA degree	304 (17.5)	288 (17.8)	16 (13.5)		
College graduate or above	338 (23.9)	319 (24.4)	19 (15.5)		
BMI, no. (weighted %)[a]				34.40	<0.001
Normal (<25)	442 (23.5)	387 (22.0)	55 (46.0)		
Overweight (25–30)	662 (38.3)	622 (38.6)	40 (33.8)		
Obesity (>30)	673 (38.2)	653 (39.4)	20 (20.2)		
Smoking status, no. (weighted %)[a]				1.25	0.350
Yes	382 (18.9)	354 (18.7)	28 (23.1)		
No	1,395 (81.1)	1,308 (81.3)	87 (76.9)		
Physical activity, no. (weighted %)[a]				1.72	0.277
Yes	350 (20.8)	332 (21.1)	18 (23.1)		
No	1,427 (79.2)	1,330 (78.9)	97 (76.9)		
Diabetes, no. (weighted %)[a]				1.03	0.406
Yes	362 (16.9)	345 (17.1)	17 (15.8)		
No	1,415 (83.1)	1,317 (82.9)	98 (84.2)		
Hypertension, no. (weighted %)[a]				3.59	0.162
Yes	878 (45.0)	814 (44.5)	64 (53.9)		
No	899 (55.0)	848 (55.5)	51 (46.1)		
Alcohol consumption, no. (weighted %)[a]				0.02	0.871
≥12 times per year	247 (13.8)	234 (13.8)	13 (14.3)		
<12 times per year	1,530 (86.2)	1,428 (86.2)	102 (85.7)		
Exposure to secondhand smoke, no. (weighted %)[a]				1.77	0.441
Yes	452 (22.5)	421 (22.2)	31 (27.8)		
No	1,325 (77.5)	1,241 (77.8)	84 (72.2)		
Sedentary behavior, no. (weighted %)[a]				0.05	0.872
Yes	1,025 (60.3)	957 (60.3)	68 (59.3)		
No	752 (39.7)	705 (39.7)	47 (40.7)		

(Continued)

TABLE 1 (Continued)

Characteristic	Total ($N = 1,777$)	No osteoporosis ($N = 1,662$)	Osteoporosis ($N = 115$)	T/χ^2	*P*-value
Arthritis, no. (weighted %)[a]				8.71	0.016
Yes	677 (39.4)	617 (38.5)	60 (53.1)		
No	1,100 (60.6)	1,045 (61.5)	55 (46.9)		
Thyroid problems, no. (weighted %)[a]				5.54	0.038
Yes	253 (16.4)	436 (15.9)	32 (24.7)		
No	1,774 (83.6)	1,653 (84.1)	121 (75.3)		
Hypercholesterolemia, no. (weighted %)[a]				1.15	0.301
Yes	763 (44.4)	712 (44.7)	51 (39.3)		
No	1,014 (55.6)	950 (55.3)	64 (60.7)		
GFR, no. (weighted %)[a]				15.88	<0.001
<60 ml/min/1.73 m^2	265 (13.2)	235 (12.5)	30 (25.7)		
60–90 ml/min/1.73 m^2	810 (47.7)	762 (47.9)	48 (44.4)		
≥90 ml/min/1.73 m^2	702 (39.1)	665 (39.7)	37 (29.8)		
Annual household income, no. (weighted %)[a]				26.77	<0.001
$0–$19,999	327 (11.2)	299 (10.8)	28 (18.5)		
$20,000–$34,999	332 (13.8)	303 (13.3)	29 (20.6)		
$35,000–$74,999	421 (24.3)	390 (23.7)	31 (34.5)		
$75,000 and over	697 (50.7)	670 (52.2)	27 (26.4)		

[a]Numbers of participants are unweighted. All percentage estimates are weighted.

TABLE 2 Blood levels of heavy metals by osteoporosis status in US middle-aged and elderly people from NHANES[a].

Heavy metals	No osteoporosis ($N = 1,162$)					Osteoporosis ($N = 115$)				
	GM	Q1	Q2	Q3	Q4	GM	Q1	Q2	Q3	Q4
Lead (μg/dL)	1.16	<0.77	0.78–1.13	1.13–1.64	>1.64	1.21	<0.82	0.82–1.23	1.23–1.83	>1.83
Cadmium (μg/L)	0.32	<0.18	0.18–0.28	0.28–0.51	>0.51	0.55	<0.30	0.30–0.43	0.43–0.84	>0.84
Mercury (μg/L)	0.98	<0.47	0.47–0.92	0.92–1.87	>1.87	0.86	<0.43	0.43–0.75	0.75–1.46	>1.46
Selenium (μg/L)	196.91	<181.41	181.41–196.81	196.81–211.28	>211.28	182.31	<165.95	165.95–183.39	183.39–198.8	>198.8
Manganese (μg/L)	8.90	<7.22	7.22–8.84	8.84–10.64	>10.64	8.95	<7.0	7.0–8.87	8.87–11.45	>11.45

[a]All GM and Q1–Q4 estimates are weighted.

0.27; 95% CI, 0.14–0.53; $p < 0.001$) in model 3 in women (Supplementary Table S7). Model 1 and model 2 produced similar results to those of model 3 in both the men and women subgroup analyses. In the subgroup analysis stratified by smoking status, a significantly positive relationship was found between the blood Cd level and the prevalence of osteoporosis in the non-smoking subgroup, while no significant relationship was found in the smoking subgroup. Blood Se level showed a protective effect in the fourth quartile in both the smoking and non-smoking subgroups (Supplementary Tables S8, S9).

Discussion

The present study explored the correlation between blood heavy metals and the higher prevalence of osteoporosis in a US population of middle-aged and elderly people. Based on the representative sample of the US population in NHANES (2013–2014 and 2017–2018), we found that Cd was independently associated with a higher prevalence of osteoporosis, while Se was independently associated with a lower prevalence of osteoporosis, and Pb, Hg, and Mn showed no statistically significant effect on the prevalence of osteoporosis.

Age, sex, and BMI are traditional risk factors for osteoporosis. The amount of bone in an individual peaks in young adulthood and one experiences subsequent loss with aging (19). Women lose bone more rapidly due to the lack of estrogen with aging, while men experience a slow loss of bone (20). Guidelines have recommended BMD screening for osteoporosis in women aged 65 years or older but clinical risk assessment tools for screening osteoporosis in younger women (21, 22). In the present study, the average age of participants in the osteoporosis group was older than that of participants in the non-osteoporosis group, which was consistent

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TABLE 3 Univariate logistic analysis of osteoporosis in NHANES.

Characteristic	Univariate		
	OR	95% CI	P-value
Age (≥60 years)	3.38	1.74–6.56	<0.001
Male	0.21	0.20–0.48	<0.001
Race			
Mexican	0.28	0.08–0.96	0.043
Other Hispanic	1.21	0.42–3.46	0.723
Non-Hispanic white	0.69	0.28–1.68	0.416
Non-Hispanic Black	0.76	0.26–2.25	0.619
Education			
Less than 9th grade	2.08	1.03–4.20	0.042
9–11 grade	2.01	0.97–4.18	0.062
High school graduate or equivalent	1.80	0.80–4.05	0.157
Some college or AA degree	1.20	0.56–2.57	0.644
BMI			
Overweight (25–30)	0.25	0.14–0.44	<0.001
Obesity (>30)	0.42	0.27–0.66	<0.001
Smoking status	1.31	0.75–2.29	0.348
Physical activity	0.70	0.36–1.35	0.284
Diabetes	0.74	0.37–1.50	0.405
Hypertension	1.46	0.85–2.52	0.170
Alcohol consumption	1.04	0.63–1.73	0.871
Exposure to secondhand smoke	1.35	0.63–2.88	0.441
Sedentary behavior	0.96	0.56–1.63	0.872
Arthritis	1.80	1.1–2.94	0.018
Thyroid problems	1.73	1.02–2.93	0.041
Hypercholesterolemia	0.80	0.53–1.22	0.305
GFR			
<60 ml/min/1.73 m^2	2.75	1.57–4.81	<0.001
60–90 ml/min/1.73 m^2	1.24	0.78–1.95	0.367
Annual household income			
$0–$19,999	3.40	1.53–7.51	0.003
$20,000–$34,999	3.06	1.28–7.32	0.012
$35,000–$74,999	2.88	1.40–5.90	0.004
Pb			
Q2	0.95	0.43–2.08	0.892
Q3	1.19	0.63–2.27	0.531
Q4	1.33	0.69–2.56	0.399
Cd			
Q2	8.58	2.68–27.40	<0.001
Q3	15.19	5.95–38.82	<0.001
Q4	17.90	4.70–68.20	<0.001
Hg			
Q2	0.79	0.46–1.38	0.113
Q3	0.96	0.57–1.62	0.875
Q4	0.53	0.24–1.66	0.413
Se			
Q2	0.51	0.28–0.93	0.027
Q3	0.36	0.19–0.70	0.002
Q4	0.22	0.13–0.35	<0.001
Mn			
Q2	0.78	0.38–1.62	0.505
Q3	0.69	0.37–1.31	0.256
Q4	1.24	0.69–2.23	0.478

All OR (95% CI) estimates are weighted.

with that mentioned in previous studies. Studies demonstrated that aging may cause interstitial inflammation and fibrosis in renal tubuli, which are closely related to the excretion of heavy metals (23). A recent study revealed that the renal burden of Hg increases with age (24). Another study in southwestern China showed that higher blood heavy metals were found in older individuals compared with younger adults (25). A previous NHANES 2005–2006 study revealed a positive association between BMI and BMD (26), which was similar to the results of the present study. The NHANES 99-02 data showed that environmental exposure to Cd was negatively correlated with BMI (27). Another NHANES study reported that blood Hg levels were inversely correlated with BMI for adults (28). The present study showed similar results.

The relationship between blood Cd level and osteoporosis has been revealed in a small number of cross-sectional studies (29). Moreover, a recent study reported that Cd exposure was associated with an up to 23% increase in the incidence of osteoporosis, and the absolute cost of the burden of osteoporosis-related fractures caused by Cd is estimated to range between EUR€ 0.12 and 2.6 billion (30). Furthermore, Chung revealed that blood Cd concentrations of >1.0 μg/L and >0.5 μg/L were independent risk factors for incident osteoporosis in 243 participants and in 121 women, respectively, from the 2001 to 2002 Korea Genome and Epidemiology Study (31). The present study showed similar results. However, the sample size of the present study is relatively large and the research population is middle-aged and elderly populations, those who are more likely to have osteoporosis since it is a threat related to the aging population. A recent NHANES (2011–2018) study of young adults from 20 to 35 years revealed that blood Cd was independently negatively associated with lumbar BMD in women rather than men (32). However, a few studies explored the relationship between blood Cd and osteoporosis in men. This positive relationship was found in women in the present study but not in men. Moreover, the smoking subgroup was first discussed, the results

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TABLE 4 Multivariate logistic analysis of osteoporosis in NHANES.

Characteristic	Model 1			Model 2			Model 3		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age (≥60 years)	3.78	1.96–7.28	<0.001	3.58	1.81–7.09	<0.001	3.39	1.63–7.05	0.001
Male	0.37	0.24–0.59	<0.001	0.38	0.23–0.61	<0.001	0.38	0.23–0.63	<0.001
Race									
Mexican	0.28	0.09–0.83	0.021	0.26	0.09–0. 74	0.012	0.25	0.08–0.76	0.014
Other Hispanic	1.09	0.39–3.10	0.867	1.01	0.36–2.82	0.982	0.97	0.35–2.66	0.954
Non-Hispanic white	0.64	0.28–1.65	0.353	0.69	0.25–1.90	0.468	0.65	0.23–1.81	0.412
Non-Hispanic Black	0.64	0.21–1.96	0.434	0.69	0.21–2.22	0.530	0.70	0.22–2.28	0.559
Education									
Less than 9th grade				1.60	0.60–4.33	0.351	2.21	0.78–6.22	0.137
9–11 grade				1.50	0.57–3.93	0.411	1.90	0.64–5.65	0.247
High school graduate or equivalent				1.52	0.56–4.16	0.416	1.70	0.58–5.04	0.336
Some college or AA degree				1.27	0.48–3.37	0.637	0.44	1.56–1.27	0.543
BMI									
Overweight (25–30)				0.43	0.26–0.72	0.002	0.41	0.26–0.66	<0.001
Obesity (>30)				0.23	0.12–0.44	<0.001	0.21	0.10–0.43	<0.001
Smoking status							0.44	0.16–1.27	0.130
Physical activity							0.84	0.41–1.72	0.629
Diabetes							0.73	0.31–1.69	0.456
Hypertension							1.15	0.65–2.05	0.625
Alcohol consumption							0.62	0.34–1.13	0.115
Exposure to secondhand smoke							1.26	0.50–3.18	0.637
Sedentary behavior							1.18	0.58–2.41	0.648
Arthritis				1.32	0.72–2.41	0.367	1.37	0.75–2.53	0.310
Thyroid problems				1.05	0.58–1.88	0.881	1.04	0.58–1.89	0.892
Hypercholesterolemia							0.92	0.55–1.52	0.731
GFR									
<60 ml/min/1.73 m^2				1.44	0.75–2.76	0.272	1.37	0.73–2.58	0.329
60–90 ml/min/1.73 m^2				0.79	0.48–1.31	0.361	0.79	0.48–1.32	0.374
Annual household income									
$0–$19,999				1.96	0.83–4.61	0.124	1.88	0.77–4.54	0.164
$20,000–$34,999				2.68	1.12–6.37	0.026	2.46	0.97–6.20	0.057
$35,000–$74,999				2.86	1.28–6.39	0.010	2.84	1.25–6.48	0.013
Pb									
Q2	0.86	0.40–1.88	0.705	0.73	0.32–1.64	0.444	0.69	0.31–1.55	0.365
Q3	0.78	0.40–1.51	0.459	0.60	0.33–1.63	0.112	0.64	0.33–1.25	0.189
Q4	0.76	0.41–1.39	0.382	0.52	0.30–0.94	0.030	0.53	0.28–0.98	0.044
Cd									
Q2	7.62	2.01–29.03	0.003	10.01	2.16–46.39	0.003	10.01	2.05–48.83	0.004
Q3	12.38	3.88–39.60	<0.001	14.23	3.59–56.39	<0.001	14.15	3.31–60.52	<0.001
Q4	15.64	3.22–76.08	0.001	13.51	2.22–82.29	0.004	17.98	2.54–127.07	0.004

(Continued)

TABLE 4 (Continued)

Characteristic	Model 1			Model 2			Model 3		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Hg									
Q2	0.93	0.52–1.66	0.801	0.89	0.48–1.68	0.728	0.89	0.47–1.67	0.710
Q3	1.16	0.68–1.96	0.592	1.21	0.69–2.12	0.516	1.23	0.69–2.21	0.486
Q4	0.62	0.28–1.37	0.235	0.69	0.31–1.54	0.366	0.61	0.27–1.37	0.229
Se									
Q2	0.52	0.27–1.02	0.056	0.50	0.26–0.95	0.035	0.51	0.27–0.95	0.032
Q3	0.46	0.21–1.03	0.059	0.57	0.26–1.26	0.164	0.56	0.24–1.27	0.165
Q4	0.34	0.14–0.39	<0.001	0.26	0.15–0.25	<0.001	0.26	0.15–0.45	<0.001
Mn									
Q2	0.53	0.21–1.30	0.163	0.61	0.28–1.35	0.225	0.62	0.29–1.31	0.212
Q3	0.47	0.22–0.99	0.049	0.57	0.25–1.29	0.177	0.53	0.23–1.22	0.135
Q4	0.71	0.33–1.54	0.390	0.97	0.49–1.93	0.940	0.90	0.46–1.79	0.770

Model 1: Adjusted by age, gender, and race.
Model 2: Adjusted by age, gender, race, education, BMI, arthritis, thyroid problems, GFR, and annual household income.
Model 3: Adjusted by age, gender, race, education, smoke, diabetes, hypertension, physical activity, BMI, alcohol consumption, exposure to secondhand smoke, sedentary behavior, arthritis, thyroid problems, hypercholesterolemia, GFR, and annual household income.
All OR (95% CI) estimates are weighted.

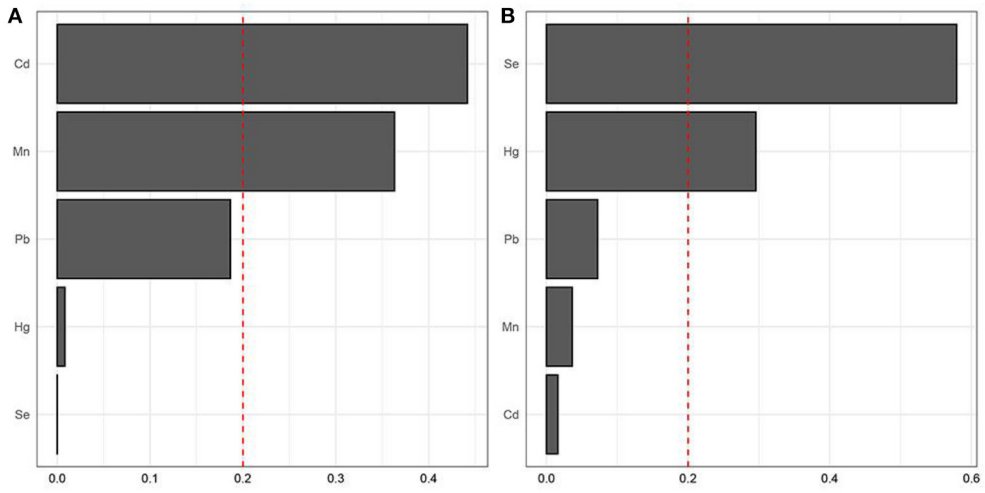

FIGURE 2
Identification of blood heavy metals in the mixture using the WQS model. **(A)** positive WQS model; **(B)** negative WQS model.

revealed that smoking did not affect the relationship between blood Cd and the prevalence of osteoporosis. Furthermore, a recent study involving 488 women showed no correlation between blood Cd and osteoporosis (33). The potential mechanisms underlying the relationship between Cd and osteoporosis have been explored, including impairing the viability, proliferative ability, and osteogenic differentiation of bone marrow mesenchymal stem cells (BMMSCs) through the NF-κB and P2X7-PI3K-AKT signaling pathways (14, 34). Thus, the dysfunction of BMMSCs might be the main cause of Cd-related osteoporosis. *In vitro* studies showed that Cd stimulated osteoclastogenesis by increasing RANKL expression (35). Moreover, recent studies suggested that Cd induces bone osteoblast apoptosis *via* ROS (36). In addition, a further study demonstrated that Cd suppressed osteogenesis by inhibiting the Wnt/β-catenin pathway (37). *In vivo* studies further demonstrated that Cd induces a decreased expression of Runx2 and matrix proteins such as ALP, OCN, and COL1a2 (38). Another study found that Cd affected BMMSC differentiation by stimulating adipogenesis at the expense of osteoblastogenesis (39). Furthermore, other potential mechanisms, including Cd-related NF-κB and P2X7-PI3K-AKT signaling pathways, have recently been demonstrated to impair the viability, proliferative ability, and osteogenic differentiation of BMMSCs (14, 34).

Low blood Se status has been demonstrated to be correlated with skeletal disease, especially female the prevalence of osteoporosis (40, 41). A significant and positive relationship was observed between BMD and Se in a study involving 280 Spanish women (15). Beukhof et al. demonstrated that Se status was positively associated with BMD in a cohort of 387 healthy aging European men (42). In addition, some other studies revealed that Se was negatively associated with fractures induced by osteoporosis (43–45). Our findings were consistent with the findings of these studies. Furthermore, the present study also demonstrated that blood Se reduced the prevalence of osteoporosis in men. Moreover, this relationship was found in both the smoking group and the non-smoking subgroups. However, some previous studies did not suggest a relationship between Se and BMD in healthy women (46). In addition, no relationship between Se and osteoporosis has been reported in either an Asian or a European population (47–49). These results might be observed due to the differences in sample characteristics and loss of power (91–290 subjects). The potential mechanism for this viewpoint has been demonstrated *in vitro*, with evidence suggesting that Se enhances the osteoblastic differentiation of BMMSCs by downregulating the differentiation and formation of mature osteoclasts (50). Other *in vitro* studies have demonstrated that Se influences osteoblastic differentiation and subsequent bone resorption by regulating oxidative stress (51, 52). Previous studies revealed that inadequate levels of Se may alter bone metabolism and delay bone growth. *In vitro* studies showed that Se had a positive effect on osteoblastic differentiation and subsequent bone resorption by regulating oxidative stress (53). In addition, Wnt/LRP8/ApoER2 pathway was suggested as a fundamental intracellular Se transportation pathway for altering bone metabolism (54). Animal studies also found that bone metabolism changed with Se deprivation. Such effects were related to a decrease in GPX1 activity, blood concentrations of calcium, plasma insulin-like growth factor, pituitary growth hormone, and an increase in blood 1,25-dihydroxyvitamin D_3, parathyroid hormone, and urinary calcium concentration (52). These changes were demonstrated to be associated with bone volume and BMD reduction, impairing bone microarchitecture (55).

The relationship between blood Pb and bone health has been reported in several epidemiological studies, but with inconsistent conclusions. A previous NHANES study (NHANES III) of adults aged ≥50 years showed that blood Pb was inversely correlated with BMD among white participants (56). In contrast, a significant inverse relationship between Pb and osteoporosis has been reported in the Korea National Health and Nutrition Examination Survey (2008–2011) (7). However, another previous study showed that blood Pb was not associated with BMD (57), which was consistent with that mentioned in the present study. In addition, we performed further analysis with gender and smoking subgroups and observed no relationship. A previous NHANES study (2005–2010) showed that a low blood Hg level was associated with an elevated risk of osteoporosis in young men (20–29 years) and women (30–39 years) (58). However, this relationship between the middle-aged population and the elderly population remains unclear. Our study showed that blood Hg was not associated with an increased prevalence of osteoporosis in low or medium blood Hg levels. However, a high blood Hg level was found to show a positive relationship with a higher prevalence of osteoporosis in men but not in women. High blood Hg levels were found to be associated with reduced BMD in the femur neck in the Korean National Health and Nutrition Examination Survey (2008–2010) (59). These inconsistent findings on the relationships of blood Hg with osteoporosis may be due to the heterogeneity between these studies. The relationship between blood Mn and osteoporosis remains unclear. A previous study of 91 elderly men showed no correlations between blood Mn level and BMD (47). Another research of 304 retired workers revealed that a high Mn exposure level was correlated with a higher risk of osteoporosis (60). No relationship was observed in the present study. This finding was similar to that of a previous study with a small sample size (61). However, further subgroup analysis showed that a higher blood Mn level was positively associated with a higher prevalence of osteoporosis in men and non-smoking subjects. These inconsistent findings may have contributed to the different biological specimens and the variation in Mn exposure levels.

The present studies showed that elevated blood Pb, Hg, and Mn levels were not correlated with a higher prevalence of osteoporosis. However, some studies showed either a positive or a negative relationship between these heavy metals and BMD (11, 62). The possible mechanism for the positive relationship may be attributed to oxidative stress-related toxicity in inhibiting the function of osteoblasts (63). Thus, it remains controversial as to whether the contents of Pb, Hg, and Mn can directly influence BMD and affect the pathogenesis of osteoporosis. The positive relationship between Cd exposure and a higher prevalence of lower BMD were proven in both animal models and human-based studies. These biological mechanisms are complex and are not fully understood. Excessive Cd exposure will reduce the production of calcitriol, decompose the collagen matrix in the bone, interfere with the mineralization of bone cells, inhibit the activity of osteoblasts, and stimulate the activity of osteoclasts, thus damaging bone health (10). The relationship between Se and bone health has been widely studied. As an essential component of selenoprotein, Se plays an important role in the maintenance of bone homeostasis through cell proliferation regulation and antioxidant protection (55). Further studies are worth being conducted to determine the relationship between Se exposure and osteoporosis and to explore the underlying mechanism.

However, there are several limitations to the present study. First, the present study used a cross-sectional design, and no causal inference between blood heavy metals and the prevalence of osteoporosis can be made. Second, although demographic, medical history, and lifestyle variables have been adjusted using logistic regression in the present study, confounding variables may still exist and affect the correction between blood heavy metals and the prevalence of osteoporosis. In addition, other variables, such as diet and hypertriglyceridemia, were not included in this analysis. Third, blood heavy metals were measured only one time and this type of measurement might not reflect a continuous exposure, thus measurement errors were inevitable. Finally, the number of participants in the osteoporosis group was relatively small and other treatment variables (vitamin D and bisphosphate) were not included in the analysis; further

larger sample studies are needed to confirm the results. However, our study also carries some strengths. First, the present study was based on a relatively large dataset from the US population. Second, DXA is more accurate for the diagnosis of osteoporosis, and, finally, we performed further subgroup analysis on the relationship between blood heavy metals and the prevalence of osteoporosis.

Conclusion

In conclusion, our study demonstrated that blood Cd level aggravated the prevalence of osteoporosis, while blood Se level could be a protective factor for the prevalence of osteoporosis among the US middle-aged and older populations. However, the results need to be confirmed in a prospective study.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The NHANES protocol is approved by the National Center for Health Statistics Institutional Review Board, and written informed consent is obtained. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HWe and ZH: conception and design. XW: administrative support. HWa: provision of study materials or patients. XD and SZ: collection and assembly of data, data analysis, and interpretation. All authors wrote the manuscript and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1045020/full#supplementary-material

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Exploring the relationship between air quality and health shocks to the elderly: A retrospective cross-sectional study in China

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Methods: We selected 5,172 microdata on individuals from the China Health and Retirement Longitudinal Study (CHARLS) 2018. The binary logit model, the ordered logit model, and the stepwise regression were employed to compare the effects of air pollution on self-rated health (SRH) and activities of daily living (ADL) in an elderly population. The effects on health shocks were explored in different age groups, different gender groups, different regions and different sources of pollutants, respectively.

Results: We found that air pollution significantly increased the risk of health shocks in the elderly population, especially in the 60–69 year age group, and the eastern/central region, where NO_2 and O_3 were important pollutant sources.

Conclusion: Targeted management of the environment is necessary to improve the health status of China's elderly population. In addition, paying attention to the health status of vulnerable populations is needed to achieve social equity.

KEYWORDS

air pollution, health shocks, the elderly, self-rated health (SRH), activities of daily living

1. Introduction

Haze is a major manifestation of air pollution (AP) that influences most urban areas of China, especially in the northern regions. Respirable particulate matter in haze contains various chemicals, such as sulfur dioxide, metal elements and radioactive substances, which have a major impact on human health (1). A recent study published by the World Health Organization (WHO) in 2018 states that ~7 million people die globally each year as a result of exposure to fine particles in polluted air. In its 2022 air quality database update, WHO states that almost the entire global population (99%) breathes air that contains high levels of pollutants; air quality has already passed beyond the limit of the WHO guideline and pollution is 90% higher than it was 4 years ago (2). The report "Toward an Environmentally Sustainable Future" also states that <1% of China's 500 largest cities meet the WHO recommended air quality standards (3).

Moreover, with the development of China's economy, the standard of living and health of the people have improved significantly, and the life expectancy of the elderly population has increased. According to China's seventh National Census, the population will total 1,411.78 million in 2021. The elderly population, aged 65 and above, is 190.64 million, which accounts for 13.5% of the total population, and has increased by 4.63 percentage points compared with

the sixth National Census in 2010 (4). According to the prevailing international standards for judging aging societies, China has long since become an aging society. When compared with developed countries, China's aging population has several characteristics, such as a large and rapidly increasing number of elderly people (5). Older people are usually in poorer health, with deep levels of multiple morbidity and chronic diseases (6). The elderly population is chronically exposed to diseases, and air pollution is an important environmental risk factor that has an impact on both physical and mental health. Older people have been exposed to poor air quality over many years, accompanied by a decline in physical function and resistance, loss of health, accelerated depreciation of physical health capital in the face of air pollution, and a greater likelihood of disease impact (7–9). Despite advances in medical technology, increased national investment in health over the years, and updated air governance policies, older people are still at serious risk of health shocks and tend to have a greater prevalence of comorbidities (10), which already pose a challenge to the public health service system.

The level of air quality reflects the degree of AP, which is affected by the type and concentration of pollutants in the air. Currently, the Air Quality Index (AQI), the concentration of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), inhalable particles (PM_{10}), ozone (O_3), respirable particulate matter (PM_{10}) and fine particulate matter ($PM_{2.5}$) are the primary indicators used to assess air quality (11, 12). Group differences have been confirmed by research on population health and air quality, and the elderly are particularly vulnerable to the adverse effects of air pollution (13, 14). Hence, some studies have specifically addressed health issues in older populations and found that air pollution has negative effects on health status and mental health (15–17), significantly increasing the probability of ADL disability (18, 19). However, in an aging society, the sudden deterioration of health conditions suffered by the senior population should be more of a public concern. Previous research using microdata has mostly concentrated on positive health scores or disability. This study introduces the variable of health shock and attempts to combine previous studies to measure the impact of exposure in terms of deterioration in self-rated health and the ability to perform daily behaviors.

Based on the above research background, we investigated the extent to which AP affected the health impacts of older people, using data from the air quality historical data query platform and the China Health and Retirement Longitudinal Study (CHARLS) 2018, selecting people aged 60 years and older as the study population.

2. Materials and methods

2.1. Study population

The micro-data used in this paper came from the China Health and Retirement Tracking Survey, a national baseline of the China Health and Retirement Longitudinal Study (CHARLS), organized by the National Development Institute of Peking University and launched in 2011. CHARLS data focused on middle-aged and older people, aged 45 and above, and were updated to the 2018 sample survey data. In sampling, CHARLS used a stratified (personal GDP by urban area and rural county) multi-stage (county/district, village/community, households) random sampling method proportional to population size (PPS), with strict control of sample quality, so that the data represented the overall situation in China. In this paper, people aged 60 years and older were selected as the study population. In addition to being easily exposed to AP, this group has the traits of rarely moving their residences and hardly changing their socio-economic status (11). Therefore, it is easier to explore the correlation by analyzing the elderly population.

AP can be divided into two categories: indoor AP and outdoor AP (12). Owing to the differences in the sources of major pollutants in different regions of China and at different times in the same region, we used data on six common air pollutant indicators in Chinese cities and selected the air quality composite indicator as a proxy variable for AP in each region. The AQI, which is calculated based on hourly concentration readings of the above six categories of pollutants, is a reliable indicator for quantitative assessment of health risks (20, 21). The China Ambient Air Quality Standard (CAAQS) (GB 3095-2012) was implemented in 2012 after the Chinese Ministry of Environmental Protection (CMEP) announced the Ambient Air Quality Index Technical Provisions (Trial) (HJ 633-2012) (22, 23). The higher the AQI value, the more serious the AP (22). AP data were obtained from the air quality historical data query platform, which provides a rich and reliable data source for AP-related research (24–26). Considering that there may be a certain lag in the effect of AP on individual health shocks, we selected the average value of 2017–2018 to examine the relationship between air quality and individuals' loss of independent living due to physical dysfunction and to explore what caused the loss of health in older people. Monthly air quality data (including date, AQI, range, quality class, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3, and city) for 2017 and 2018 for nearly 400 cities in China were crawled using PYTHON 3.9.7. To ensure the quality of our data, we selected $PM_{2.5}$ in 2018 from another database (27) and proofread the data with the $PM_{2.5}$ obtained in our study. The average values are 39.541 $\mu g/m^3$ in the Historical Data Platform and 39.217 $\mu g/m^3$ in the Data Center of Ministry of Ecology and Environment; therefore it can be considered that our air quality data are reliable. The 2018 China Statistical Yearbook's urban and environmental chapters provided the city-level data (28), and a few missing data were supplemented with provincial data. The database used in this paper was made available to the academic community with the approval of the Peking University Ethics Committee; air quality data and city-level data were public and therefore did not require ethical approval.

This paper first matched the PSU (province, city, name, and area type) sub-data from the CHARLS survey (containing information on an individual's province, city name, and area type) with 2018 personal information to locate the city where the respondent was located, and then used the city name information to match the individual micro-data with the AP data. In the end, 123 cities were successfully matched, and a total of 5,172 samples were obtained after selecting people aged 60 years and above.

2.2. Variable selection

2.2.1. Definition of healthy outcome

Health shocks, as a complex concept, are not agreed upon in existing research. Most studies have used changes in self-rated health status (SRH) to measure health shocks: a worse SRH than the previous year or a sharp deterioration in SRH is considered a health shock (29, 30). More recently, researchers have considered limitations in daily activities as a direct indicator of health shocks (31, 32). The term "health shock" was used in this paper to refer to negative health events associated with the loss of an individual's ability to live independently due to physical impairment and was measured by two indicators, a subjective self-assessment of respondent health, SRH (29), and an objective self-assessment of the respondent's ability to perform activities of daily living (31). The CHARLS questionnaire's SRH was measured by asking the respondents "How do you think your health is?" The question was divided into five levels: "very good," "good," "fair," "poor" and "very poor."

Good functional status is fundamental to maintaining the independence of older people. Objectively, older people are prone to a variety of illnesses that can impair their health, which can lead to a decline in their ability to perform activities of daily living (ADL) (33). The assessment of ADL can provide a basis for diagnosing illnesses, predicting the needs of social services for the elderly, developing treatment plans, and rationalizing the placement of the elderly (34). ADL include Basic Activities of Daily Living (BADL) and Instrumental Activities of Daily Living (IADL), and this paper selected BADL to better reflect the impact of negative health events on the respondents (35). The ADL scale in the CHARLS questionnaire asked respondents whether they had difficulties in daily life, such as dressing and bathing.

2.2.2. Exposure assessment for air quality index

Fine particulate air pollution $<2.5\,\mu m$ diameter ($PM_{2.5}$) is only one of the main sources of AP and an air quality index that takes into account all sources of pollutants is a more appropriate proxy variable for air pollution (20, 21). The range of the AQI is 0 to 500. The pollutant with the highest concentration is regarded as the primary pollutant when the AQI is higher than 50. We took the annual average value of AQI of the area where the senior population was located as the proxy indicator to reflect long-term AP. Additionally, because the data quality is a major concern, the independent variable AQI was replaced with six single indicators in our paper's robustness check (13).

2.2.3. Measurement of control variables

Referring to Grossman's health needs theory and Zeng et al. (37) regarding the delineation of control variables, and modified to fit the needs of the study, the individual control variables were divided into three categories: demographic characteristics, enabling variables, and social welfare (36, 37). Demographic characteristics included sex, age, marital status, education level, and type of residence. Enabling factors are the tendency for this group to acquire health shocks more than others, a tendency that can be predicted from pre-onset personal characteristics, such as smoking, drinking and a history of present illness (HPI). Social benefits were more focused on pensions for those over 60 years of age. Marital status was reclassified according to the six options in the questionnaire: married (including cohabiting and temporarily not living with spouse due to work or other reasons) and unmarried (including separated, divorced, widowed, never married). The level of education was divided into four categories: (1) primary school and below; (2) junior high school; (3) senior high school; and (4) college or above. Respondents were classified as living in a town if in the center of the city/town or the combination zone between urban and rural areas, with the remainder in villages. Smoking and alcohol consumption, as unhealthy lifestyles, have health consequences, and participating groups are more likely to experience health shocks (29), so we considered "whether they smoke" and "whether they drink" as a control variable. Many older people in China share the responsibility of caring for their grandchildren, and pensions are the main source of socio-economic support for older people with chronic diseases in the face of shocks (35). Older people, therefore, are better able to withstand the threat of health shocks if they have health benefits such as pensions. The CHARLS questionnaire asked respondents "Do you currently receive, expect to receive or contribute to the pension for public servants, or pension for public institution employees, or basic pension for enterprise employees?" to define whether the respondent has a pension. Considering that pre-existing diseases may affect the reliability of the results; we selected three diseases most closely related to AP (38–41). The CHARLS questionnaire asked respondents "Have you been diagnosed with chronic lung diseases, stroke or asthma by a doctor?" to define whether the respondent had HPI.

When measuring the relationship between environmental quality and public health, it is necessary to take into account the overall effect as comprehensively as possible. This paper selected two urban macro variables to control the intensity of regional environmental regulation (42, 43). The water quality was determined by the sewage treatment rate and the green space was measured by the green coverage rate of the built-up area.

2.3. Statistical analysis

Generally, linear regression and ordered logit regression are used to study SRH. We used logit regression to judge health status more directly. Herein, ordered logit regression was conducted based on the results of the questionnaire survey. Respondents were assigned a value of "2" if their health status was poor or very poor; "1" if their health status was fair; "0" if their health status was good or very good. The model was

$$H_{ij} * = \alpha + \beta_1 * \mathrm{Aqi}_{ij} + \beta_2 * Control_{ij} + \varepsilon_{ij} \quad (1)$$

Where H represents the micro-individual SRH index, Aqi represents the AQI, Control represents the control variable and ε represents the random perturbation term, i denotes the micro-individual, j denotes the province in which the micro-individual i is located, α denotes the value of the surrogate estimated parameter variable, and β_1 , β_2 denote the effect of AP and other control variables on the health status of individuals.

Based on ADL competency according to the questionnaire items, respondents were marked as "1" if they met any of the above criteria, or as "0" if no symptoms occurred, and a binary logit regression model was constructed.

$$ln(\frac{\rho}{1-\rho}) = \partial + \gamma_1 * \mathrm{Aqi}_{ij} + \gamma_2 * Control_{ij*} + \varepsilon_{ij*} \quad (2)$$

Where ρ represents the probability that ADL = 1 and "1–ρ" represents the probability that ADL = 0. In this study, the stepwise regression method was used to introduce variables into the model one by one to ensure that only significant variables were included in the regression equation before each new variable was introduced. All statistical procedures in this paper were implemented by STATA 17.0.

3. Results

3.1. Descriptive statistics of analysis samples

Overall, women accounted for the vast majority of respondents, 79% of the total sample. The highest age was 98 years, with 62.35% of the population between 60 and 69 years old and over 8% of the total population aged over 80 years. Owing to the low level of education in China before the 1970's, more than 76% of the elderly had an education level below junior high school. In terms of place of residence, more than 74% of respondents were from rural areas and only a small proportion had a pension; 20% of the total population had a very good or good SRH status and 32% had a poor or very poor one. It is pleasing to note that only 18% of seniors had an ADL shock, indicating that most seniors can take care of themselves in daily life. At the same time, 6.38% of seniors smoked and 18.97% drank alcohol, indicating that most seniors adopt a healthy lifestyle. Overall, 12.88% of seniors suffered from lung-related diseases, stroke, or asthma. In terms of air quality, the average AQI value was between 77 and 78. 78% of people were living in an environment with an AQI between 50 and 100, with good air quality. However, the results of 5,172 samples reveal that there is a significant difference in air quality levels among cities, with the maximum AQI being three times higher than the minimum. Obviously, compared with the sewage treatment rate, the green coverage rate is not ideal, and there is a gap between cities. The description of the variables and the results of the survey are shown in Tables 1, 2.

3.2. Effects of air quality index on health shocks

The results of the ordered logit regression (Table 3) show that the effect of AQI on SRH is significant at the 0.05 level after the inclusion of the relevant control variables, implying that AP has a significant positive effect on the deterioration of SRH among the elderly. Models 1 to 4 are the stepwise test results of AQI and SRH. Model 1 exhibits that, without any control variables, AQI successfully passes the significance test and the estimated coefficient of AQI is 0.26, which is significant at the level of 5%. Individual control variables and urban-level control variables in models 2 to 4 are gradually included as control variables, and AQI still has a significant positive impact on SRH (OR = 1.004; 95% CI:1.001–1.007; $P < 0.05$). Among the control variables, SRH is significantly influenced by age (OR = 0.016; 95% CI: 0.007–0.024; $P < 0.01$), sex (OR = 0.724; 95% CI: 0.623–0.841; $P < 0.05$), residence (OR = 0.796; 95% CI: 0.685–0.926; $P < 0.01$), pension (OR = 0.681; 95% CI: 0.575–0.807; $P < 0.01$), smoking (OR = 1.464; 95% CI: 1.160–1.847; $P < 0.01$), drinking (OR = 0.647; 95% CI: 0.562–0.745; $P < 0.01$). Age, smoking, and HPI (OR = 2.710; 95% CI: 2.307–3.184; $P < 0.01$) have negative effects.

In binary logit regression (Table 3), model 1 demonstrates that the estimated coefficient of AQI is 0.274, which is significant at the level of 10%, in the absence of any control variables. After accounting for all control variables, the estimated coefficient of AQI is 0.399 (OR = 1.005; 95% CI: 1.001–1.009; $P < 0.05$). Similarly, we also found that age (OR = 0.951; 95% CI: 0.939–0.963; $P < 0.01$) has a significant negative impact on ADL.

3.3. Heterogeneity analysis between subgroups

3.3.1. Comparative analysis of different ages, sexes, and regions

To analyze the difference in the relationship between air quality and health shocks, heterogeneity tests were conducted based on age, gender, and regional groups. According to the division of age from Hu et al. (11) and Zeng et al. (37), our samples were divided into 60–69 and 70+ years (we classified these two groups as "young-older" and "older," respectively. The gender groups were divided into male samples and female samples. Regional groups were divided into eastern, central, and western regions according to geographical location. The regression analyses were conducted on these sub-samples to examine how the effects of AP on health shocks in older people differed across age, sex, and regional groups. The effect of AQI on SRH and ADL is significant in the "young-older" group (Table 4). Specifically, the estimated coefficients are 0.1074 for SRH ($P < 0.05$) and 0.0694 ($P < 0.05$) for ADL, respectively. The "older" group did not pass the significance test. Compared with the "older" group, air quality has a significantly greater impact on the "young-older" group. AQI has a significant effect on impaired daily behavior in regions with different levels of economic development, but we did not observe a statistical significance in SRH. Specifically, as shown in Table 5, the estimated coefficient of ADL in the eastern region is 0.1159 ($P < 0.05$); the estimated coefficient of ADL in the central region is 0.2444 ($P < 0.01$). Finally, we conducted interaction effect analyses, the results showed that there were significant differences in age groups ($P < 0.01$) and regional groups ($P < 0.1$), but no significant difference in sex groups (details in the Table 6). Therefore, it can be considered that AQI has a differential impact with regard to health shocks at different age or regional groups.

TABLE 1 Statistical description of analysis samples created from CHARLS.

	Self-rated health					Activities of daily living			
	Very good/Good	Fair	Very poor/Poor			No difficulty	Difficulty		
	$N = 1,038$	$N = 2,465$	$N = 1,669$	[a]$\chi 2$	P	$N = 4228$	$N = 944$	$\chi 2$	P
Age group				26.7544	0.000			40.2321	0.000
60–69	698	1,563	964			2,551	674		
70+	340	902	705			3,831	220		
Sex				38.9079	0.000			204.5593	0.000
Female	768	1,937	1,398			3515	588		
Male	270	528	271			713	356		
Education				29.1640	0.000			17.0521	0.001
Primary school	483	1,218	897			2144	454		
Junior high	282	649	446			1,150	227		
Senior high	192	382	232			620	186		
College	81	216	94			314	77		
Marital				16.1117	0.000			29.4200	0.000
Single	203	539	431			1,022	151		
Married	835	1,926	1,238			3,206	793		
Residence				77.9096	0.000			20.4121	0.000
Village	720	1,752	1,368			3,194	646		
Town	318	713	301			1,034	298		
Pension				121.5664	0.000			48.1332	0.000
No	785	1,897	1,493			3,489	686		
Yes	253	568	176			739	258		
Smoke				0.0884	0.957			30.9441	0.000
No	970	2,310	1,562			3,996	846		
Yes	68	155	107			232	98		
Drink				72.2044	0.000			92.8579	0.000
No	763	1,983	1,445			3,531	660		
Yes	275	482	224			697	284		
HPI				239.5507	0.000			58.6268	0.000
No	979	2,207	1,320			3,641	865		
Yes	59	258	349			587	79		

[a]chi-square test and p-value.

3.3.2. Impact degree of exposure to six pollutants

Considering that different sources of pollutants have different degrees of health effects, the environmental variable was replaced by the average concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 from 2017 to 2018 to test the robustness of the previous conclusions (13). According to Table 7, PM_{10} ($P < 0.05$), O_3 ($P < 0.01$), and NO_2 ($P < 0.01$) have significant effects on SRH of the elderly. According to the results in Table 8, $PM_{2.5}$ ($P < 0.05$), PM_{10} ($P < 0.01$), CO ($P < 0.05$), O_3 ($P < 0.01$), and NO_2 ($P<0.01$) have significant effects on the ADL of the elderly. After replacing variables, they still pass the significance test, indicating that the results of the previous model are reliable. Under the same conditions, in areas where O_3 and NO_2 are the main sources of pollutants, the residents are more vulnerable to health shocks.

4. Discussion

This paper used CHARLS2018 data, binary logit regression modeling, ordered logit regression modeling and stepwise regression to investigate the impact of AP on the health of the elderly. We took the annual average value of the AQI of the area

TABLE 2 Overall characteristics of [a] environmental factors in China (2017-2018).

			Self-rated health					Activities of daily living	
			Very good/good	Fair	Very poor/poor			No difficulty	Difficulty
	[d]F	*P*	*N* = 1,038	*N* = 2,465	*N* = 1,669	[e]*t*	*P*	*N* = 4,228	*N* = 944
Mean ± SD									
AQI	2.22	0.1086	78.590 ± 19.722	78.001 ± 18.816	77.049 ± 20.317	3.29	0.0697	77.580 ± 19.543	78.853 ± 19.281
[c]$PM_{2.5}$(μg /m^3)	2.12	0.1206	42.872 ± 13.637	42.976 ± 13.286	42.106 ± 14.564	3.60	0.0578	42.502 ± 13.892	43.444 ± 13.274
PM_{10}(μg /m^3)	2.59	0.0752	74.207 ± 24.410	73.157 ± 23.146	72.090 ± 24.562	3.78	0.0519	72.718 ± 23.852	74.389 ± 23.947
SO_2(μg /m^3)	3.33	0.0359	16.169 ± 7.980	15.505 ± 7.098	15.932 ± 8.010	0.84	0.3597	15.730 ± 7.623	15.981 ± 7.420
CO (mg /m^3)	1.93	0.1452	0.917 ± 0.230	0.925 ± 0.225	0.910 ± 0.232	4.76	0.0291	0.915 ± 0.229	0.933 ± 0.226
O_3(μg /m^3)	5.03	0.0066	93.962 ± 12.360	92.666 ± 12.084	92.569 ± 12.191	4.18	0.0409	92.731 ± 12.175	93.628 ± 12.210
NO_2(μg /m^3)	6.67	0.0013	31.527 ± 9.850	31.526 ± 9.625	30.470 ± 9.767	7.21	0.0073	31.014 ± 9.741	31.955 ± 9.689
[b]Green			41.377 ± 5.772	40.928 ± 6.022	41.433 ± 5.838			41.363 ± 5.588	41.785 ± 6.134
Sewpro			95.785 ± 1.708	95.624 ± 1.692	95.723 ± 1.724			95.670 ± 1.725	95.652 ± 1.624

Mean ± SD: mean ± standard deviation.

[a] Variables from the air quality historical data query platform and yearbooks are city-level.

[b] *Sewpro:* Sewage treatment rate (%) = (sewage treatment volume / total sewage discharge) × 100%.

Green: Green Ratio (%) = (vertical projected area of green plants / urban area) × 100%.

[c] $PM_{2.5}$(μg /m^3), PM_{10}(μg /m^3), SO_2(μg /m^3), CO (mg /m^3), O_3 (μg /m^3) and NO_2 (μg /m^3) represent the concentration of pollutants in the air.

[d] Analysis of Variance and *p* value.

[e] Two-group t-test and *p* value.

where the elderly population was located as the proxy indicator to reflect long-term AP and divided the health impact into two dimensions: self-assessment of health and daily behavioral ability. AQI and six types of pollutants were included as independent variables, which not only shows the impact of different sources of pollutants on health shocks, but also supports the reliability of our results. The study found that AP had a positive effect on the occurrence of health shocks in older people. This was reflected in impaired ADL and poor SRH. It is worth noting that the effect of AP on health shocks in older people shows some heterogeneity, with the effect of AP on health shocks in older people being more pronounced in the 60–69 year age group, the eastern/central regions with better economic development, and in areas with high concentrations of NO_2 and O_3 in the air.

AP damages both physical and mental health (15–17), especially affecting the self-rated health of low socio-economic groups (13) and increasing the probability of ADL disability (18, 19). Previous studies concerning older age groups mostly concentrated on the effects on mortality but did not assess the extent to which AP affects negative health events among residents in an aging society. Our study, for the first time, examines the connection between air quality and its effects on health shocks in senior citizens. This study introduces the variable of "health shocks" and tries to combine early studies to measure the impact on health by using the deterioration of SRH and ADL. As an undefined concept, health shocks can be creatively defined as adverse occurrences that the elderly undergo with aging and degradation of physical function. Our analysis suggested that the air quality has an impact on their daily living ability as well as self-rated health, both of which are associated with an increase in health expenditure (44, 45). Therefore, the first marginal contribution of this study is to extend the horizon of research on health shocks in the context of aging. In addition, environmental issues are a major problem worldwide. Our study also enriches the systematic analyses of environmental pollution, providing fresh micro evidence for the impact of AP on the health of the elderly population.

Previous analyses of age and gender heterogeneity have not come to a consensus owing to the complexity of the source of contaminants (13, 18, 43). Compared with women, men are more likely to work outside and are susceptible to AP for a longer period of time (13), their health is thereby more negatively affected (43); nevertheless, female residents have the traits of a long life expectancy but greater inhalation of cooking fumes at home, which leads to ADL disability (18). Based on biophysical differences in vulnerability (age or baseline health) (46), it can be considered that people over 60 years old have a more significant and negative ADL disability (18). Interestingly, individuals facing the same environmental conditions show different health responses through defensive and compensatory behaviors in practical terms (47, 48). Elderly people over 70 are more likely to spend less time outdoors during periods of high pollution and choose to stay at home. As a result, the cumulative health damage is small in this age group, while older people between the ages of 60 and 70 years tend to work outside and provide intergenerational care (45, 49). Existing studies have categorized young-older people aged 60–69 years as a vulnerable group (50), but research on this group is insufficient, with most surveys reporting on the health of the entire older population. Different age groups have significantly different access to environmental resources and abilities to avoid environmental externalities (45); therefore, physical and mental health issues in this younger group should be explored in the future. Regional differences in the effects of AP on residents' health are significant

TABLE 3 Odds ratios (95% Confidence Intervals) and regression coefficient of cross-sectional impact of 2-year exposure to air pollution on health shocks among Chinese elderly, CHARLS 2018.

	Model 1		Model 2		Model 3		Model 4 ORs (95% CI)	
	SRH (95%CI)	ADL (95%CI)	SRH (95%CI)	ADL (95%CI)	SRH (95%CI)	ADL (95%CI)	SRH (95%CI)	ADL (95%CI)
[a]AQI	[b]0.260**	0.274*	0.212**	0.318**	0.259**	0.337**	0.256**	0.399**
	[c](0.058, 0.463)	(−0.004, 0.551)	(0.007, 0.418)	(0.030, 0.607)	(0.052, 0.465)	(0.043, 0.630)	[d]1.004 (1.001, 1.007)	1.005 (1.001, 1.009)
Age			−0.017***	−0.053***	−0.017***	−0.052***	−0.017***	−0.052***
			(−0.025, −0.009)	(−0.065, −0.040)	(−0.026, −0.009)	(−0.065, −0.039)	0.016 (0.007, 0.024)	0.951 (0.939, 0.963)
Sex			0.406***	1.157***	0.303***	1.031***	0.303***	1.030***
			(0.277, 0.536)	(0.996, 1.318)	(0.153, 0.452)	(0.843, 1.219)	0.724 (0.623, 0.841)	2.811 (2.333, 3.389)
Married			0.114*	0.120	0.083	0.103	0.083	0.108
			(−0.018, 0.247)	(−0.082, 0.323)	(−0.051, 0.218)	(−0.102, 0.308)	0.916 (0.801, 1.048)	1.124 (0.917, 1.378)
Resid			0.410***	0.237***	0.242***	0.084	0.242***	0.080
			(0.288, 0.533)	(0.070, 0.404)	(0.091, 0.394)	(−0.126, 0.294)	0.796 (0.685, 0.926)	1.067 (0.866, 1.315)
Educa			0.075	−0.052	0.057	−0.072	0.057	−0.069
			(−0.050, 0.200)	(−0.235, 0.130)	(−0.069, 0.184)	(−0.257, 0.114)	(−0.069, 0.184)	(−0.255, 0.116)
			0.218***	0.382***	0.157**	0.342***	0.157**	0.347***
			(0.065, 0.371)	(0.178, 0.587)	(0.002, 0.313)	(0.133, 0.550)	(0.002, 0.313)	(0.139, 0.556)
			0.223**	0.191	0.149	0.142	0.149	0.142
			(−0.019, 0.427)	(−0.098, 0.481)	(−0.060, 0.358)	(−0.154, 0.438)	0.935 (0.883, 0.991)	1.101 (1.017, 1.193)
Pension					0.452***	0.338***	0.452***	0.332***
					(0.283, 0.621)	(0.112, 0.563)	0.681 (0.575, 0.807)	1.337 (1.069, 1.674)
Smoke					−0.314***	−0.031	−0.314***	−0.027
					(−0.547, −0.081)	(−0.315, 0.254)	1.464 (1.160, 1.847)	0.913 (0.688, 1.212)
Drink					0.404***	0.335***	0.404***	0.339***
					(0.262, 0.545)	(0.154, 0.517)	0.647 (0.562, 0.745)	1.439 (1.202, 1.724)
HPI					−0.866***	−0.614***	−0.866***	−0.612***
					(−0.972, −0.759)	(-0.766, −0.463)	2.710 (2.307, 3.184)	0.570 (0.442, 0.735)
Green							−0.001	0.004
							0.981 (0.959, 1.003)	1.021 (0.989, 1.055)
Sewpro							0.001	−0.029
							0.981 (0.959, 1.003)	0.961 (0.917, 1.007)

Marri, Marital status; Resid, Residence; Educa, Education; HPI, history of present illness.

[a]The AQI were ln-transformed in these models.

[b]Stepwise regression Coefficient: Standard errors in parentheses, clustered at the Provincial level. *, **, and *** indicate significance at the levels of 10, 5, and 1%, respectively.

[c]95% confidence intervals.

[d]The column of model 4 is the confidence interval of Odds ratios (ORs) (95% CI).

TABLE 4 Heterogeneity of SRH and ADL among different age groups of residents affected by air quality index.

	Age > 60		60–69		70+		[a]Age#AQI	
	(1)		(2)		(3)		(4)	
	SRH	ADL	SRH	ADL	SRH	ADL	SRH	ADL
AQI	0.0822**	0.0534**	0.1074**	0.0694**	0.0558	0.0253	−0.0001	−0.0135***
	(0.0410)	(0.0132)	(0.0287)	(0.0119)	(0.4232)	(0.4579)	(0.9472)	(0.0000)
cons	0.4044	0.2960	0.3933	0.0088	0.1614	0.7075		
	(0.4511)	(0.2931)	(0.5528)	(0.9803)	(0.8590)	(0.1216)		
Obs	5,172		3,225		1,947		5,172	
adj. R^2	0.0824	0.0644	0.0927	0.0752	0.0679	0.0495		

[a]The column of (4) is the interaction effects between age factors and air quality.
Standard errors in parentheses, clustered at the Provincial level. *, **, and ***indicate significance at the levels of 10, 5, and 1%, respectively. The control variable results are not listed here.

TABLE 5 Heterogeneity of SRH and ADL among different regional groups of residents affected by air quality index.

	Region		East		West		Central		[a]Region1#AQI		Region2#AQI	
	(1)		(2)		(3)		(4)		(5)		(6)	
	SRH	ADL	SRH	ADL	SRH	ADL	SRH	ADL	SRH	ADL	SRH	ADL
AQI	0.0821**	0.0532**	0.0515	0.1159**	0.0530	0.0533	−0.0011	0.2444***	−0.2157	0.1642	0.7942*	0.0068
	(0.0411)	(0.0133)	(0.6071)	(0.0262)	(0.5455)	(0.2489)	(0.9939)	(0.0013)	(0.6256)	(0.6027)	(0.0878)	(0.9836)
Cons	0.7909	0.7498***	1.2163	2.4510***	1.0771	−0.2679	1.3838	1.4921**				
	(0.1480)	(0.0086)	(0.3721)	(0.0008)	(0.4441)	(0.6956)	(0.1989)	(0.0108)				
Obs	5,172		1,774		1,783		1,615		5,172		5,172	
adj. R^2	0.0847	0.0761	0.0952	0.0984	0.0628	0.0984	0.0869	0.0984				

[a]The columns of (5) and (6) are the interaction effects between regional factors and air quality.
Standard errors in parentheses, clustered at the Provincial level. *, **, and ***indicate significance at the levels of 10, 5, and 1%, respectively. The control variable results are not listed here.

TABLE 6 Heterogeneity of SRH and ADL among different gender groups of residents affected by air quality index.

			Male		Female		[a]Sex#AQI	
	(1)		(2)		(3)		(4)	
	SRH	ADL	SRH	ADL	SRH	ADL	SRH	ADL
AQI	0.0772*	0.0447**	0.1496*	0.1248**	0.0604	0.0300	0.3233	0.3622
	(0.0523)	(0.0370)	(0.0776)	(0.0248)	(0.1802)	(0.1805)	(0.3159)	(0.1618)
cons	0.7750	0.7545***	−1.6841	0.7114	1.3586**	0.7717***		
	(0.1575)	(0.0092)	(0.1661)	(0.3830)	(0.0265)	(0.0083)		
Obs	5172		1069		4103		5172	
adj. R^2	0.0826	0.0530	0.1158	0.0660	0.0700	0.0289		

[a]The column of (4) is the interaction effects between sex factors and air quality.
Standard errors in parentheses, clustered at the Provincial level. *, **, and *** indicate significance at the levels of 10, 5, and 1%, respectively. The control variable results are not listed here.

in central China, which is consistent with previous studies (43, 51). However, we found that there is an internal difference in the air quality and ADL of the elderly in the central and western regions. This study updates the previous practice of dividing regions into two categories (East and Midwest) (51). According to the air quality data we studied, the average AQI in the eastern and central regions is 85 and 83, respectively, higher than 66 in the western regions. With regard to the significant difference in the east, a possible explanation is that the level of economic development in the east is higher than that in the west (35, 51), and the AP is serious, which has a more significant impact on the elderly exposed to pollutants. Based on data from the 2018 China Statistical Yearbook, 1,774 samples from the east show that the average per capita gross domestic product (GDP) is 79,065 Chinese Yuan (CNY), compared with 46,481 CNY in the western regions and 46,153 CNY in the central regions (28). Although the heterogeneity analysis was divided by geographical location, our result is similar to that grouped by GDP (18), and we have consistently concluded the significance of the high GDP group. Interestingly, Liu et al. (51) found the heterogeneity in the Midwest regions, but the health of the eastern population was not sensitive to AP (51). We suspect that the reason for the difference is that, on the one hand, we selected the

TABLE 7 Results of SRH and pollutant heterogeneity analysis.

	(1) SRH	(2) SRH	(3) SRH	(4) SRH	(5) SRH	(6) SRH
$PM_{2.5}$	0.0030					
	(0.1468)					
PM_{10}		0.0027**				
		(0.0240)				
SO_2			0.0004			
			(0.9150)			
CO				0.0728		
				(0.5347)		
O_3					0.0073***	
					(0.0018)	
NO_2						0.0080***
						(0.0042)
Control	YES	YES	YES	YES	YES	YES

Standard errors in parentheses, clustered at the Provincial level. *, **, and ***indicate significance at the levels of 10, 5, and 1%, respectively.

TABLE 8 Results of ADL and pollutant heterogeneity analysis.

	(1) ADL	(2) ADL	(3) ADL	(4) ADL	(5) ADL	(6) ADL
$PM_{2.5}$	0.0070**					
	(0.0161)					
PM_{10}		0.0045***				
		(0.0090)				
SO_2			0.0046			
			(0.3587)			
CO				0.3763**		
				(0.0228)		
O_3					0.0101***	
					(0.0031)	
NO_2						0.0127***
						(0.0013)
Control	YES	YES	YES	YES	YES	YES
Cons	4.0699*	4.5990**	3.0791	2.8509	4.3806**	3.4585
	(0.0643)	(0.0395)	(0.1553)	(0.1845)	(0.0455)	(0.1066)

Standard errors in parentheses, clustered at the Provincial level. *, **, and ***indicate significance at the levels of 10, 5, and 1%, respectively.

samples in 2018 from CHARLS, while Liu et al. used the samples in 2015 from CHARLS (All data is available from https://charls.pku.edu.cn); on the other hand, we evaluated the deterioration of health, while the previous study reported the positive score of health status.

With regard to the significant impact path of pollution, our findings are consistent with previous studies. Briefly, NO_2 and O_3 proved to be more relevant to health (17, 52). NO_2 is produced by vehicle emissions, petrochemical refineries, power plants and fuel combustion, and NO combines with O_3 in the atmosphere to produce NO_2 (53, 54). Deeply penetrating the lungs, NO can induce respiratory problems such as dyspnea, bronchospasm, and even pulmonary edema when inhaled in significant volumes (54–56). Concentrations exceeding 2.0 parts per million can affect T-lymphocytes, particularly CD8+ cells and NK cells that trigger immunological responses (56). Long-term exposure to high concentrations of NO_2 leads to lung disease, impairs the sense of smell, and irritates the eye and nasal mucosa (53, 56).

Ozone production is highly non-linearly related to volatile organic compounds (VOCs) and NOx. Ground-level ozone is produced through chemical reactions between NOx and natural sources (soil and rock weathering, volcanic ash, sea salt and biomass particles) or VOCs emitted by human activities (53, 55). Ozone exposure causes the formation of malondialdehyde in the mouse epidermis, depleting vitamins C and E and leading to skin disease (57). In addition, ozone has a low water solubility and enters the lungs deeply after inhalation (58). Over 3 years of tracking, major European cities reported daily ozone concentrations and daily death rates. The number of daily deaths, respiratory deaths, and cardiovascular deaths all increased in direct proportion to an increase in ozone concentration (59). Exposure to NO_2 and O_3 in air pollutants has led to an increase in emergency hospital admissions for cardiovascular and respiratory diseases (54, 55). However, most of the samples selected in our study were from rural areas, and the urbanization level is low, so the AP situation in cities was not well represented. Previous research included SO_2, NO_2 and PM_{10}, pointing out that the concentration of SO_2 and PM_{10} is the main factor affecting the disability of residents' ADL (18). In addition to physiological health, the increase of NO_2 and O_3 concentrations was also significantly related to depressive symptoms in the elderly (13, 17). We analyzed the six types of pollutants separately for supplementary demonstration. Hence, our second marginal contribution is to update the existing heterogeneity analysis on the impact of AP on health. Understanding the real extent of unexpected and serious health deterioration experienced by the elderly in the face of changes in the air quality at the individual level will also help local governments to formulate measures according to the heterogeneity and inequality of groups and regions.

Despite the practical relevance of the results of the analysis, there are some limitations to this study. First, the average value of AQI can empirically reflect the impact of long-term exposure to AP on residents' health status. It is undeniable that there are biases and fewer fine data compared with spatial data. Second, the matched samples were predominantly female and living in rural areas, which may affect the applicability and reliability of the findings to some extent. Third, as CHARLS2018 did not ask how long individuals had lived in their current residence, we failed to control for the residence time of the respondents. This problem can be solved by using CHARLS databases in 2015 and 2018, which is an important direction for further research. Finally, because limited by the sample data, the synergistic effects among pollutants are not explored in depth in this paper. By gradually addressing the above issues, we can further inform the government on air pollution management.

5. Conclusion

In this study, we found that air pollution has a significant positive impact on health shocks in old age. The government should focus on increasing efforts to combat environmental pollution and develop a long-term environmental health work plan. Second, the government should pay particular attention to the health status of older groups, especially those without pension support, in rural areas, and young-older people with low levels of education, who are among those at high risk of health shocks. The serious consequences of health shocks can be addressed by increasing the availability of pensions and spreading knowledge of environmental and health sciences. Finally, as young-older people are exposed to air pollution when working outside the home or caring for grandchildren, it is particularly important that they take the necessary measures to protect themselves to mitigate the health effects of air pollution.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://charls.pku.edu.cn.

Author contributions

XL and AX provided research ideas. XL contributed to data analysis and manuscript writing. YL and WD contributed to critical revisions of the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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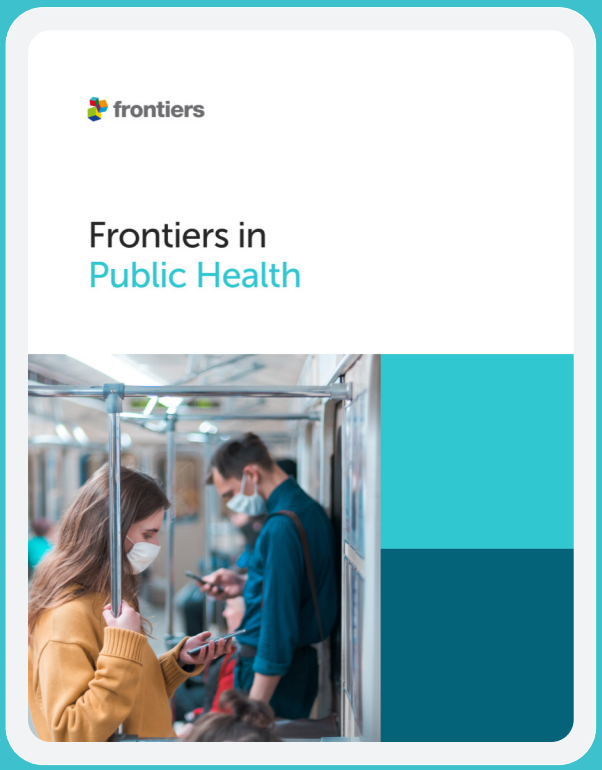

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