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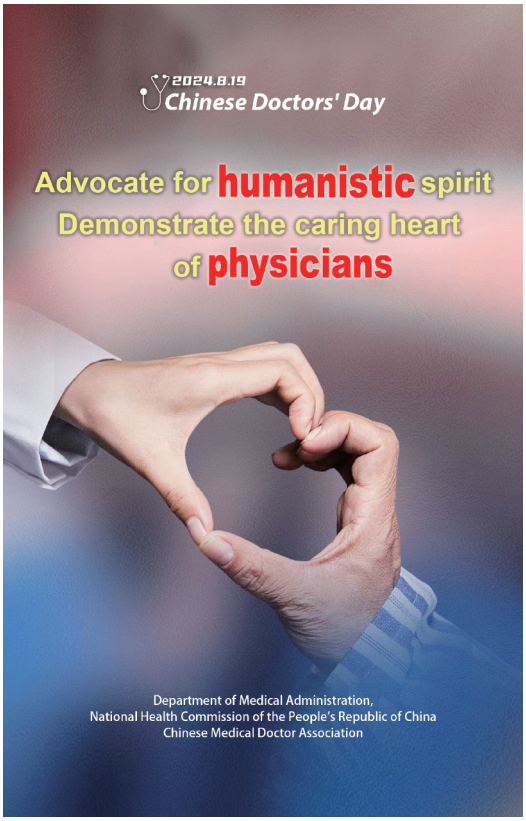

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Preplanned Studies

Assessment of the Respiratory Disease Mortality Risk from Single and Composite Exposures to $PM_{2.5}$ and Ozone — Guangzhou City, Guangdong Province, China, 2018–2021

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Summary

What is already known about this topic?

Fine particulate matter ($PM_{2.5}$) and ozone (O_3) are prevalent pollutants in the atmosphere, which threaten human health, especially the respiratory system. Typically, people are exposed to a mixture of various pollutants in the environment. Thus, the single and combined effects of both pollutants need to be investigated.

What is added by this report?

$PM_{2.5}$ and O_3 increase the risk of death from lung cancer, chronic obstructive pulmonary disease (COPD), and respiratory diseases, with their lagged and cumulative effects analyzed, indicating an acute effect. In addition, combined exposure to both pollutants can significantly affect disease deaths.

What are the implications for public health practice?

This study provides further evidence of the single and combined effects of $PM_{2.5}$ and O_3 on respiratory diseases, emphasizing the need for sustained efforts in air pollution control, with greater attention to the synergistic management of air pollutants.

Air pollution continues to be a significant risk factor for disability and is associated with approximately 6.67 million global deaths annually (*1*). According to the 2018 Guangdong Ecological Environment Report, ozone (O_3) and fine particulate matter ($PM_{2.5}$), accounting for 55.5% and 17.0% of primary pollutants, respectively, are the predominant contaminants in the Pearl River Delta region's 9 cities (*2*). It has been established that $PM_{2.5}$ and O_3 are positively associated with the incidence and mortality rates of respiratory diseases, which may also have interaction effects between O_3 and $PM_{2.5}$ on population health (*3*).

In this study, we employed a generalized additive model (GAM) to analyze the associations between O_3 and $PM_{2.5}$ concentrations and mortality rates from respiratory diseases, chronic obstructive pulmonary disease (COPD), and lung cancer in Guangzhou. Additionally, we applied the quantile g-computation (QG-C) model to assess the combined effects of these pollutants on mortality related to respiratory conditions. Our findings contribute to a more comprehensive environmental health risk assessment and support the formulation of integrated prevention and control strategies.

Meteorological data, the daily maximum 8-hour average concentration of O_3 and the 24-hour average concentration of $PM_{2.5}$, during 2018–2021, were sourced from the Guangdong Multi-Trigger Smart Early Warning System. Respiratory diseases, COPD, and lung cancer, which are attributed to death, were classified using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes with J00-J99, J40-J47, and C34, respectively.

R (version 4.2.2; R Core Team, Vienna, Austria) equipped with the "mgcv" and "dlnm" packages was utilized to develop GAMs to investigate the non-linear relationships between pollutant exposure and mortality from selected diseases. Both lagged concentrations and moving averages of pollutants were integrated into the models to consider delayed and cumulative effects. The QG-C method, utilizing the "qgcomp" package, estimated the joint effects of $PM_{2.5}$ and O_3 exposure, with the lowest quantile serving as the reference point (*4*). Subgroup analyses were performed based on age (less than 85 years and 85 years or older), sex, seasonal variations (April to September as warm and October to March as cold), and the coronavirus disease 2019 (COVID-19) pandemic periods (2018–2019 and 2020–2021).

The outcomes of the single-pollutant exposure analysis are presented as excess risk (*ER*) with a 95%

confidence interval (*CI*) corresponding to every 10 μg/m^3 increment in pollutant levels. For combined exposure effects, relative risks (*RR*s) and their 95% *CI*s are reported per quartile increase in pollutant concentration. Z tests were employed to assess differences between subgroups, with a *P* less than 0.05 denoting statistical significance.

During 2018 and 2021, Guangzhou recorded 29,258 deaths from respiratory diseases, 11,036 from COPD, and 16,901 from lung cancer (Supplementary Table S1, available at https://weekly.chinacdc.cn/). The mortality rates for respiratory diseases and COPD declined in both genders, whereas lung cancer mortality rates varied throughout the period (Supplementary Table S2, available at https://weekly.chinacdc.cn/).

The average daily concentrations were 29.34 μg/m^3 for $PM_{2.5}$ and 90.63 μg/m^3 for O_3. O_3 levels exhibited a slight increase, whereas $PM_{2.5}$ levels showed a significant decline (Supplementary Figure S1A–B, available at https://weekly.chinacdc.cn/). The monthly trends in O_3 and $PM_{2.5}$ concentrations in Guangzhou varied significantly. According to the meteorological data, the daily average temperature was 22.71 °C, and the average relative humidity was 79.14% in Guangzhou. (Supplementary Figure S1C–D). $PM_{2.5}$ levels showed a distinct seasonal pattern, peaking in winter and reaching the lowest levels in summer. Autocorrelation analysis revealed a non-stationary sequence, indicating a decrease in pollutant concentrations over time. Unlike $PM_{2.5}$, O_3 concentrations did not exhibit any annual variability; however, they still displayed a seasonal pattern, with the highest levels of pollution from April to September (Supplementary Figure S1E–F).

As demonstrated in Table 1 and Supplementary Figure S2 (available at https://weekly.chinacdc.cn/), the highest and most statistically significant increased risk was observed on the first day (lag0) for both O_3 and $PM_{2.5}$ (P<0.05). As the lag time extended, the correlations between these pollutants and mortality rates gradually diminished and were no longer significant after three days (lag3), suggesting that O_3 and $PM_{2.5}$ primarily have acute impacts on respiratory diseases. Both $PM_{2.5}$ and O_3 exhibited cumulative effects on mortality from all selected diseases. The maximum cumulative effects of $PM_{2.5}$ and O_3 on all-cause mortality were seen at lag03, except that of O_3 on respiratory disease occurred at lag04. However, when $PM_{2.5}$ was set as a covariate, no significant association was observed between O_3 exposure and lung cancer mortality (Supplementary Table S3, available at https://weekly.chinacdc.cn/).

The results of the subgroup analysis assessing the impact of O_3 and $PM_{2.5}$ on mortality from selected diseases across various demographics and the COVID-19 pandemic period are presented (Figure 1, and Supplementary Table S4, available at https://weekly.chinacdc.cn/). The analysis revealed minimal significant differences in the effects across age groups, sexes, and throughout the COVID-19 pandemic, suggesting that these factors may not significantly modify the association between O_3/$PM_{2.5}$ exposure and mortality risk from selected diseases. Notably, the

TABLE 1. Excess risk associated with exposure to $PM_{2.5}$ or O_3 on respiratory disease mortality.

Lag time	$PM_{2.5}$, *ER* (95% *CI*) (%)			O_3, *ER* (95% *CI*) (%)		
	Respiratory diseases	COPD	Lung cancer	Respiratory diseases	COPD	Lung cancer
Lag0	1.08 (0.62, 1.55)*	1.00 (0.26, 1.74)*	1.42 (0.81, 2.04)*	0.37 (0.19, 0.55)*	0.50 (0.20, 0.79)*	0.34 (0.12, 0.57)*
Lag1	0.86 (0.49, 1.23)*	0.77 (0.18, 1.36)*	1.09 (0.61, 1.58)*	0.30 (0.16, 0.44)*	0.39 (0.16, 0.62)*	0.26 (0.08, 0.44)*
Lag2	0.63 (0.35, 0.92)*	0.54 (0.09, 1.00)*	0.76 (0.38, 1.13)*	0.23 (0.12, 0.33)*	0.29 (0.11, 0.46)*	0.17 (0.04, 0.31)*
Lag3	0.41 (0.18, 0.63)*	0.32 (−0.05, 0.68)	0.43 (0.13, 0.73)*	0.15 (0.07, 0.23)*	0.18 (0.04, 0.32)*	0.09 (−0.02, 0.19)
Lag4	0.18 (−0.04, 0.40)	0.09 (−0.26, 0.44)	0.10 (−0.19, 0.38)	0.08 (−0.00, 0.16)	0.07 (−0.06, 0.20)	0.00 (−0.09, 0.10)
Lag5	−0.04 (−0.30, 0.21)	−0.14 (−0.54, 0.27)	−0.23 (−0.57, 0.11)	0.00 (−0.09, 0.10)	−0.03 (−0.19, 0.13)	−0.08 (−0.20, 0.04)
Lag01	2.65 (1.47, 3.82)*	2.51 (0.62, 4.39)*	3.65 (2.10, 5.20)*	0.77 (0.30, 1.23)*	1.14 (0.37, 1.91)*	0.72 (0.13, 1.31)*
Lag02	3.06 (1.78, 4.34)*	2.61 (0.55, 4.67)*	3.83 (2.15, 5.52)*	1.03 (0.54, 1.52)*	1.40 (0.59, 2.22)*	0.79 (0.16, 1.41)*
Lag03	3.28 (1.91, 4.66)*	2.72 (0.51, 4.93)*	3.90 (2.08, 5.71)*	1.12 (0.61, 1.64)*	1.46 (0.61, 2.32)*	0.85 (0.20, 1.51)*
Lag04	3.15 (1.69, 4.62)*	2.70 (0.35, 5.04)*	3.42 (1.48, 5.35)*	1.14 (0.60, 1.68)*	1.41 (0.52, 2.31)*	0.77 (0.08, 1.46)*
Lag05	2.77 (1.23, 4.31)*	2.32 (−0.15, 4.80)	2.92 (0.88, 4.96)*	1.07 (0.50, 1.63)*	1.23 (0.29, 2.17)*	0.64 (−0.08, 1.36)*

Abbreviation: *ER*=excess risk; *CI*=confidence interval; COPD=chronic obstructive pulmonary disease; $PM_{2.5}$=fine particulate matter; O_3=ozone.
* P<0.05.

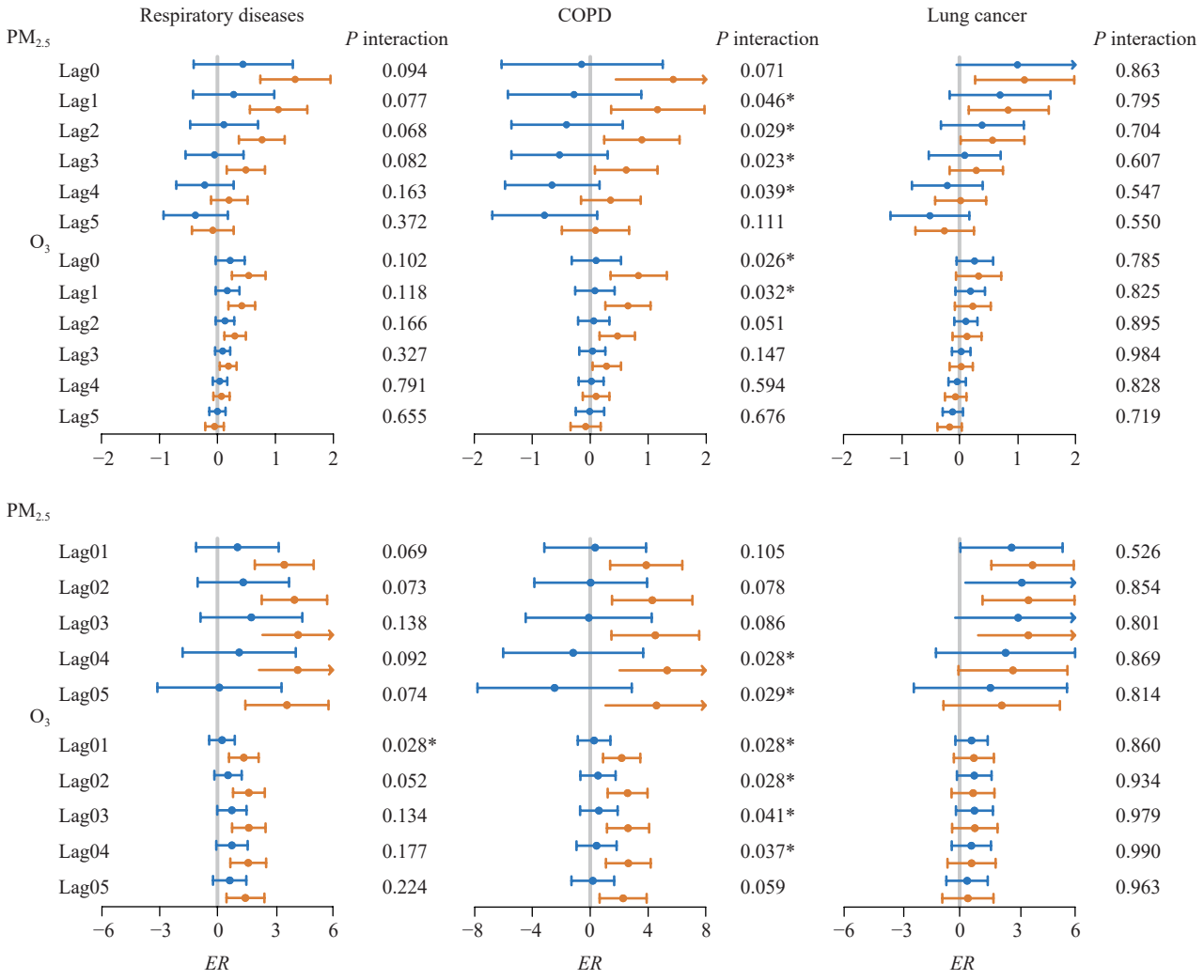

FIGURE 1. Effects of changes in $PM_{2.5}$ and O_3 concentrations on mortality across cool and warm season subgroups under various lag conditions.
Note: Single lags lag0 to lag5 and cumulative lags lag01 to lag05. Blue represents the cold group; yellow represents the warm group.
Abbreviation: *ER*=excess risk; COPD=chronic obstructive pulmonary disease; $PM_{2.5}$=fine particulate matter; O_3=ozone.
* $P<0.05$.

warm season exhibited a higher *ER* for mortality from COPD associated with exposure to O_3 or $PM_{2.5}$ (Figure 1). Furthermore, $PM_{2.5}$ exposure demonstrated a more pronounced effect on COPD mortality in males compared to females, whereas the reverse was observed for lung cancer. In terms of age, $PM_{2.5}$ exposure had a stronger impact on individuals aged above 85 years, whereas O_3 showed greater effects on those under 85 years.

Spearman correlation analysis revealed positive correlations between $PM_{2.5}$ and O_3, indicating potential interactions between these pollutants. In terms of meteorological factors, O_3 showed a positive correlation with temperature and a negative correlation with relative humidity. Conversely, $PM_{2.5}$ exhibited negative correlations with both temperature and relative humidity (Supplementary Table S5, available at https://weekly.chinacdc.cn/).

The QG-C model demonstrated that combined exposure to $PM_{2.5}$ and O_3 was significantly associated with increased mortality due to all selected diseases, of which the weights of two pollutants were presented in Supplementary Figure S3 (available at https://weekly.chinacdc.cn/). For females and individuals aged below 85, this combined exposure was identified as a risk factor for mortality. Among males, concurrent exposure to $PM_{2.5}$ and O_3 was also linked to an increased risk of mortality from lung cancer.

Furthermore, during the warm seasons, the correlation between combined exposure to $PM_{2.5}$ and O_3 and mortality from all examined diseases was evident, suggesting that higher temperatures may significantly influence respiratory-related diseases (Table 2).

DISCUSSION

In recent years, public concern over air pollution in China, specifically regarding $PM_{2.5}$ and O_3 exposure, has escalated. Standards set by the Chinese Ambient Air Quality Standards (AAQSs) reveal that from 2018 to 2021, only 68.99% of days met the $PM_{2.5}$ criteria. Furthermore, the compliance for O_3 was even lower, with just 35.25% of days meeting the AAQSs. This data underscores the persistent air pollution threat facing residents of Guangzhou and highlights the urgent need for enhanced pollution control measures.

It has been found that higher concentrations of $PM_{2.5}$ and O_3 were positively correlated with an increased risk of death from respiratory diseases in this study by using a time-series design. Many epidemiological studies have consistently demonstrated significant correlations between $PM_{2.5}$ and O_3 exposure and both the incidence and mortality of respiratory conditions, particularly lung-related diseases (*5*). The associations found in this study seem to be stronger than those reported elsewhere. This discrepancy could be attributed to Guangzhou's unique geographical characteristics (*6*), such as its extended warm seasons and elevated temperatures, which may enhance respiratory rates and lung ventilation, thereby heightening vulnerability to air pollutants.

Our findings indicate a positive association between combined exposure to $PM_{2.5}$ and O_3, and increased mortality from all selected diseases. This association may be mechanistically supported by the ability of particulate matter to reduce ultraviolet radiation penetration, thus interfering with O_3 photochemical reactions. Additionally, exposure to both $PM_{2.5}$ and O_3 can stimulate oxidative stress in lung tissues, suggesting there are biological interactions and combined effects between these pollutants (*7*).

This study also presents several limitations. First, it assumes that air pollutant concentrations from monitoring stations reflect the population exposures. Second, the dataset only includes Guangzhou, which limits the generalizability of the findings. Lastly, the study's time-series analysis design is unable to assess the long-term risks associated with air pollution.

Exposure to $PM_{2.5}$ and O_3 in the atmosphere is linked to an increased risk of respiratory diseases, COPD, and lung cancer mortality. The combined effects of $PM_{2.5}$ and O_3 further exacerbate mortality rates associated with these conditions. Given that the current levels of $PM_{2.5}$ and O_3 continue to pose health risks, it is crucial to enhance health protection and disease control strategies for the population in

TABLE 2. Association of combined $PM_{2.5}$ and O_3 exposure with mortality risk according to the QG-C model.

Group	Died of respiratory diseases	Died of COPD	Died of lung cancer
Total population	1.03 (1.01, 1.05)†	1.03 (1.00, 1.07)*	1.05(1.02, 1.08)†
Age group (years)			
≥85	1.03 (1.00, 1.06)*	1.03 (0.99, 1.08)	1.02 (0.95, 1.09)
<85	1.04 (1.01, 1.06)†	1.04 (0.99, 1.08)	1.05 (1.03, 1.08)†
Sex			
Male	1.01 (0.99, 1.04)	1.03 (0.99, 1.07)	1.05 (1.02, 1.08)†
Female	1.06 (1.03, 1.1)†,§	1.04 (0.98, 1.10)	1.06 (1.01, 1.11)*
Season			
Cold	1.00 (0.97, 1.03)	0.99 (0.95, 1.04)	1.02 (0.99, 1.06)
Warm	1.04 (1.02, 1.07)†,§	1.04 (1.00, 1.08)*	1.04 (1.00, 1.07)*
Time			
COVID-19	1.02 (0.99, 1.05)	1.03 (0.99, 1.07)	1.02 (0.99, 1.05)
non-COVID-19	1.01 (0.99, 1.04)	1.02 (0.98, 1.06)	1.06 (1.02, 1.09)†

Abbreviation: COPD=chronic obstructive pulmonary disease; COVID-19=coronavirus disease 2019.
* $P<0.05$;
† $P<0.01$;
§ statistically significant compared to males or cold group.

Guangzhou.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTAL MATERIAL

The GAMs Model Equation

$$Log[E(Y_t)] = X + s\left(time, \frac{7df}{year}\right) + s(hum, \upsilon) + s(temp, \upsilon) + DOW + PH + intercept \quad (1)$$

where *E(Y)* denotes the expected number of daily deaths from respiratory diseases, chronic obstructive pulmonary disease (COPD), or lung cancer on day t;

X represents O_3 (or $PM_{2.5}$);

s represents a smooth basis function;

time represents a time series.

df represents degrees of freedom. Drawing from prior research, a natural cubic spline function was employed with seven degrees of freedom per year to account for natural variations in mortality rates over time.

hum represents the daily average relative humidity;

temp represents the daily average temperature;

υ represents degrees of freedom;

DOW (day of the week) represents weekday variables;

PH (public holiday) represents holiday variables.

According to the AIC criterion, the value of υ for humidity was set at 2, and υ for temperature was set at 3.

Multiple Sensitivity Analyses

We performed several sensitivity analyses to assess the stability of the relationship between air pollutants and mortality due to respiratory diseases, COPD, and lung cancer. Initially, besides the aforementioned single-pollutant models, dual-pollutant models were employed to adjust for potential confounders from co-existing pollutants.

SUPPLEMENTARY TABLE S1. Descriptive analysis of disease-related deaths in Guangzhou City, 2018–2022.

Type of diseases	Subgroups	Number of diseases	$\bar{x}$ ±s
Respiratory diseases	Sex		
	Male	18,318	12.54±4.40
	Female	10,940	7.49±3.22
	Age, years		
	≥85	13,460	9.21±3.55
	<85	15,798	10.81±3.89
	Total	29,258	20.03±6.08
COPD	Sex		
	Male	8,062	5.52±2.79
	Female	2,974	2.04±1.57
	Age, years		
	≥85	4,915	3.36±2.08
	<85	6,121	4.19±2.35
	Total	11,036	7.55±3.47
Lung cancer	Sex		
	Male	11,635	7.96±2.93
	Female	5,266	3.60±1.93
	Age, years		
	≥85	2,065	1.41±1.19
	<85	14,836	10.15±3.32
	Total	16,901	11.57±3.56

Note: $\bar{x}$=the daily average mortality of each subgroup during 2018 to 2021 in Guangzhou; *s*=standard deviation.
Abbreviation: COPD=chronic obstructive pulmonary disease.

SUPPLEMENTARY TABLE S2. Gender-standardized mortality rates in Guangzhou City from 2018 to 2021 (per 100,000).

Disease type	Gender	2018	2019	2020	2021
Respiratory diseases	Male	50.23	53.37	43.11	47.94
	Female	29.49	30.66	25.02	24.77
COPD	Male	24.88	22.37	18.60	19.97
	Female	9.17	7.76	6.75	6.28
Lung cancer	Male	31.91	29.26	30.28	32.02
	Female	13.11	12.57	13.46	13.58

Abbreviation: COPD=chronic obstructive pulmonary disease.

SUPPLEMENTARY TABLE S3. Sensitivity analysis of the dual-pollutant model in Guangzhou from 2018 to 2021.

Lag time	$PM_{2.5}$, *ER* (95% *CI*) (%)			O_3, *ER* (95% *CI*) (%)		
	Respiratory diseases	COPD	Lung cancer	Respiratory diseases	COPD	Lung cancer
Lag0	1.15 (0.63, 1.67)*	0.98 (0.16, 1.82)*	1.49 (0.80, 2.18)*	0.31 (0.11, 0.52)*	0.48 (0.14, 0.82)*	0.16 (−0.10, 0.42)
Lag1	0.91 (0.50, 1.32)*	0.76 (0.10, 1.42)*	1.14 (0.59, 1.69)*	0.25 (0.09, 0.41)*	0.37 (0.11, 0.64)*	0.11 (−0.09, 0.32)
Lag2	0.67 (0.35, 0.99)*	0.53 (0.03, 1.04)*	0.79 (0.37, 1.22)*	0.19 (0.07, 0.31)*	0.27 (0.07, 0.47)*	0.07 (−0.08, 0.22)
Lag3	0.43 (0.19, 0.68)*	0.31 (−0.08, 0.70)	0.45 (0.13, 0.78)*	0.13 (0.04, 0.22)*	0.17 (0.02, 0.32)*	0.03 (−0.09, 0.14)
Lag4	0.19 (−0.03, 0.41)	0.09 (−0.27, 0.44)	0.11 (−0.19, 0.40)	0.07 (−0.01, 0.15)	0.07 (−0.06, 0.20)	−0.02 (−0.12, 0.08)
Lag5	−0.05 (−0.30, 0.21)	−0.14 (−0.54, 0.27)	−0.23 (−0.58, 0.11)	0.01 (−0.09, 0.11)	−0.03 (−0.19, 0.13)	−0.06 (−0.18, 0.06)
Lag01	2.75 (1.34, 4.17)*	2.41 (0.14, 4.69)*	4.18 (2.3, 6.06)*	0.4 (−0.18, 0.97)	0.88 (−0.07, 1.83)	−0.08 (−0.81, 0.66)
Lag02	3.3 (1.82, 4.78)*	2.73 (0.35, 5.11)*	4.37 (2.4, 6.34)*	0.67 (0.09, 1.25)*	1.23 (0.26, 2.2)*	0.05 (−0.69, 0.80)
Lag03	3.55 (2.01, 5.09)*	2.83 (0.36, 5.31)*	4.36 (2.32, 6.41)*	0.87 (0.28, 1.46)*	1.41 (0.43, 2.39)*	0.18 (−0.57, 0.93)
Lag04	3.47 (1.88, 5.07)*	2.84 (0.27, 5.40)*	3.89 (1.77, 6.02)*	0.96 (0.36, 1.56)*	1.42 (0.43, 2.41)*	0.24 (−0.53, 1.00)
Lag05	3.11 (1.45, 4.76)*	2.42 (−0.24, 5.08)	3.32 (1.12, 5.53)*	0.94 (0.33, 1.55)*	1.24 (0.23, 2.25)*	0.2 (−0.57, 0.98)

Abbreviation: *ER*=excess risk; *CI*=confidence interval; COPD=chronic obstructive pulmonary disease; $PM_{2.5}$=fine particulate matter; O_3=ozone.
* $P<0.05$.

SUPPLEMENTARY TABLE S4. Effect modification by different subgroups on the associations between exposure at lag 0–5 to $PM_{2.5}$/O_3 and respiratory-related diseases.

Subgroup	Lag time	$PM_{2.5}$, *ER* (95% *CI*) (%)			O_3, *ER* (95% *CI*) (%)		
		Respiratory diseases	COPD	Lung cancer	Respiratory diseases	COPD	Lung cancer
<85 years	Lag0	1.06 (0.46, 1.67)*	0.80 (−0.18, 1.78)	1.46 (0.81, 2.12)*	0.43 (0.20, 0.66)*	0.52 (0.13, 0.91)*	0.36 (0.12, 0.60)*
	Lag1	0.86 (0.39, 1.34)*	0.61 (−0.16, 1.40)	1.13 (0.61, 1.65)*	0.36 (0.17, 0.54)*	0.44 (0.13, 0.75)*	0.27 (0.08, 0.46)*
	Lag2	0.67 (0.30, 1.04)*	0.43 (−0.17, 1.03)	0.80 (0.40, 1.20)*	0.29 (0.15, 0.43)*	0.36 (0.13, 0.59)*	0.19 (0.04, 0.33)*
	Lag3	0.47 (0.17, 0.76)*	0.24 (−0.24, 0.73)	0.47 (0.15, 0.79)*	0.22 (0.11, 0.32)*	0.28 (0.10, 0.46)*	0.10 (−0.01, 0.22)
	Lag4	0.27 (−0.01, 0.55)	0.06 (−0.40, 0.52)	0.15 (−0.16, 0.45)	0.14 (0.04, 0.25)*	0.20 (0.03, 0.37)*	0.02 (−0.09, 0.12)
	Lag5	0.07 (−0.26, 0.41)	−0.12 (−0.67, 0.42)	−0.18 (−0.54, 0.18)	0.07 (−0.05, 0.20)	0.12 (−0.08, 0.33)	−0.07 (−0.20, 0.06)
	Lag01	2.76 (1.23, 4.28)*	1.70 (−0.80, 4.20)	3.91 (2.26, 5.56)*	1.04 (0.43, 1.64)*	1.37 (0.36, 2.38)*	0.79 (0.16, 1.42)*
	Lag02	3.28 (1.61, 4.94)*	1.97 (−0.75, 4.70)	4.06 (2.26, 5.85)*	1.28 (0.65, 1.92)*	1.66 (0.58, 2.73)*	0.85 (0.19, 1.52)*
	Lag03	3.59 (1.81, 5.38)*	2.33 (−0.59, 5.25)	4.22 (2.28, 6.15)*	1.47 (0.80, 2.14)*	1.92 (0.80, 3.05)*	0.92 (0.22, 1.62)*
	Lag04	3.42 (1.52, 5.33)*	2.19 (−0.92, 5.3)	3.78 (1.72, 5.84)*	1.50 (0.80, 2.20)*	1.99 (0.80, 3.17)*	0.85 (0.12, 1.58)*
	Lag05	3.13 (1.12, 5.13)*	1.79 (−1.5, 5.07)	3.29 (1.12, 5.47)*	1.48 (0.75, 2.22)*	1.88 (0.65, 3.12)*	0.74 (−0.03, 1.51)
≥85 years	Lag0	1.12 (0.46, 1.77)*	1.25 (0.20, 2.31)*	1.17 (−0.55, 2.92)	0.31 (0.06, 0.56)*	0.47 (0.05, 0.90)*	0.25 (−0.38, 0.88)
	Lag1	0.86 (0.34, 1.38)*	0.97 (0.13, 1.81)*	0.81 (−0.56, 2.19)	0.23 (0.03, 0.43)*	0.33 (−0.00, 0.67)	0.16 (−0.33, 0.66)
	Lag2	0.59 (0.19, 1.00)*	0.69 (0.04, 1.34)*	0.44 (−0.61, 1.51)	0.15 (0.00, 0.30)	0.19 (−0.06, 0.45)	0.07 (−0.30, 0.45)
	Lag3	0.33 (0.01, 0.66)*	0.41 (−0.11 ,0.93)	0.08 (−0.77, 0.93)	0.08 (−0.04, 0.19)	0.05 (−0.15, 0.25)	−0.01 (−0.30, 0.28)
	Lag4	0.07 (−0.23, 0.38)	0.13 (−0.36, 0.62)	−0.28 (−1.09, 0.53)	−0.00 (−0.11, 0.11)	−0.09 (−0.28, 0.10)	−0.10 (−0.37, 0.17)
	Lag5	−0.18 (−0.55, 0.18)	−0.15 (−0.73, 0.43)	−0.64 (−1.61, 0.33)	−0.08 (−0.21, 0.06)	−0.23 (−0.46, −0.00)	−0.19 (−0.52, 0.15)
	Lag01	2.6 (0.93, 4.27)*	3.6 (0.9, 6.29)*	2.19 (−2.22, 6.6)	0.45 (−0.21, 1.11)	0.85 (−0.27, 1.96)	0.22 (−1.42, 1.87)
	Lag02	2.91 (1.09, 4.73)*	3.48 (0.55, 6.41)*	2.75 (−2.03, 7.53)	0.72 (0.03, 1.42)*	1.09 (−0.09, 2.26)	0.34 (−1.38, 2.07)
	Lag03	3.04 (1.09, 4.99)*	3.29 (0.14, 6.45)*	2.15 (−2.99, 7.3)	0.72 (−0.01, 1.45)	0.89 (−0.34, 2.12)	0.39 (−1.43, 2.20)
	Lag04	2.95 (0.88, 5.02)*	3.43 (0.09, 6.77)*	1.22 (−4.26, 6.69)	0.72 (−0.04, 1.48)	0.70 (−0.59,1.99)	0.22 (−1.68,2 .12)
	Lag05	2.45 (0.27, 4.63)*	3.07 (−0.45, 6.6)	0.64 (−5.13, 6.4)	0.58 (−0.22, 1.38)	0.43 (−0.93,1.78)	−0.05 (−2.03, 1.94)
Female	Lag0	1.42 (0.68, 2.17)*	0.43 (−0.91, 1.78)	1.90 (0.82, 3.00)*	0.56 (0.27, 0.85)*	0.38 (−0.16, 0.93)	0.40 (0.00, 0.80)*
	Lag1	1.11 (0.52, 1.70)*	0.28 (−0.78, 1.36)	1.54 (0.68, 2.41)*	0.43 (0.21, 0.66)*	0.28 (−0.15, 0.71)	0.33 (0.02, 0.65)*
	Lag2	0.79 (0.34, 1.25)*	0.14 (−0.69, 0.97)	1.17 (0.51, 1.84)*	0.30 (0.13, 0.47)*	0.17 (−0.15, 0.50)	0.26 (0.02, 0.50)*
	Lag3	0.48 (0.12, 0.85)*	−0.01 (−0.67, 0.66)	0.81 (0.28, 1.34)*	0.18 (0.04, 0.31)*	0.07 (−0.19, 0.32)	0.19 (0.01, 0.38)*
	Lag4	0.17 (−0.18, 0.52)	−0.16 (−0.78, 0.48)	0.44 (−0.06, 0.95)	0.05 (−0.08, 0.17)	−0.04 (−0.28, 0.20)	0.12 (−0.05, 0.30)
	Lag5	−0.14 (−0.55, 0.27)	−0.30 (−1.04, 0.45)	0.08 (−0.52, 0.69)	−0.08 (−0.23, 0.07)	−0.15 (−0.44 ,0.15)	0.05 (−0.16, 0.26)
	Lag01	3.7 (1.81, 5.58)*	1.83 (−1.6, 5.27)	4.39 (1.65, 7.14)*	1.21 (0.47, 1.96)*	1.83 (−1.6, 5.27)	1.03 (−0.01, 2.07)*
	Lag02	3.86 (1.81, 5.91)*	1.01 (−2.75, 4.76)	5.52 (2.53, 8.51)*	1.47 (0.69, 2.25)*	1.01 (−2.75, 4.76)	1.15 (0.06, 2.25)*
	Lag03	3.84 (1.64, 6.05)*	0.62 (−3.42, 4.65)	6.25 (3.05, 9.46)*	1.45 (0.62, 2.27)*	0.62 (−3.42, 4.65)	1.34 (0.20, 2.49)*
	Lag04	3.7 (1.35, 6.05)*	0.2 (−4.08, 4.49)	6.02 (2.61, 9.44)*	1.36 (0.50, 2.23)*	0.2 (−4.08, 4.49)	1.34 (0.13, 2.54)*
	Lag05	3.3 (0.82, 5.78)*	−0.31 (−4.83, 4.22)	5.55 (1.94, 9.16)*	1.27 (0.36, 2.17)*	−0.31 (−4.83, 4.22)	1.28 (0.02, 2.55)*

Continued

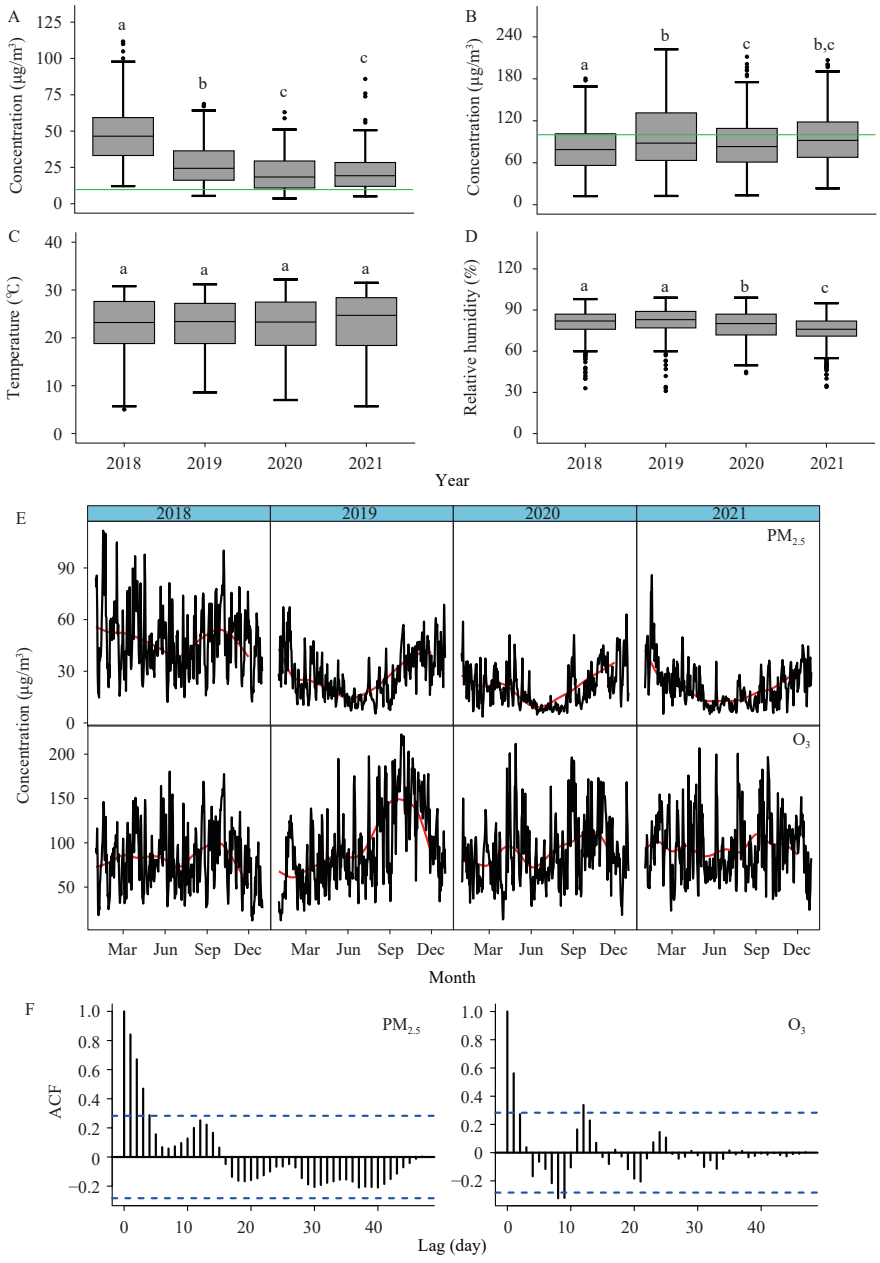
Subgroup	Lag time	$PM_{2.5}$, *ER* (95% *CI*) (%)			O_3, *ER* (95% *CI*) (%)		
		Respiratory diseases	COPD	Lung cancer	Respiratory diseases	COPD	Lung cancer
Male	Lag0	0.90 (0.32, 1.48)*	1.22 (0.36, 2.09)*	1.21 (0.48, 1.96)*	0.26 (0.04, 0.49)*	0.54 (0.19, 0.89)*	0.32 (0.04, 0.59)*
	Lag1	0.72 (0.26, 1.18)*	0.96 (0.27, 1.65)*	0.89 (0.31, 1.48)*	0.22 (0.04, 0.40)*	0.43 (0.16, 0.71)*	0.23 (0.01, 0.44)*
	Lag2	0.54 (0.19, 0.90)*	0.70 (0.17, 1.24)*	0.58 (0.12, 1.03)*	0.18 (0.05, 0.31)*	0.33 (0.12, 0.53)*	0.13 (−0.03, 0.30)
	Lag3	0.37 (0.08, 0.65)*	0.44 (0.02, 0.87)*	0.26 (−0.10, 0.62)	0.14 (0.03, 0.24)*	0.22 (0.06, 0.38)*	0.04 (−0.08, 0.17)
	Lag4	0.19 (−0.08, 0.46)	0.18 (−0.22, 0.59)	−0.06 (−0.40, 0.29)	0.10 (−0.00, 0.19)	0.12 (−0.03, 0.27)	−0.05 (−0.17, 0.07)
	Lag5	0.01 (−0.31, 0.34)	−0.07 (−0.55, 0.41)	−0.37 (−0.79, 0.04)	0.05 (−0.07, 0.17)	0.01 (−0.17, 0.20)	−0.14 (−0.29, 0.01)
	Lag01	2.08 (0.6, 3.56)*	2.8 (0.59, 5.01)*	3.41 (1.54, 5.29)*	0.50 (−0.09, 1.09)	1.33 (0.43, 2.22)*	0.58 (−0.14, 1.30)
	Lag02	2.67 (1.05, 4.28)*	3.27 (0.86, 5.67)*	3.2 (1.15, 5.24)*	0.76 (0.14, 1.38)*	1.61 (0.66, 2.56)*	0.62 (−0.13, 1.38)
	Lag03	3.05 (1.32, 4.78)*	3.58 (1, 6.16)*	2.97 (0.77, 5.17)*	0.93 (0.28, 1.58)*	1.69 (0.70, 2.69)*	0.63 (−0.16, 1.43)
	Lag04	2.93 (1.09, 4.77)*	3.71 (0.97, 6.46)*	2.36 (0.02, 4.7)*	1.00 (0.32, 1.68)*	1.67 (0.63, 2.72)*	0.52 (−0.32, 1.35)
	Lag05	2.55 (0.61, 4.49)*	3.39 (0.49, 6.28)*	1.85 (−0.63, 4.32)	0.95 (0.24, 1.66)*	1.52 (0.43, 2.62)*	0.35 (−0.52, 1.22)
During the COVID-19 pandemic	Lag0	0.97 (0.02, 1.93)*	1.02 (−0.55, 2.62)	1.02 (−0.18, 2.24)	0.41 (0.14, 0.68)*	0.65 (0.19, 1.10)*	0.10 (−0.23, 0.43)
	Lag1	0.71 (−0.06, 1.49)	0.82 (−0.45, 2.11)	0.76 (−0.21, 1.73)	0.31 (0.09, 0.52)*	0.48 (0.12, 0.85)*	0.06 (−0.20, 0.33)
	Lag2	0.45 (−0.16, 1.07)	0.63 (−0.39, 1.66)	0.49 (−0.27, 1.27)	0.20 (0.04, 0.37)*	0.32 (0.04, 0.60)*	0.02 (−0.18, 0.23)
	Lag3	0.20 (−0.32, 0.71)	0.43 (−0.43, 1.29)	0.23 (−0.41, 0.87)	0.10 (−0.03, 0.24)	0.16 (−0.07, 0.39)	−0.02 (−0.18, 0.15)
	Lag4	−0.06 (−0.57, 0.45)	0.23 (−0.61,1.08)	−0.03 (−0.66, 0.60)	0.00 (−0.13, 0.13)	−0.00 (−0.22, 0.22)	−0.06 (−0.22, 0.10)
	Lag5	−0.32 (−0.90, 0.27)	0.04 (−0.93, 1.01)	−0.29 (−1.02, 0.44)	−0.10 (−0.25, 0.05)	−0.16 (−0.42, 0.09)	−0.10 (−0.28, 0.09)
	Lag01	3.03 (0.54, 5.51)*	3.7 (−0.43, 7.84)	3.35 (0.22, 6.49)*	0.81 (0.09, 1.53)*	1.54 (0.33, 2.75)*	0.16 (−0.73, 1.04)
	Lag02	3.29 (0.57, 6.01)*	3.97 (−0.54, 8.48)	3.55 (0.13, 6.98)	1.14 (0.37, 1.9)*	1.96 (0.67, 3.24)*	0.22 (−0.72, 1.16)
	Lag03	2.87 (−0.06, 5.81)	3.09 (−1.79, 7.96)	3.32 (−0.37, 7.01)	1.12 (0.31, 1.94)*	1.85 (0.49, 3.21)*	0.25 (−0.74, 1.25)
	Lag04	2.42 (−0.72, 5.57)	3.12 (−2.11, 8.36)	2.48 (−1.47, 6.44)	1.01 (0.15, 1.87)*	1.61 (0.16, 3.05)*	0.11 (−0.95, 1.16)
	Lag05	1.47 (−1.92, 4.85)	3.00 (−2.64, 8.64)	1.75 (−2.49, 5.99)	0.78 (−0.14, 1.69)	1.11 (−0.42, 2.65)	−0.07 (−1.19, 1.05)
Before the COVID-19 pandemic	Lag0	1.11 (0.53, 1.69)*	0.82 (−0.11, 1.76)	1.26 (0.48, 2.06)*	0.28 (0.02, 0.54)*	0.34 (−0.08, 0.77)	0.50 (0.15, 0.84)*
	Lag1	0.86 (0.39, 1.33)*	0.59 (−0.17, 1.36)	0.95 (0.31, 1.59)	0.23 (0.02, 0.44)*	0.28 (−0.06, 0.62)	0.38 (0.10, 0.65)*
	Lag2	0.61 (0.23, 0.99)*	0.36 (−0.26, 0.98)	0.63 (0.12, 1.15)	0.18 (0.02, 0.34)*	0.21 (−0.06, 0.49)	0.25 (0.03, 0.47)*
	Lag3	0.36 (0.05, 0.68)*	0.13 (−0.38, 0.64)	0.32 (−0.11, 0.75)	0.13 (−0.00, 0.26)	0.15 (−0.07, 0.37)	0.13 (−0.05, 0.31)
	Lag4	0.12 (−0.18, 0.42)	−0.10 (−0.58, 0.38)	0.00 (−0.40, 0.41)	0.08 (−0.04, 0.20)	0.09 (−0.12, 0.29)	0.01 (−0.16, 0.17)
	Lag5	−0.13 (−0.46, 0.20)	−0.33 (−0.86, 0.20)	−0.31 (−0.76, 0.15)	0.03 (−0.11, 0.17)	0.02 (−0.22, 0.26)	−0.12 (−0.31, 0.08)
	Lag01	2.50 (1.06, 3.95)	2.13 (−0.22, 4.48)	3.62 (1.65, 5.59)*	0.52 (−0.16, 1.2)	0.94 (−0.2, 2.08)	1.18 (0.26, 2.10)*
	Lag02	3.04 (1.42, 4.66)	2.08 (−0.55, 4.71)	3.70 (1.5, 5.89)*	0.77 (0.03, 1.5)*	1.11 (−0.11, 2.34)	1.2 (0.21, 2.18)*
	Lag03	3.60 (1.82, 5.38)	2.53 (−0.37, 5.43)	3.78 (1.36, 6.20)*	0.99 (0.21, 1.77)*	1.33 (0.02, 2.63)*	1.31 (0.26, 2.35)*
	Lag04	3.54 (1.59, 5.48)	2.71 (−0.46, 5.87)	3.17 (0.53, 5.80)*	1.11 (0.28, 1.94)*	1.45 (0.06, 2.84)*	1.21 (0.09, 2.32)*
	Lag05	3.05 (0.96, 5.13)	1.61 (−1.79, 5.00)	2.61 (−0.22, 5.44)	1.08 (0.21, 1.96)*	1.32 (−0.15, 2.79)	1.03 (−0.14, 2.21)

Abbreviation: *ER*=excess risk; *CI*=confidence interval; COPD=chronic obstructive pulmonary disease; COVID-19=coronavirus disease 2019; $PM_{2.5}$=fine particulate matter; O_3=ozone.
* $P<0.05$.

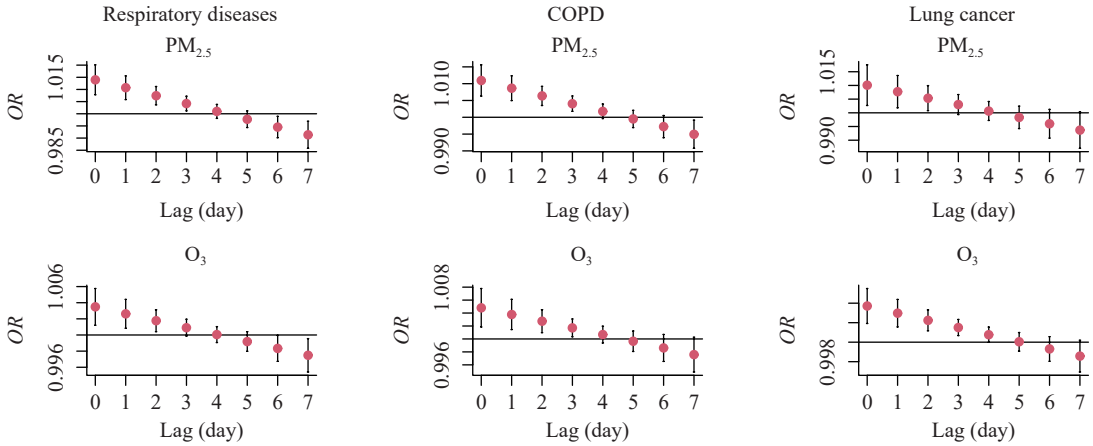
SUPPLEMENTARY TABLE S5. Spearman correlation test between O_3, $PM_{2.5}$, and meteorological factors.

Pollutants	O_3	$PM_{2.5}$	Temperature	Humidity
O_3	1.00			
$PM_{2.5}$	0.40*	1.00		
Temperature	0.17*	−0.34*	1.00	
Humidity	−0.44*	−0.22*	0.17*	1.00

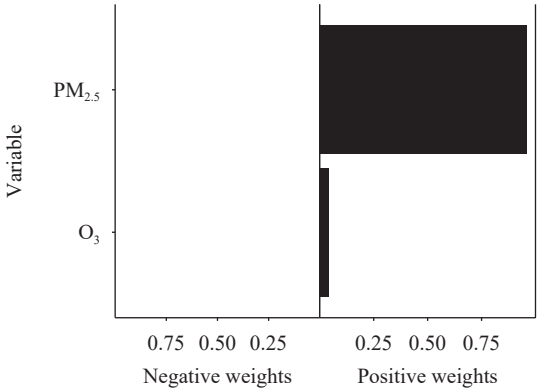
Abbreviation: *ER*=excess risk; *CI*=confidence interval; COPD=chronic obstructive pulmonary disease; $PM_{2.5}$=fine particulate matter of 2.5 micrometers; O_3=ozone.
* *P*<0.05.



SUPPLEMENTARY FIGURE S1. Concentrations of (A) $PM_{2.5}$ and (B) O_3, (C) distributions of temperature and (D) relative humidity, and (E) time series of $PM_{2.5}$ and (F) O_3 with autocorrelation in Guangzhou City, China, from 2018 to 2021.
Note: The green line represents the threshold value for each pollutant, while the red line shows the 7-day average concentration of each pollutant. The different letters (A, B, C, and D) signify statistically significant differences (*P*<0.05) between years.
Abbreviation: $PM_{2.5}$=fine particulate matter; O_3=ozone; ACF=autocorrelation function.



SUPPLEMENTARY FIGURE S2. Daily effects of $PM_{2.5}$ and O_3 on the number of deaths from respiratory diseases, COPD, and lung cancer in Guangzhou, 2018–2021.
Abbreviation: *OR*=odds ratio; COPD=chronic obstructive pulmonary disease; $PM_{2.5}$=fine particulate matter; O_3=ozone.



SUPPLEMENTARY FIGURE S3. The weights of $PM_{2.5}$ and O_3 in the QG-C model.
Abbreviation: $PM_{2.5}$=fine particulate matter; O_3=ozone.

Preplanned Studies

Analysis of Intelligent Equipment Usage for Work-Related Musculoskeletal Disorders Prevention in Miners — Shanxi Province, China, 2023

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Summary

What is already known about this topic?

Work-related musculoskeletal disorders (WMSDs) are prevalent in the workforce and occur across various industries. Surveys show that the prevalence of WMSDs among miners is generally over 50%.

What is added by this report?

High levels of intelligent equipment usage (IEU) can decrease the prevalence of WMSDs among miners by 7.49% and reduce pain by 13.69% on average. Stepwise regression analysis proved that IEU can reduce the harmful effects of workload on WMSDs.

What are the implications for public health practice?

New Quality Productive Forces (NQPF) should also focus on health productivity. Disease prevention departments should consider the impact of NQPFs on occupational health and actively guide intelligent equipment design.

Work-related musculoskeletal disorders (WMSDs) are health problems of the locomotor apparatus that are induced or aggravated by work. If the mechanical workload exceeds the musculoskeletal system's load-bearing capacity, injuries to ligaments, bones, muscles, and tendons are typical consequences (*1*). Coal mining is characterized by heavy workloads, and miners typically engage in prolonged postures requiring repetitive operations and heavy load carrying, which can easily trigger local muscle fatigue and ultimately lead to the development of WMSDs. According to research from the China CDC, the prevalence of WMSDs in the population working in key industries was estimated to be 41.2% (*2*). One survey of Indian underground coal miners reported that approximately 65.45% of them complained of WMSD pain (*3*). Data from another study in China indicate that the total symptom prevalence of WMSDs among coal miners has reached 75.6%; the five body parts with the highest symptom prevalence include the lower back (54.1%), neck (42.1%), shoulder (37.2%), knee (29.1%), and back (28.1%), in order of prevalence (*4*). The "National Occupational Disease Prevention and Control Plan (2021–2025)" prioritizes research on the causes of WMSD damage (*5*).

China is vigorously developing new quality productive forces (NQPF) and upgrading traditional industries with AI and other technologies. In 2020, the Chinese government released the "Guiding Opinions on Accelerating the Intelligent Development of Coal Mines." This document proposed that all coal mines will realize intelligent mining by 2035. The essence of intelligent mining is using intelligent equipment to replace miners engaged in dangerous, heavy, and repetitive labor. One example is the use of inspection robots. According to the "Typical Case Collection of Intelligent Construction in Coal Mines" published by the China National Energy Administration in 2023, inspectors at the Tang Kou coal mine previously inspected the mine hoist 22 times daily, with each inspection taking 30 minutes. With the intelligent inspection robot, the robot completes all on-site inspections, and the inspector only needs to operate it remotely from the control room (*6*). Therefore, intelligent mining can potentially reduce the prevalence of WMSDs among miners. However, relevant literature is lacking, and this study aims to investigate this issue from the perspective of intelligent equipment usage (IEU).

In June–July 2023, this study used single-stage cluster sampling to select underground miners from six coal mines with different levels of intelligent automation in Shanxi Province for a questionnaire survey. Three coal mines were designated as intermediate intelligent coal mines and three as primary intelligent coal mines. A total of 2,245 questionnaires were collected, of which 2,165 were deemed valid. All participants were male and employed in underground production units, such as excavation,

mining, maintenance, ventilation, and transport teams. According to labor law in China, female workers are prohibited from working in underground mines. All questionnaires were electronic and distributed to miners through the coal mine human resources departments. The entire process was completed under the guidance of investigators at the participants' workplaces.

The questionnaire collected data on four areas: IEU, workload, WMSDs prevalence, and pain level. Self-reported IEU data were collected using questionnaires covering two aspects: 1) direct IEU ("I work with a lot of intelligent equipment," IEU-D); and 2) indirect IEU ("There is a lot of intelligent equipment in my workplace," IEU-I). Questionnaire responses were scored on a 5-point Likert scale (from 1 to 5), ranging from "very inconsistent" to "very consistent." Scores were classified as low (1 and 2), medium (*3*), and high (4 and 5). The workload scale, adapted from a similar scale developed by Johansson et al. in 1991 (*7*), comprised four questions: 1) "In the course of your work, are you exposed to inappropriate work postures (e.g., bending, twisting)?"; 2) "Do you have to lift heavy objects at work?"; 3) "Do you sweat every day at work?"; and 4) "Do you think your job is unsafe?" Responses were scored on a 5-point scale (from 1 to 5), ranging from "never" to "always." Miners' WMSDs prevalence was measured using the Chinese Musculoskeletal Disorder Questionnaire (CMDQ) developed by the China CDC. WMSDs were defined as pain, numbness, or limited movement in a relevant body part lasting >1 week, or lasting <1 week but occurring >2 times in the past 12 months; response options were yes or no. Miners' pain levels in different body parts were assessed using a visual analog scale (VAS). Scores ranged from 0 to 10, indicating "no pain" to "unbearable and severe pain." The questionnaire's Cronbach's α coefficient was 0.858, and its Kaiser-Meyer-Olkin (KMO) value was 0.719, demonstrating good reliability and validity.

Table 1 shows the miners' WMSDs prevalence rates at different IEU-D levels. Higher levels of IEU-D correspond to lower WMSDs prevalence rates. Based on the odds ratio (*OR*), the differences in WMSDs prevalence rates were statistically significant at different levels of intelligent automation. Compared with the low IEU-D group, the high IEU-D group showed a 7.49% average decrease in WMSDs prevalence rates. The most notable improvements were in the knees, upper back, and neck. Compared with the low IEU-D group, the prevalence of WMSDs in these areas decreased by more than 8% in the high IEU-D group.

Table 2 describes the differences in body pain at different levels of IEU-D, suggesting that IEU can significantly improve pain associated with WMSDs. Compared to the low IEU-D group, the average pain in all body parts was 13.69% lower in the high IEU-D group. The most pronounced pain reduction occurred in the following body parts, ranked in order of pain severity: hips/thighs, elbows, knees, upper back, ankles/feet, and neck. Pain decreases in these areas were all greater than 10%.

The primary occupational hazards for WMSDs include heavy physical loads, repetitive operations, and poor posture, categorized as workload (*8*). Age, position, and length of service are definitive individual influencing factors (*9*). Although not included in this study, these individual factors can influence regression results and were controlled for in the analysis. The following regression equation describes the moderation:

$$P = \beta_0 + \alpha_1 A + \alpha_2 L + \alpha_3 J + \beta_1 W + \beta_2 I + \beta_3 WI + \varepsilon \quad (1)$$

P value represents the degree of pain in different body parts. Age (A), length of service (L), and job position (J) are control variables. Workload (W) is the independent variable. The moderator variable is IEU level (I). β_1 and β_2 represent the direct effects of W and I, and β_3 represents the moderator effect. If $\beta_3 \neq 0$, it proves that there is a moderating effect.

It can be seen in Table 3, we gradually added the following variables to the stepwise regression model: independent variable (W), moderator variable (I), and interaction term (W×I). From Model 1 to Model 4, the effects of all variables were significant, with Model 4 demonstrating the most significant results. $\beta_1 = 0.068$ and $\beta_2 = -0.068$ show that workload positively affected the degree of body pain, while IEU negatively affected it. $\beta_3 = -0.183$ indicates that IEU acts as a negative moderator, diminishing the effect of workload on the degree of body pain.

The analysis above explains the effect of IEU on WMSDs. IEU not only directly reduces the prevalence of WMSDs but also significantly reduces the harmful effects of workload on WMSDs.

DISCUSSION

As a chronic condition, WMSDs place a substantial burden on healthcare systems and decrease productivity. Epidemiological data on WMSDs in coal miners, a high-risk group, are representative of trends

TABLE 1. WMSDs prevalence of miners with different levels of IEU-D in Shanxi Province, China, 2023.

Body part	IEU-D	Number	Number of WMSDs	Rate of WMSDs(%)	*OR* (95% *CI*)	*P*
Neck	Low	559	417	74.597	1.473	<0.050
	Medium	729	544	74.623	1.475	<0.050
	High	877	584	66.591	1	
Shoulders	Low	559	360	64.401	1.254	<0.050
	Medium	729	476	65.295	1.304	<0.050
	High	877	518	59.065	1	
Upper back	Low	559	348	62.254	1.409	<0.050
	Medium	729	465	63.786	1.504	<0.050
	High	877	473	53.934	1	
Lower back	Low	559	381	68.157	1.336	<0.050
	Medium	729	493	67.627	1.304	<0.050
	High	877	540	61.574	1	
Wrists/hands	Low	559	316	56.530	1.346	<0.050
	Medium	729	406	55.693	1.301	<0.050
	High	877	431	49.145	1	
Elbows	Low	559	291	52.057	1.375	<0.050
	Medium	729	374	51.303	1.334	<0.050
	High	877	387	44.128	1	
Hips/thighs	Low	559	260	46.512	1.341	<0.050
	Medium	729	331	45.405	1.282	<0.050
	High	877	345	39.339	1	
Knees	Low	559	339	60.644	1.429	<0.050
	Medium	729	437	59.945	1.388	<0.050
	High	877	455	51.881	1	
Ankles/feet	Low	559	276	49.374	1.374	<0.050
	Medium	729	350	48.011	1.302	<0.050
	High	877	364	41.505	1	

Abbreviation: WMSDs=work-related musculoskeletal disorders; IEU-D=direct intelligent equipment usage; *OR*=odds ratio; *CI*=confidence interval.

in other occupations. By replacing manual labor with intelligent equipment, IEU reduces the intense repetitive work required of miners, thereby lowering the risk of WMSDs and disease onset. Compared with low levels of IEU-D, high levels can reduce WMSDs prevalence rates among miners by 7.49% and decrease WMSDs pain by an average of 13.69%. This study found the following declines in the prevalence rate of WMSDs by body part: ankles/feet (15.94%), hips/thighs (15.42%), elbows (15.23%), knees (14.45%), upper back (13.36%), wrists/hands (13.06%), neck (10.73%), lower back (9.66%), and shoulders (8.29%). Declines in WMSDs pain by body part were as follows: hips/thighs (19.07%), elbows (16.47%), knees (16.39%), upper back (15.45%), wrists/hands (14.01%), ankles/feet (13.61%), neck (11.23%), shoulders (9.01%), and lower back (7.97%). Considering age, length of service, position, and workload, stepwise regression analysis revealed that IEU can reduce WMSDs pain and moderate the harmful effects of workload.

The NQPFs should also focus on health productivity. MSDs are the second leading cause of non-fatal disability worldwide, affecting over 1.63 billion people (*10*). WMSDs, a preventable subset of MSDs, can be mitigated by improving working conditions. As a form of NQPF, intelligence mining presents a win-win scenario for productivity and occupational health. However, evaluations of intelligence mining often neglect the associated occupational health benefits, leading to an underestimation of its positive impact. From a life-

TABLE 2. WMSDs pain with different levels of IEU-D in Shanxi Province, China, 2023.

Body part	Low IEU-D		Medium IEU-D		High IEU-D		F	*P*
	Number	Pain degree*	Number	Pain degree*	Number	Pain degree*		
Neck	559	3.322±2.773	729	3.361±2.651	877	2.949±2.743	5.540	<0.01
Shoulders	559	2.964±2.908	729	2.912±2.741	877	2.697±2.842	1.906	<0.01
Upper back	559	2.900±2.918	729	2.925±2.810	877	2.452±2.803	6.946	<0.01
Lower back	559	3.301±2.978	729	3.296±2.937	877	3.038±3.034	1.985	<0.01
Elbows	559	2.422±2.847	729	2.403±2.786	877	2.023±2.755	5.073	<0.01
Wrists/hands	559	2.599±2.888	729	2.517±2.823	877	2.235±2.782	3.441	<0.01
Hips/thighs	559	2.197±2.851	729	2.156±2.870	877	1.778±2.674	5.307	<0.01
Knees	559	2.995±3.069	729	2.864±2.980	877	2.505±2.967	5.314	<0.01
Ankles/feet	559	2.270±2.875	729	2.225±2.841	877	1.961±2.790	2.656	<0.01

Abbreviation: WMSDs=work-related musculoskeletal disorders; IEU-D=direct intelligent equipment usage; SD=standard deviation.
* Pain degree: Mean±SD.

TABLE 3. Step-wise regression results of the degree of pain associated with WMSDs.

Dependent variable	Coefficient	Model 1	Model 2	Model 3	Model 4
Intercept	β_0	0.485	0.024	0.835	0.170
Age (A)	α_1	0.194†	0.195†	0.199†	0.203†
length of service (L)	α_2	0.114†	0.111†	0.112†	0.131†
Job position (J)	α_3	−0.116†	−0.116†	−0.115†	−0.113†
Workload (W)	β_1		0.055*	0.024	0.068*
IEU level (I)	β_2			−0.092†	−0.068*
W×I	β_3				−0.183†
R^2		0.083	0.086	0.094	0.126
ΔR^2		0.083	0.003	0.008	0.032
F-test		65.626†	7.064*	18.034†	78.143†

Abbreviation: WMSDs=work-related musculoskeletal disorders.
* $P<0.01$;
† $P<0.001$.

cycle perspective, intelligence mining is valuable in preventing WMSDs in older miners. Public health departments can introduce occupational health evaluation standards and certification systems to provide a basis for assessing the health benefits of intelligent equipment. Notably, at high IEU-D, prevalence rates of WMSDs in the neck, shoulders, upper back, lower back, and wrists remain higher than 50%, indicating substantial potential for further WMSD control. Public health departments can provide increased technical support for intelligent equipment design, enhancing ergonomic compatibility. Coal mines, bearing primary responsibility for miners' health, should prioritize ergonomic requirements when selecting intelligent equipment. In positions necessitating poor posture, repetitive motions, or weight-bearing work, coal mines should implement regular job rotation.

This study was subject to some limitations. First, there was potential recall bias, as WMSD prevalence rates relied heavily on miners' recollections Second, the cross-sectional design precluded comparative analysis before and after intelligent mining implementation. As intelligent mining advances, the impact of IEU on WMSDs may evolve. Future studies could employ a follow-up cohort to analyze long-term effects.

Intelligent mining is not only a new quality productive force but also a health productivity force. WMSDs are preventable workplace diseases. Public health departments should capitalize on this opportunity, using coal mines as a pilot industry, to develop ergonomics certification for intelligent equipment. This will help companies integrate intelligent transformation with WMSDs prevention.

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Preplanned Studies

Association of Thallium Exposure with Decreased Renal Function among Chinese Adults — China, 2017–2018

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Summary

What is already known about this topic?

Thallium (Tl) is significantly more toxic than heavy metals such as lead, cadmium, and mercury. However, previous studies examining the relationship between Tl exposure and the risk of chronic kidney disease (CKD) have yielded inconsistent results.

What is added by this report?

The study demonstrated that elevated urinary Tl levels were associated with a higher prevalence of CKD and a reduced estimated glomerular filtration rate (eGFR), particularly among older adults. These findings were consistent in the restricted cubic spline (RCS) analyses.

What are the implications for public health practice?

This study identified Tl as a risk factor for decreased renal function, underscoring the need to enhance surveillance of Tl to mitigate the disease burden of CKD.

Thallium (Tl) is a highly toxic metal that has been designated as a priority environmental pollutant by the United States Environmental Protection Agency and included in China's 12th and 13th Five-Year Plans (*1*). While Tl is known to be nephrotoxic in cases of acute and subacute exposure, data on nephrotoxicity resulting from chronic exposure remain limited (*2*). The global incidence and prevalence of chronic kidney disease (CKD) have increased dramatically, making it a significant public health concern. In 2017, there were 697.5 million cases of CKD at all stages worldwide (*3*). Given China's large population, the economic and disease burden posed by CKD on both society and the national healthcare system are considerable (*4*). Consequently, extensive epidemiological studies are urgently needed to identify risk factors for CKD. Prior research has identified significant associations between Tl exposure and decreased kidney function (*5*–*6*), though the findings have not been consistent. This study investigates the association between urinary Tl and renal function, and further evaluates the potential mediating effect of inflammatory biomarkers, using data from the China National Human Biomonitoring (CNHBM) program.

In this study, participants younger than 18 years old and those with missing data on urinary Tl, serum creatinine (SCr), and inflammatory biomarkers were excluded. Following these exclusions, a total of 9,238 participants were included in the final analysis. The concentration of urinary Tl was measured using multi-element analysis via inductively coupled plasma mass spectrometry (ICP-MS) (PerkinElmer NexION 350, Turku, Finland).

This study utilized the Modification of Diet in Renal Disease (MDRD) equation to calculate the estimated glomerular filtration rate (eGFR), incorporating SCr, age, and gender. This method provides significant advantages in distinguishing various stages of CKD. The GFR measures the rate at which the glomeruli filter metabolites, waste, and toxins from plasma to produce ultrafiltrate, serving as a comprehensive indicator of kidney function. Clinical guidelines use eGFR for diagnosing and staging CKD, classifying eGFR values of less than 60 mL/[min·(1.73 m^2)] as indicative of CKD (*7*).

Continuous variables were presented as weighted mean (standard error, SE) or median (P_{25}–P_{75}), while categorical variables were represented as weighted percentages. Differences between continuous variables were assessed using analysis of variance or the rank sum test, depending on data distribution, and chi-square tests were employed for categorical variables. $P<0.05$ were considered statistically significant. Detailed definitions of covariates are provided in the Supplementary Material. The association between urinary Tl and CKD was examined using a multiple logistic regression model. Subsequently, a multiple

linear regression model was applied to estimate the regression coefficients (β) and 95% confidence interval (*CI*) of eGFR with respect to urinary Tl levels. A restricted cubic spline (RCS) with knots at the 25th, 50th, and 75th percentiles was utilized to explore dose-response relationships. To evaluate the role of inflammatory biomarkers, such as hypersensitive C-reactive protein (CRP), neutrophils, lymphocytes, and white blood cells (WBC), in the relationship between urinary Tl and eGFR, a mediation analysis was conducted using the mediation R package. Subgroup and sensitivity analyses were also performed, with detailed results available in the Supplementary Material (available at https://weekly.chinacdc.cn/).

The weighted median (P_{25}–P_{75}) of urinary Tl was 0.27 (0.16, 0.45) μg/L. The prevalence of CKD was 7.75%, and the weighted mean value of eGFR was 93.89 mL/[min·(1.73 m^2)]. Additional baseline characteristics of the participants are detailed in Supplementary Table S1 (available at https://weekly.chinacdc.cn/).

The highest quartile of urinary Tl was associated with an increased risk of CKD, exhibiting an adjusted odds ratio (*OR*) of 1.77 (95% *CI*: 1.04, 3.02) compared to the lowest quartile. Furthermore, for each additional interquartile range (*IQR*) of urinary Tl, the risk of CKD increased by 14% (*OR*=1.14, 95% *CI*: 1.02, 1.26) (Table 1). There was also a negative relationship between urinary Tl and eGFR, with a decrease in eGFR of 1.45 units (β=−1.45, 95% *CI*: −2.88, −0.02) for each unit increase in urinary Tl (Supplementary Table S2, available at https://weekly.chinacdc.cn/).

Urinary Tl exhibited a positive linear dose-response relationship with the risk of CKD within the RCS (*P* for linearity <0.05). Furthermore, RCS analysis indicated a negative downward dose-response association between urinary Tl and eGFR (*P* for linearity <0.05) (Figure 1).

Compared with the lowest quartile of urinary Tl, the second, third, and highest quartiles were all positively associated with the neutrophil ratio (*P*<0.05). Additionally, the third and highest quartiles of urinary Tl exhibited a negative relationship with the lymphocyte ratio (*P*<0.05) (Table 2). Each unit increase in the lymphocyte ratio corresponded with a 0.69 mL/[min·(1.73 m^2)] (95% *CI*: −1.30, −0.09) decrease in eGFR (Supplementary Table S3, available at https://weekly.chinacdc.cn/). However, mediation analysis results indicated no mediating role for the lymphocyte ratio in the association between Tl and eGFR (Supplementary Table S4, available at https://weekly.chinacdc.cn/).

Subgroup analyses stratified by gender and age group revealed a significant positive association between urinary Tl levels and CKD in women. Further examination by age indicated more pronounced positive effects in older adults (Supplementary Table S5, available at https://weekly.chinacdc.cn/). Sensitivity analyses, utilizing eGFR calculated via the CKD Epidemiology Collaboration (CKD-EPI) equation, corroborated these findings, demonstrating a stable association between urinary Tl levels and reduced renal function (Supplementary Table S6, available at https://weekly.chinacdc.cn/).

TABLE 1. Weighted odds ratios (95% *CI*) of CKD associated with urinary Tl concentration among Chinese adults in 2017–2018.

Urinary Tl	*OR* (95% *CI*)				
	Crude model	Model 1*	Model 2†	Model 3§	Model 4¶
Q1 (Reference)	1.00	1.00	1.00	1.00	1.00
Q2	0.93 (0.72, 1.20)	1.16 (0.88, 1.52)	1.14 (0.86, 1.50)	1.18 (0.90, 1.55)	1.14 (0.86, 1.51)
Q3	0.92 (0.66, 1.26)	1.27 (0.90, 1.80)	1.24 (0.87, 1.76)	1.29 (0.90, 1.87)	1.19 (0.81, 1.76)
Q4	1.51 (1.01, 2.24)**	2.08 (1.34, 3.24)**	1.99 (1.28, 3.10)**	2.09 (1.26, 3.48)**	1.77 (1.04, 3.02)**
Per *IQR*	1.14 (1.04, 1.24)**	1.19 (1.09, 1.30)**	1.18 (1.07, 1.29)**	1.19 (1.07, 1.31)**	1.14 (1.02, 1.26)**

Note: Q1=urinary Tl ≤0.16 μg/L; Q2=0.16 μg/L<urinary Tl≤0.28 μg/L; Q3=0.28 μg/L<urinary Tl≤0.46 μg/L; Q4=urinary Tl>0.46 μg/L.
Abbreviation: *CI*=confidence interval; CKD=chronic kidney disease; Tl=thallium; *OR*=odds ratio; *IQR*=interquartile range; BMI=body mass index; UCr=urine creatinine; TC=total cholesterol; Cd=cadmium; Pb=lead; Hg=mercury; As=arsenic.
* Adjusted for age, sex, education, residence, marital status, and household income.
† Additionally adjusted for smoking status, drinking status, meat consumption, and vegetable consumption.
§ Additionally adjusted for hypertension, diabetes, BMI, UCr, and TC.
¶ Additionally adjusted for urinary Cd, urinary Pb, urinary Hg, and urinary As.
** *P*<0.05.

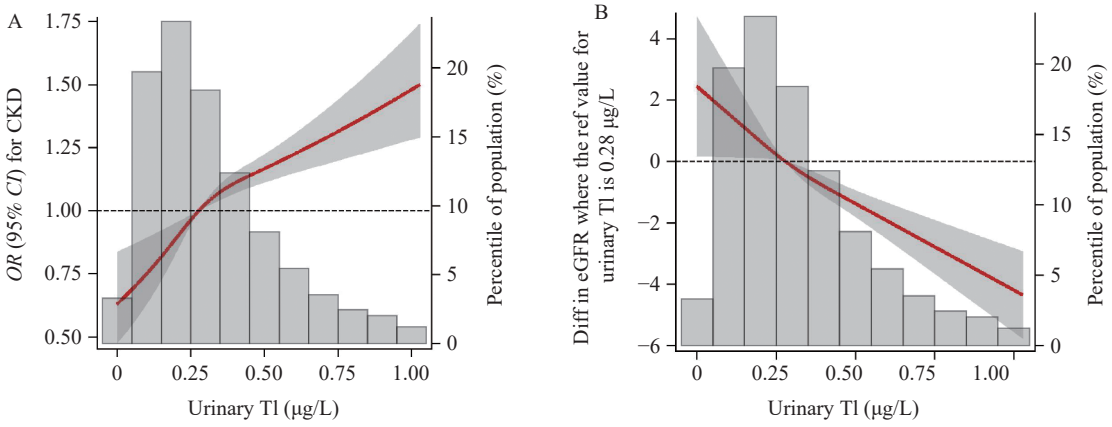

FIGURE 1. Restricted cubic spline for the association of urinary Tl with CKD and eGFR among Chinese adults in 2017–2018. (A) the dose-response relationship between urinary Tl and CKD; (B) the dose-response relationship between urinary Tl and eGFR.
Note: In the Figure 1A and 1B, the reference value was set at the 50th percentage of urinary Tl. Models were adjusted for age, sex, education, residence, marital status, household income, smoking status, drinking status, meat consumption, vegetable consumption, hypertension, diabetes, BMI, UCr, TC, urinary Cd, urinary Pb, urinary Hg, and urinary As.
Abbreviation: *OR*=odds ratio; *CI*=confidence interval; Tl=thallium; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; BMI=body mass index; UCr=urine creatinine; TC=total cholesterol; Cd=cadmium; Pb=lead; Hg=mercury; As=arsenic.

TABLE 2. Weighted regression coefficients (β) and 95% *CI* for the association of urinary Tl with inflammatory indicators among Chinese adults in 2017–2018.

Urinary Tl	β (95% *CI*)			
	CRP	Neutrophil ratio	Lymphocyte ratio	WBC
Q1 (Reference)	0	0	0	0
Q2	−0.30 (−0.74, 0.13)	1.06 (0.12, 2.30)*	0.59 (−2.44, 3.62)	0.07 (−0.14, 0.27)
Q3	0.08 (−0.50, 0.66)	1.13 (0.01, 2.25)*	−1.46 (−2.61, −0.32)*	0.06 (−0.11, 0.23)
Q4	−0.11 (−0.73, 0.52)	1.19 (0.09, 2.30)*	−1.26 (−2.44, −0.08)*	0.13 (−0.10, 0.36)
Per *IQR*	−0.07 (−0.19, 0.05)	0.37 (−0.01, 0.75)	−0.50 (−1.07, 0.08)	0.02 (−0.06, 0.10)

Note: Q1=urinary Tl≤0.16 μg/L; Q2=0.16μg/L<urinary Tl≤0.28 μg/L; Q3=0.28 μg/L<urinary Tl≤0.46 μg/L; Q4=urinary Tl>0.46 μg/L.
Abbreviation: *CI*=confidence interval; Tl=thallium; CRP=C−reactive protein; WBC=white blood cell count; *IQR*=interquartile range; BMI=body mass index; UCr=urine creatinine; TC=total cholesterol.
Adjusted for age, sex, education, residence, marital status, household income, smoking status, drinking status, meat consumption, vegetable consumption, hypertension, diabetes, BMI, UCr, and TC.
* P<0.05.

DISCUSSION

Our study found a significant positive association between higher urinary Tl exposure and increased prevalence of CKD, as well as a decrease in eGFR. Notably, the positive associations with CKD were more pronounced in older adults.

The association between Tl and renal function remains inconclusive based on previous epidemiological studies. Urinary Tl has not been linked to an increased prevalence of CKD in the Chinese community of older adults in both single exposure and mixed metal exposure analyses (*8*). Conversely, a positive association has been reported between Tl and higher SCr- and cystatin-C-based eGFR in occupational populations, with the association persisting after adjustments for cadmium (Cd) and antimony (Sb) (*5*). Our study supports the hypothesis that Tl is associated with decreased renal function, aligning with a study in China that found significant impairment in kidney function among six children exposed to Tl (*6*). Discrepancies in results could be due to differences in participant characteristics, such as age and exposure concentrations. In our study, we adjusted for CKD risk factors, including hypertension, diabetes, total cholesterol (TC), BMI, and urinary metals, enhancing the robustness of our findings. We observed a stronger

association between Tl and CKD in women. Prior research has suggested that females may be more susceptible to kidney damage from heavy metals, possibly due to reduced estrogen production, which can diminish antioxidative capacity (*9*). A study in Taiwan, China, documented a decline in eGFR with age among subjects exposed to multiple metals (*10*). Our results are consistent with this finding, showing a higher risk of CKD in the 60–79 age group. The mechanism of Tl toxicity to the kidney remains incompletely understood. Animal studies have demonstrated nephrotoxic effects of Tl, with rat kidneys showing the highest accumulation of the metal (*11*). Previous research has indicated that high Tl exposure is associated with elevated CRP levels, suggesting that inflammation partly mediates effects of Tl on lung function (*12*). In this study, we identified an increased neutrophil ratio and a decreased lymphocyte ratio in individuals with high urinary Tl, indicating a positive association between Tl and inflammatory responses. Further in vivo and in vitro research is needed to explore the mechanisms underlying this relationship.

This cross-sectional study design limits our ability to determine the temporal relationship between exposure and outcome, introducing the risk of reverse causality. However, previous research using data from National Health and Nutrition Examination Survey (NHANES) has shown that as eGFR decreases, urinary Tl concentrations also decline, while urinary metal concentrations tend to rise with improved kidney function (*13*). These findings indicate that variations in renal function could affect urinary metal concentrations, potentially underestimating the true association between urinary metals and disease risk.

This study is subject to some limitations. First, urine microalbumin was not assessed, relying solely on eGFR for defining CKD, which could potentially underestimate the prevalence of CKD. Second, urinary Tl levels were measured using convenience samples rather than 24-hour urine collections, possibly introducing bias in estimating actual Tl exposure.

Tl exposure primarily occurs through the consumption of vegetables and potable water contaminated with Tl. Industrialization, along with the rapid development of mining and metal smelting, has exacerbated Tl contamination in surface water and soil. It is imperative to enhance monitoring of Tl levels in potable water, vegetables, and aquatic organisms, particularly in areas prone to Tl pollution such as those near Tl mining sites, thermal power plants, and metal smelting facilities. The current standards for Tl in surface and drinking water were established two decades ago and require urgent revision based on recent scientific findings. Moreover, existing toxicological data on both carcinogenic and non-carcinogenic effects of Tl are scarce, necessitating further research to better understand its potential health risks. Our study identified a significant link between Tl exposure and an increased risk of CKD and reduced eGFR, particularly among older adults. Given the critical issue of metal pollution, it is crucial to mitigate or eliminate renal toxic metal exposure to lessen the impact on renal function decline.

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SUPPLEMENTARY MATERIALS

Methods

Study design: We utilized data from the China National Human Biomonitoring (CNHBM) project, a nationally representative biomonitoring initiative. CNHBM aims to establish baseline levels of internal exposure to environmental chemicals in the Chinese population and to monitor long-term trends. Employing a three-stage sampling design, CNHBM collected data from a total of 21,888 participants across 152 primary sampling units (PSUs) in 31 provinces of China between 2017 and 2018. Investigators from local county or district CDC offices conducted assessments of general household characteristics, household economic status, and sources of environmental chemical exposure using PSU and survey unit questionnaires. Details regarding sample collection, questionnaire survey, and physical examination have been previously documented (*1*). Ultimately, CNHBM recruited 21,746 participants. This study received approval from the ethics committees of the National Institute of Environmental Health, Chinese Center for Disease Control and Prevention (201701). All participants provided written informed consent.

Laboratory measurements: After an overnight fast of more than 8 hours, we collected 4 mL of heparinized blood, 12 mL of fasting blood without anticoagulants, and 80 mL of a single random urine sample in the morning. We diluted 0.5 mL of blood with a solution containing 0.1% nitric acid and 0.01% Triton X-100 and 1 mL of urine with 1% nitric acid, followed by centrifugation. The concentration of heavy metals in the urine was measured using inductively coupled plasma mass spectrometry (ICP-MS) (PerkinElmer NexION 350, Turku, Finland) with multi-element analysis. For quality control, parallel samples were analyzed simultaneously for every 30 samples. Spiked recoveries and relative standard deviations (RSD) were assessed at three concentration levels (2.5 μg/L, 5 μg/L, and 10 μg/L). The spiked recoveries of urinary Tl ranged from 87% to 98%, with RSD values within 9%. The limit of detection (LOD) for urinary Tl was 0.002 μg/L. For the 1.2% of urine samples below the LOD, 1/2 LOD values were imputed. Clinical biochemical parameters were measured using an automated biochemical analyzer (Hitachi 7180, Kyoto, Tokyo, Japan), including serum creatinine (SCr), fasting blood glucose (FBG), and total cholesterol (TC). Urine creatinine (UCr) levels were determined using picric acid spectrophotometry at local chemical laboratories.

Covariates: The covariates in our study were collected using standardized questionnaires administered by trained interviewers. The individual questionnaire gathered data on variables including age, sex (male or female), residence (rural or urban), education level (middle school or less, high school, or college or higher), marital status (married or not), alcohol consumption (yes or no), and smoking status (yes or no). Income was categorized into three groups: "<10,000 Chinese Yuan (CNY)," "10,000–100,000 CNY," and ">100,000 CNY." Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Dietary intake information was collected using a reliable and validated food frequency questionnaire (FFQ) designed specifically for the Chinese population, focusing on the dietary habits of subjects over the past year (*2*). Self-reported frequency of meat and vegetable consumption was classified into two categories: <14 and ≥14 times per week, using the median as the bisecting point. Participants were classified as having diabetes if they had a fasting serum glucose level of ≥7.0 mmol/L (126 mg/dL), a self-reported physician diagnosis of diabetes, or were currently taking insulin or oral hypoglycemic medications. Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, a self-reported physician diagnosis, or current use of antihypertensive medication. Urinary concentrations of cadmium (Cd), mercury (Hg), lead (Pb), and arsenic (As) were included as covariates to account for the effects of other metals.

Subgroup analysis: We performed a subgroup analysis to examine the association effects across various demographics. Initially, we evaluated the relationship between Tl and CKD within different gender groups. Subsequently, a stratified analysis was conducted across distinct age categories (18–39, 40–59, 60–79) to delve deeper into these associations.

Sensitivity analysis: To validate the robustness of our results, we conducted multiple sensitivity analyses. We replicated the analysis using eGFR calculated with the CKD Epidemiology Collaboration (CKD-EPI) equation (*3*).

SUPPLEMENTARY TABLE S1. General characteristics among the Chinese population stratified by quartiles of urinary Tl concentration among Chinese adults in 2017–2018.

Characteristics	Total	Quartiles of urinary Tl				*P*
		Q1	Q2	Q3	Q4	
Age, mean±SE, year	47.52±0.25	49.55±0.57	47.11±0.48	46.28±0.40	47.21±0.47	<0.001
BMI, mean±SE, kg/m^2	24.52±0.12	24.55±0.18	24.70±0.20	24.41±0.14	24.41±0.13	0.444
eGFR, mean±SE, mL/[min·(1.73 m^2)]	93.89±1.68	94.52±2.40	95.52±1.92	94.69±1.71	90.61±2.12	<0.001
UCr, mean±SE, g/L	1.25±0.04	0.85±0.04	1.19±0.04	1.39±0.04	1.60±0.12	<0.001
TC, mean±SE, mmol/L	5.22±0.03	5.20±0.04	5.23±0.06	5.24±0.04	5.22±0.05	0.499
CRP, mean±SE, mg/L	2.16±0.09	2.27±0.20	1.95±0.09	2.29±0.19	2.16±0.23	0.036
Neutrophil ratio, mean±SE, %	58.34±0.32	57.82±0.41	58.55±0.40	58.43±0.56	58.54±0.44	0.729
Lymphocyte ratio, mean±SE, %	33.91±0.65	34.01±0.46	35.12±1.91	33.17±0.45	33.20±0.36	0.671
WBC, mean±SE, 10^9/L	6.13±0.05	5.99±0.08	6.14±0.09	6.16±0.07	6.24±0.10	0.006
Urinary Tl, median (P_{25}–P_{75}), μg/L	0.27 (0.16–0.45)	0.11 (0.07–0.13)	0.21 (0.18–0.24)	0.35 (0.31–0.39)	0.68 (0.55–0.93)	<0.001
Urinary Cd, median (P_{25}–P_{75}), μg/L	0.65 (0.32–1.32)	0.29 (0.14–0.57)	0.51 (0.30–0.95)	0.82 (0.49–1.41)	1.39 (0.75–2.50)	<0.001
Urinary Pb, median (P_{25}–P_{75}), μg/L	1.08 (0.61–1.72)	0.67 (0.32–1.22)	0.99 (0.61–1.59)	1.19 (0.45–1.79)	1.43 (0.94–2.18)	<0.001
Urinary Hg, median (P_{25}–P_{75}), μg/L	0.22 (0.10–0.48)	0.11 (0.04–0.21)	0.19 (0.10–0.37)	0.27 (0.15–0.58)	0.39 (0.21–0.80)	<0.001
Urinary As, median (P_{25}–P_{75}), μg/L	20.87 (11.32–40.13)	10.21 (5.73–19.00)	17.42 (10.44–31.27)	26.08 (15.19–44.67)	36.19 (22.27–61.78)	<0.001
Sex, No. (%)						0.002
Men	4,597 (37.94)	1,273 (43.50)	1,192 (36.44)	1,084 (36.15)	1,048 (35.91)	
Women	4,641(62.06)	966 (56.50)	1,196 (63.56)	1,210 (63.85)	1,269 (64.09)	
Educational, No. (%)						0.021
Middle school or less	5,836 (58.31)	1,511 (62.64)	1,517 (59.53)	1,343 (52.06)	1,465 (59.00)	
High school	1,872 (22.18)	417 (20.50)	472 (21.43)	489 (25.01)	494 (21.80)	
College or higher	1,530 (19.52)	311 (16.85)	399 (19.04)	462 (22.94)	358 (19.20)	
Residence, No. (%)						0.093
Rural	4,104 (37.26)	1,116 (42.39)	1,045 (36.02)	924 (33.92)	1,019 (36.93)	
Urban	5,134 (62.74)	1,123 (57.61)	1,343 (63.98)	1,370 (66.08)	1,298 (63.07)	
Marital status, No. (%)						0.144
Unmarried/divorced/widowed	1,506 (14.35)	396 (16.29)	418 (14.60)	374 (13.35)	318 (13.13)	
Married	7,732 (85.65)	1,843 (83.71)	1,970 (85.40)	1,920 (86.65)	1,999 (86.87)	
Annual income, No. (%)						<0.001
<10,000 CNY	1,367 (12.74)	431 (16.95)	369 (12.33)	297 (11.38)	270 (10.36)	
10,000–100,000 CNY	6,740 (72.51)	1,596 (71.26)	1,754 (74.78)	1,660 (70.29)	1,730 (73.51)	
>100,000 CNY	1,131 (14.75)	212 (11.79)	265 (12.88)	337 (18.33)	317 (16.14)	
Drinking status, No. (%)						0.235
No	5,254 (49.08)	1,360 (51.46)	1,391 (49.71)	1,243 (46.13)	1,260 (49.03)	
Yes	3,984 (50.92)	879 (48.54)	997 (50.29)	1,051 (53.87)	1,057 (50.97)	
Smoking status, No. (%)						0.309
No	6,594 (66.81)	1,700 (69.42)	1,721 (65.25)	1,593 (66.72)	1,580 (66.03)	
Yes	2,644 (33.19)	539 (30.58)	667 (34.75)	701 (33.28)	737 (33.97)	
Meat consumption, No. (%)						<0.001
<14 times/week	6,943 (75.57)	1,861 (81.92)	1,853 (78.21)	1,688 (74.00)	1,541 (67.85)	
≥14 times/week	2,295 (24.43)	378 (18.08)	535 (21.79)	606 (26.00)	776 (32.15)	

Continued

Characteristics	Total	Quartiles of urinary Tl				*P*
		Q1	Q2	Q3	Q4	
Vegetable consumption, No. (%)						<0.001
<14 times/week	3,036 (32.26)	835 (36.65)	868 (35.55)	727 (29.74)	606 (26.77)	
≥14 times/week	6,202 (67.74)	1,404 (63.35)	1,520 (64.45)	1,567 (70.26)	1,711 (73.23)	
Hypertension, No. (%)						<0.001
No	6,147 (65.09)	1,343 (58.45)	1,591 (67.53)	1,615 (67.88)	1,598 (66.16)	
Yes	3,091 (34.91)	896 (41.55)	797 (32.47)	679 (32.12)	719 (33.84)	
Diabetes, No. (%)						0.167
No	8,284 (89.01)	1,989 (88.36)	2,123 (87.39)	2,073 (89.89)	2,099 (90.59)	
Yes	954 (10.99)	250 (11.64)	265 (12.61)	221 (10.11)	218 (9.41)	
CKD, No. (%)						0.003
No	8,402 (92.25)	2,048 (92.78)	2,197 (93.24)	2,109 (93.34)	2,048 (89.50)	
Yes	836 (7.75)	191 (7.22)	191 (6.76)	185 (6.66)	269 (10.50)	

Note: Q1=urinary Tl≤0.16 μg/L; Q2=0.16 μg/L<urinary Tl≤0.28 μg/L; Q3=0.28 μg/L<urinary Tl≤0.46 μg/L; Q4=urinary Tl>0.46 μg/L. Results were weighted to account for the complex survey design.
Abbreviation: Tl=thallium; SE=standard error; BMI=body mass index; eGFR=estimated glomerular filtration rate; UCr=urine creatinine; TC=total cholesterol; CRP=C-reactive protein; WBC=white blood cell count; CKD=chronic kidney disease; Cd=cadmium; Pb=lead; Hg=mercury; As=arsenic; CNY=Chinese Yuan.

SUPPLEMENTARY TABLE S2. Weighted regression coefficients (β) and 95% *CI* for the association of urinary Tl with eGFR among Chinese adults in 2017–2018.

Urinary Tl	*β* (95% *CI*)				
	Crude model	Model 1*	Model 2†	Model 3§	Model 4¶
Q1 (Reference)	0.00	0.00	0.00	0.00	0.00
Q2	0.99 (−1.68, 3.67)	−0.55 (−3.31, 2.20)	−0.40 (−3.13, 2.33)	−0.37 (−3.16, 2.41)	−0.21 (−3.04, 2.62)
Q3	0.17 (−3.58, 3.91)	−1.91 (−5.68, 1.85)	−1.75 (−5.53, 2.04)	−1.58 (−5.44, 2.29)	−1.22 (−5.26, 2.82)
Q4	−3.91 (−9.31, 1.49)	−5.45 (−10.88, −0.01)**	−5.06 (−10.36, 0.23)	−4.78 (−10.21, 0.64)	−4.08 (−9.55, 1.39)
Per *IQR*	−1.58 (−3.10, −0.06)**	−1.81 (−3.33, −0.29)**	−1.70 (−3.16, −0.24)**	−1.64 (−3.10, −0.19)**	−1.45 (−2.88, −0.02)**

Note: Q1=urinary Tl≤0.16 μg/L; Q2=0.16 μg/L<urinary Tl≤0.28 μg/L; Q3=0.28 μg/L < urinary Tl≤0.46 μg/L; Q4=urinary Tl>0.46 μg/L.
Abbreviation: *CI*=confidence interval; Tl=thallium; eGFR=estimated glomerular filtration rate; *IQR*=interquartile range; BMI=body mass index; UCr=urine creatinine; TC=total cholesterol; Cd=cadmium; Pb=lead; Hg=mercury; As=arsenic.
* Adjusted for age, sex, education, residence, marital status, and household income.
† Additionally adjusted for smoking status, drinking status, meat consumption, and vegetable consumption.
§ Additionally adjusted for hypertension, diabetes, BMI, UCr, and TC.
¶ Additionally adjusted for urinary Cd, urinary Pb, urinary Hg, and urinary As.
** *P*<0.05.

SUPPLEMENTARY TABLE S3. Weighted regression coefficients (β) and 95% *CI* for the association of inflammatory indicators with eGFR among Chinese adults in 2017–2018.

Variables	*β* (95% *CI*)			
	Crude model	Model 1*	Model 2†	Model 3§
CRP	−0.15 (−0.30, −0.00)	−0.05 (−0.18, 0.09)	−0.04 (−0.18, 0.10)	−0.04 (−0.18, 0.10)
Neutrophil ratio	−0.72 (−1.88, 0.45)	−0.25 (−1.28, 0.77)	−0.21 (−1.23, 0.82)	−0.30 (−1.29, 0.69)
Lymphocyte ratio	−0.27 (−1.00, 0.46)	−0.67 (−1.29, −0.05)¶	−0.73 (−1.31, −0.14)¶	−0.69 (−1.30, −0.09)¶
WBC	0.20 (−0.70, 1.09)	−0.33 (−1.07, 0.42)	−0.23 (−0.95, 0.50)	−0.24 (−0.97, 0.48)

Abbreviation: *CI*=confidence interval; eGFR=estimate glomerular filtration rate; CRP=C−reactive protein; WBC=white blood cell count; BMI=body mass index; UCr=urine creatinine; TC=total cholesterol.
* Adjusted for age, sex, education, residence, marital status, and household income.
† Additionally adjusted for smoking status, drinking status, meat consumption, and vegetable consumption.
§ Additionally adjusted for hypertension, diabetes, BMI, UCr, and TC.
¶ *P*<0.05.

SUPPLEMENTARY TABLE S4. Mediating analysis of lymphocyte in the association of urinary Tl with eGFR among Chinese adults in 2017–2018.

Variable	ADE, *β* (95% *CI*)	*P*	ACME, *β* (95% *CI*)	*P*	Proportion of mediation, *β* (95% *CI*), %	*P*
Lymphocyte ratio	−2.00 (−2.43, −1.51)	<0.001	0.01 (−0.00, 0.02)	0.132	−0.40 (−1.22, 0.08)	0.132

Note: Adjusted for age, sex, education, residence, marital status, household income, smoking status, drinking status, meat consumption, vegetable consumption, hypertension, diabetes, BMI, UCr, and TC.
Abbreviation: Tl=thallium; eGFR=estimated glomerular filtration rate; ADE=average direct effect; ACME=average causal mediation effect; BMI=body mass index; UCr=urine creatinine; TC=total cholesterol.

SUPPLEMENTARY TABLE S5. Weighted odds ratios (95% *CI*) of CKD associated with urinary Tl stratified by gender and age among Chinese adults in 2017–2018.

Groups		*OR* (95% *CI*)	*P*
Male		1.07 (0.93, 1.23)	0.352
Age group (years)	18–39	0.90 (0.48, 1.69)	0.734
	40–59	1.03 (0.84, 1.28)	0.756
	60–79	1.22 (0.97, 1.54)	0.086
Female		1.13 (1.01, 1.26)	0.029
Age group (years)	18–39	1.02 (0.84, 1.25)	0.840
	40–59	1.15 (1.00, 1.35)	0.054
	60–79	1.24 (1.05, 1.46)	0.012

Note: Adjusted for age, sex, education, residence, marital status, household income, smoking status, alcohol consumption, meat intake, vegetable intake, hypertension, diabetes, BMI, UCr, TC, urinary Cd, urinary Pb, urinary Hg, and urinary As.
Abbreviation: *CI*=confidence interval; CKD=chronic kidney disease; Tl=thallium; *OR*=odds ratio; BMI=body mass index; UCr=urine creatinine; TC=total cholesterol; Cd=cadmium; Pb=lead; Hg=mercury; As=arsenic.

SUPPLEMENTARY TABLE S6. Associations between urinary Tl and CKD with eGFR calculated by CKD-EPI equation among Chinese adults in 2017–2018.

Urinary Tl	*β* (95% *CI*)				
	Crude model	Model 1*	Model 2†	Model 3§	Model 4¶
Q1 (Reference)	1.00	1.00	1.00	1.00	1.00
Q2	0.92 (0.66, 1.28)	1.21 (0.85, 1.72)	1.19 (0.84, 1.69)	1.21 (0.85, 1.72)	1.18 (0.82, 1.70)
Q3	0.92 (0.65, 1.31)	1.41 (0.97, 2.06)	1.39 (0.95, 2.03)	1.42 (0.96, 2.10)	1.34 (0.88, 2.04)
Q4	1.27 (0.84, 1.92)	1.89 (1.21, 2.96)**	1.83 (1.16, 2.87)**	1.87 (1.15, 3.05)**	1.61 (0.92, 2.79)
Per *IQR*	1.07 (0.98, 1.16)	1.15 (1.06, 1.24)**	1.14 (1.05, 1.23)**	1.14 (1.05, 1.23)**	1.09 (0.98, 1.20)

Note: Q1=urinary Tl≤0.16 μg/L; Q2=0.16 μg/L<urinary Tl≤0.28 μg/L; Q3=0.28 μg/L<urinary Tl≤0.46 μg/L; Q4=urinary Tl>0.46 μg/L.
Abbreviation: Tl=thallium; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; *IQR*=interquartile range; BMI=body mass index; UCr=urine creatinine; TC=total cholesterol; Cd=cadmium; Pb=lead; Hg=mercury; As=arsenic.
* Adjusted for age, sex, education, residence, marital status, and household income.
† Additionally adjusted for smoking status, drinking status, meat consumption, and vegetable consumption.
§ Additionally adjusted for hypertension, diabetes, BMI, UCr, and TC.
¶ Additionally adjusted for urinary Cd, urinary Pb, urinary Hg, and urinary As.
** *P*<0.05.

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Outbreak Reports

An Occupational Dimethylacetamide Poisoning Incident Responded Efficiently in Health Emergency Response Network — Zhuhai City, Guangdong Province, China, August 2023

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Summary

What is already known about this topic?

Dimethylacetamide (DMA), a colorless liquid with low toxicity, is commonly used as a solvent in the production of synthetic materials, petroleum processing, and pharmaceutical manufacture. In comparison to substances of higher toxicity, occupational exposure to DMA presents a deceptive risk due to its insidious and subacute progression, increasing the likelihood of escalating into major incidents.

What is added by this report?

In August 2023, an incident of occupational DMA poisoning involving six cases was reported at a spandex manufacturing factory in Zhuhai City, Guangdong Province, China, following post-fire management activities. All affected individuals were employees of an equipment maintenance company tasked with cleaning polymerizers. With the coordinated efforts of the health institutions in Guangdong *Health Emergency Response Network for Poisoning Emergencies* (*HERNPE*), the situation was promptly identified and addressed.

What are the implications for public health practice?

HERNPE serves as an effective framework for enhancing the integration of health institutions across various levels, facilitating a coordinated response that combines clinical services with public health initiatives. By leveraging the leadership of national centers, *HERNPE* plays a crucial role in the early detection, prevention, and management of large-scale health events.

The *Health Emergency Response Network for Poisoning Emergencies* (*HERNPE*) in Guangdong Province represents a collaborative model established in recent years for sharing information and resources among health institutions. This network designates the Guangdong Province Hospital for Occupational Disease Prevention and Treatment (GDHOD), a recognized national facility, as its technical hub. Furthermore, municipal hospitals that collaborate with chemical laboratories serve as branch nodes, while additional health institutions function as auxiliary components. This structure supports a robust framework for managing health emergencies in the region.

On August 20, 2023, the GDHOD was consulted by a hospital in Guangzhou city concerning two inpatients from Zhuhai City diagnosed with toxic hepatopathy due to occupational exposure to dimethylacetamide (DMA). Additionally, two other workers were reported to exhibit similar symptoms. The following day, GDHOD received a report from the Zhuhai Hospital for Occupational Disease Prevention and Treatment (ZHHOD). According to this report, a group of workers, who withheld their company's information, sought occupational health screenings specifically for liver function in Zhuhai. Several of these individuals presented with elevated results in liver function tests, notably in the Alanine transaminase (ALT) indices.

Given the possibility that these cases originated from the same incident, the GDHOD and ZHHOD collaboratively responded and identified the cases as occupational acute DMA poisoning. A total of 169 workers were affected by the incident. Of those, 32 individuals, who presented with elevated ALT levels, were either hospitalized or placed under ambulatory surveillance. Eventually, 6 workers were definitively diagnosed with occupational acute DMA poisoning, categorized as 1 severe, 1 moderate, and 4 mild cases.

INVESTIGATION AND FINDINGS

All 6 male cases were employees of the same

equipment maintenance company tasked with cleaning polymerizers as part of post-fire management at a spandex manufacturing factory in Zhuhai City. Between 5 and 13 days after exposure to DMA, these individuals developed hepatopathy, which manifested as fatigue and vomiting. Additionally, all cases experienced varying degrees of skin irritation, followed by erythema and desquamation primarily affecting the limbs that had been exposed to moisture during their work activities.

A joint team from GDHOD and ZHHOD established the case definition and identified a total of 6 cases, five of whom were hospitalized (two in Guangzhou and three in Zhuhai). Subsequent investigations led to all six cases being transferred to specialized hospitals in Guangzhou via the "green lane" in the *HERNPE*. The outcomes of field investigations and laboratory analyses informed the treatment protocols. Five of the cases were successfully cured and discharged after receiving symptomatic and supportive therapy for between 12 and 35 days. The remaining case showed improvement but was discharged against medical advice after 15 days. The basic information and diagnoses are summarized in the Table 1.

A joint team embarked on a field investigation at the factory on August 21–22 and identified the primary hazard point as the cleaning of a polymerizer in a confined space during post-fire management (notably, a similar incident in 2011 involved two workers who, while performing routine cleaning in this space with inadequate protection, suffered from DMA poisoning). Following a fire that occurred four days prior, on July 20, the factory engaged four equipment maintenance companies to manage the post-fire situation. Several tonnes of manufacturing materials — predominantly spandex blended with DMA, ethylenediamine, diethylamine, and other auxiliary materials — had progressively solidified inside the polymerizer located on the third floor of the Polymerization Workshop.

According to the survey and records, only 10 workers from a single company registered to clean the polymerizer; this group included 6 cases, half of whom were newly-recruited part-time employees. An additional 159 workers were involved in cleaning, loading, unloading, and handling operations within the same workshop and might have been exposed to the same toxicants. In total, 169 workers were involved in these activities.

The process for cleaning the polymerizer in post-fire management, compared to conventional methods, was outlined as follows: 1) Detection of air quality within the polymerizer, noting poor ventilation. 2) Draining of contents from the polymerizer, including solid and liquid residues. 3) Flushing of the polymerizer with tap water, following a non-standardized standard operating procedure. 4) Manual entry into the polymerizer to scrape off residues, noting an increased residue presence and inadequate protective measures. 5) Exiting the polymerizer and removal of residues, characterized by extended duration and absence of specialized protective equipment.

Each shift lasted 8 hours per day, with workers

TABLE 1. The basic information and diagnosis of 6 cases in Zhuhai City, Guangdong Province, China, August 2023.

Patient No.	Age (years)	Duration of exposure to DMA (day)	N-methylacetamide in urine (mg/g Cr)[1], (day)[2]	Serum ALT at manifest period (U/L), (day)[2]	Serum total bilirubin at manifest period (μmol/L), (day)[2]	Main clinical manifestations[3]	Severity scale	Hospital day
Case A	46	13	1,639.78 (5 d)	474 (6 d)	269.7 (6 d)	Acute liver failure, fatigue, poor appetite, vomiting	Severe	17 (clinically cured)
Case B	48	5	239.79 (5 d)	3,499 (4 d)	43.6 (4 d)	Nausea, vomiting, fatigue, poor appetite	Mild	12 (clinically cured)
Case C	57	8	36.90 (7 d)	1,448 (5 d)	53.90 (5 d)	Nausea, fatigue, jaundice	Moderate	28
Case D	56	8	9.79 (5 d)	349 (7 d)	9.65 (7 d)	Fatigue, poor appetite	Mild	24
Case E	50	8	52.81 (6 d)	915 (4 d)	34.7 (4 d)	Poor appetite, fatigue, vomiting	Mild	35
Case F	44	6	12.86 (8 d)	252 (7 d)	10.75 (7 d)	Fatigue, poor appetite	Mild	15 (against advice)

Note: Occupational exposure limit of N-methylacetamide in urine emendating with Cr is 20.0 mg/g Cr (off the working week); (day) refer to the time of removal from DMA; Viral or biological hepatitis had been excluded for all cases.
Abbreviation: Cr=creatinine; DMA=dimethylacetamide.

organized into pairs within a group. Each pair alternated tasks every hour; while one pair entered the polymerizer to perform cleaning duties, the other remained outside to assist and rest. In total, 10 workers were equipped with long tube breathing apparatus featuring a full face mask and circulating air (sourced from a remote air supply room). Additionally, they wore rubber gloves, labor shoes, and cotton long-sleeved clothing inside the polymerizer. When outside of the polymerizer, the workers only had disposable masks and cotton gloves for protection — this was the same for the 159 other workers in the workshop. The ventilation within the factory was poor due to a malfunctioning exhaust fan, and only some windows were left open to facilitate airflow. Moreover, the factory and four other companies lacked the awareness and capability to monitor DMA exposure effectively.

The site of the incident could no longer be replicated following the conclusion of post-fire management activities. A joint team conducted on-site detection in the workshop on August 22. Laboratory results indicated that the C-STEL of DMA for two samples "near the polymerizer door" was 33.60 mg/m^3 and 36.06 mg/m^3, respectively. Meanwhile, measurements from four samples "in the workshop passageway" showed concentrations of 27.53 mg/m^3, 22.49 mg/m^3, 16.88 mg/m^3, and 12.34 mg/m^3. Based on these findings, it was inferred that DMA concentrations during the incident likely exceeded the PC-TWA of 20 mg/m^3.

Moreover, two distinct batches of manufacturing materials were sent to the GDHOD for qualitative analysis using gas chromatography-mass spectrometry (GC-MS). In the sample provided by Case A on August 19, DMA (30.09%) and dimethylformamide (DMF) (0.10%) were detected. In contrast, DMA (13.74%) and diethylamine (0.10%) were identified in the sample submitted by the joint team on August 21. Consequently, the primary cause of concern was determined to be exposure to DMA, after ruling out spandex and other auxiliary materials due to differing toxic effects or insufficient dosages.

Within two days, a joint team compiled a comprehensive list of 163 workers (excluding the 6 cases) and conducted emergency health screenings from August 23–26. Although no clinical symptoms were present, 26 workers exhibited elevated levels of ALT, with median (P_0–P_{100}) levels of 78.5 U/L (range 52.0–616.0 U/L). Additionally, 9 of these 26 workers showed high levels of urinary N-methylacetamide, with median (P_0–P_{100}) levels of 25.20 mg/g Cr (range 20.79–109.98 mg/g Cr). In response to these findings, the team established a categorical management guideline and set up ambulatory surveillance for liver pathology, which varied in frequency and duration across different individuals. The elevated ALT levels observed in some workers could potentially be considered as physiological responses to DMA exposure, with prospects of recovery facilitated by early detection. However, for the majority, these biochemical anomalies were attributed to factors such as sleep deprivation, alcohol consumption, and high-fat diets.

Furthermore, the collaborative team implemented supervision and provided industry guidelines to reduce the risk of occupational poisoning from DMA. This included the identification of hazards among 143 DMA users through the Guangdong Province Occupational Health Quality Control Platform, which reported no instances of limit exceedance in the past three years. Additionally, 14 technical guidelines, including methods for determining DMA, were issued to public health service institutions. The team also mandated that a certified chemical-waste disposal company securely store any residual waste. Following these interventions, no new cases were reported over the course of a month.

PUBLIC HEALTH RESPONSE

The emergency response timeline proceeded as follows: 1) August 20–21: The GDHOD and ZHHOD engaged in information gathering and coordinated response efforts. 2) August 21–22: conducted a survey of 5 cases and a field investigation, which identified the sixth case. 3) August 22: performed on-site detection, compiled a list of workers, and provided supervision and industry-specific guidance. 4) August 23: six cases were referred to specialized hospitals. 5) August 23–26: screened a total of 163 workers. 6) August 24–September 26: organized intensive treatment and ongoing ambulatory surveillance.

Targeted interventions within the *HERNPE* were crucial, including the exchange of information about outbreaks to facilitate early detection, especially in instances where employers might conceal information or provide false evidence. These interventions were supported by expert guidance from national authorities, the prioritization of patient admissions and referrals through designated "green lanes", the implementation of coordinated investigation and

detection efforts, and comprehensive screening and surveillance measures in large groups.

DISCUSSION

DMA has increasingly been used as a substitute for DMF due to its high thermal stability, low corrosiveness, and reduced toxicity, among other advantages. Despite these benefits, incidents of DMA poisoning have been reported periodically. According to partial data, there have been over six incidents involving more than 30 cases in China, all within the chemical fiber manufacturing industry (*1*–*2*).

DMA may target the liver, resulting in acute poisoning, and may also irritate the skin, typically displaying a subacute insidious progression or, less commonly, recurrence (*3*). Chronic exposure to DMA can lead to neurasthenia, respiratory irritation, and varying levels of hepatic damage (*4*). The presence of N-methylacetamide in urine, which positively correlates with the concentration of DMA in the air, serves as a useful biomonitoring indicator (*5*).

Several factors contributed to the severity of this mass exposure event: cases were subjected to high concentrations of DMA; the incident occurred in a confined space within the polymerizer, where toxicant levels were significantly elevated; workers engaged in post-fire management operations for extended periods without adhering to standard procedures; and lastly, both the company and its employees demonstrated inadequate awareness and implementation of protective measures. Proper emergency response protocols are crucial.

Thanks to the collaborative efforts of various health institutions, the integrated clinical and public health response system, and technical guidance from the national headquarters at *HERNPE*, this incident was efficiently identified and managed in a short timeframe, despite involving a large number of workers. This prompted an extensive demand for streamlined admission and referral processes, timely on-site detection, field investigations, diagnostic and treatment guidance, category management guidelines, and other measures.

To prevent such incidents, it is recommended that employers prioritize the hiring of personnel who possess qualifications relevant to handling hazardous chemicals and develop robust disaster management strategies. Additionally, limiting working hours and enhancing health education and personal protection initiatives are crucial. Medical institutions should enhance the sensitivity of their surveillance systems and be vigilant about patients' occupational histories or potential exposures, particularly when clusters of similar medical findings emerge within a short timeframe. Additionally, timely sharing of information through *HERNPE* is critical in the event of a mass exposure.

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Healthy China

PENG ZU Study on Healthy Aging in China (PENG ZU Cohort): Design and Goals

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ABSTRACT

Life expectancy is increasing, leading to the continuous aging of the population in China. Enhancing the health status of the older population is crucial to achieving healthy aging. The primary objective of the PENG ZU Study on Healthy Aging in China (PENG ZU Cohort) is to understand the natural progression of health status among the aging Chinese population. Specifically, the PENG ZU cohort aims to identify and validate multidimensional aging markers, uncover the underlying mechanisms of systemic aging and functional decline, and develop novel strategies and measures to delay functional decline and adverse health outcomes, while maintaining overall good health. The PENG ZU cohort consists of 26,000 individuals aged 25 to 89 years from seven major geographical regions in China. Diversified data and biospecimens are collected according to standardized procedures at baseline and follow-up visits. Baseline recruitment for the PENG ZU cohort was completed in October 2021. The extensive analysis of multidimensional health-related data and bioresources collected from the cohort is anticipated to develop methods for evaluating functional status and elucidating multilevel, cross-scale interactions and regulatory mechanisms of healthy aging. The findings from this study will enhance the understanding of health changes due to aging, facilitate efficient and effective interventions to maintain functional ability, and reduce the incidence and severity of age-related diseases, thereby further promoting healthy aging.

Human life expectancy is currently at its highest and is expected to continue rising. In China, there are 240 million individuals aged 60 years and older, and this number is projected to exceed 400 million, constituting roughly one-third of the total population by 2035 (*1*). Addressing the diverse health-related issues associated with this demographic shift presents a significant challenge for society.

Health status is a multidimensional composite state that includes physical health, mental well-being, and social adaptation (*2–3*). The health status of older individuals is influenced by various factors throughout their lives. Cohort studies are scientifically valuable for providing in-depth insights into the mechanisms of health changes and development, as well as for formulating effective intervention measures.

In 2015, the World Health Organization (WHO) released the "World Report on Ageing and Health" (*2–3*). The report emphasized that the goal of Healthy Aging is to aid in "developing and maintaining the functional ability necessary for health in old age." The core framework comprises two key concepts: "intrinsic capacity" and "functional ability," along with the interaction between the individuals and their environment. The maintenance of functional ability is fundamental to achieving healthy aging, and functional performance is a crucial factor in promoting it.

This study aims to understand the development and evolution of health status across the lifespan by establishing a comprehensive, health-oriented cohort of individuals aged 25 to 89 from seven major geographical regions in China. The cohort focuses on improving functional ability in older adults and identifying various positive factors throughout the life course. Additionally, the study will incorporate advanced multimodal analysis to measure biological aging, contributing to the prevention and/or delay of functional decline.

STUDY DESIGN

The PENG ZU Study on Healthy Aging in China is a prospective observational study.

Objectives

The primary objectives of the PENG ZU cohort are: 1) to establish a high-quality aging cohort with standardized data collection of key variables and biospecimens; 2) to use real-world data to understand the realistic processes in Chinese health status brought about by aging (natural course); 3) to evaluate functional decline associated with aging, particularly the deterioration of intrinsic capacity, identifying its trajectory over time and correlation with various health outcomes; 4) to uncover the underlying mechanisms of systemic aging and intrinsic capacity decline by identifying and validating multidimensional aging biomarkers; and 5) to develop a novel approach for big data analysis of health information, and to build evaluation and prediction models for functional decline, with translational applications.

This study focuses on key composite health events throughout the life course, including: 1) the trajectory of functional decline (e.g., intrinsic capacity, functional ability, disabilities) and its relationships with associated factors; 2) disease occurrence (e.g., heart disease, cancer, diabetes); and 3) mortality.

The goal of this project is to understand current health conditions and related influencing factors, dynamically monitor changes in population health, promptly detect age-related functional changes and health risks, provide intervention guidelines, slow functional decline and disease occurrence, as well as maintain overall health levels.

Study Population

The PENG ZU cohort is an observational study that examines health status in a real-world setting. Given the exploratory objectives of the PENG ZU cohort, calculating an epidemiological sample size is unnecessary. To ensure an adequate number of participants for follow-up visits, the study aims to recruit at least 26,000 community-based participants aged 25 to 89 years. These participants are stratified into 13 five-year age groups, each consisting of approximately 1,000 males and 1,000 females. Recruitment occurs across seven major geographical regions in China (Northeast, North China, Central China, East China, South China, Southwest, and Northwest), reflecting diverse geographical distributions and lifestyle habits. For participants aged 60 and above, follow-up visits occur biennially, whereas for those under 60, follow-up visits take place every four years. Figure 1 presents a schematic overview of the study procedures.

The inclusion criteria were as follows: 1) aged 25–89 years; 2) provided signed informed consent; 3) locally residing individuals of appropriate age with stable employment and residence; 4) free from acute diseases; 5) no progressive life-threatening diseases; 6) no mental disorders; 7) no history of alcohol or substance abuse; and 8) no criminal record. Exclusion criteria included individuals: 1) at risk of migration or relocation; or 2) with any physical or mental functional impairments preventing survey completion.

Data Collection

Participants were recruited for the study through advertisements placed in health examination centers and community settings. Volunteers from the medical examination centers are considered representative of the general population, showing consistency with community residents in terms of physical health, mental health, and social adaptation. Health information data, including demographics, physical and mental health status, and socio-economic-environmental conditions, were collected at baseline and during follow-up visits. Table 1 outlines the PENG Zu cohort study flow chart and details all data collected at baseline.

Biobanking

Biospecimens, including blood and urine, were collected at baseline and follow-up visits. Samples from various satellite centers were transported via express cold chain logistics to the National Human Genetic Resources Center Biobank (NHGRC-Biobank) in China, where they were stored in smaller aliquots at −80 ℃. The PENG ZU cohort biobank is overseen by the National Health Commission of the People's Republic of China.

Blood sample collection: After an overnight fast, all participants donated 10 mL of blood via venipuncture into two 5 mL vacuum plastic blood collection tubes: one coated with EDTA anticoagulant (Greiner Bio-One, Austria) and one with coagulant (Greiner Bio-One, Austria). The samples were processed to isolate plasma, serum, and peripheral blood mononuclear cells (PBMCs).

Urine sample collection: Participants were instructed to collect midstream first-morning urine samples in sterile screw-top containers. The urine samples were then transferred into 10 mL vacutainer tubes (Gongdong Medical Technology, China) and transported via express cold chain logistics to the

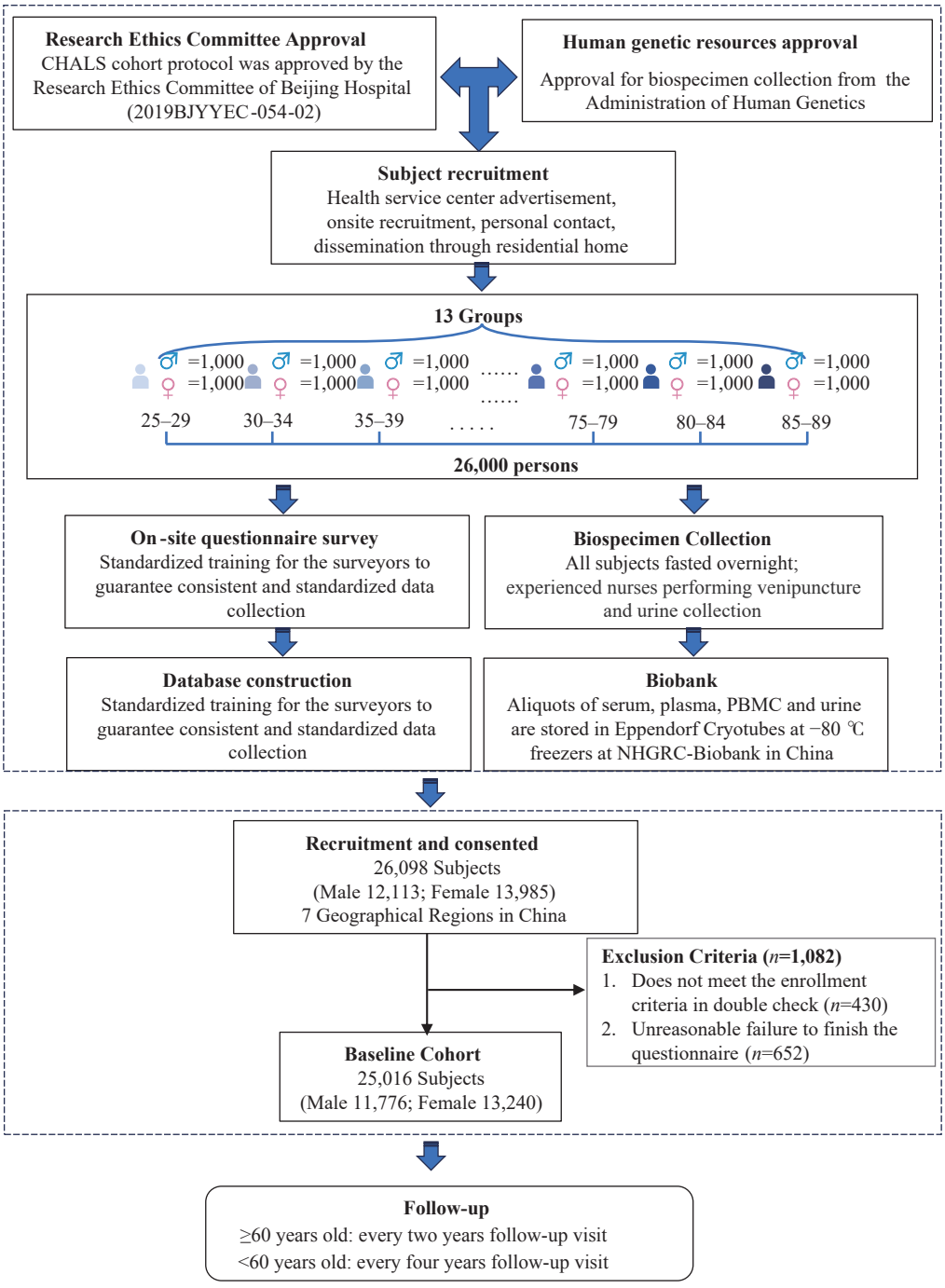

FIGURE 1. The PENG ZU cohort baseline: first wave of data collection.

NHGRC-Biobank. There, urine aliquots were prepared and stored in a −80 °C freezer within the NHGRC-Biobank.

Database Construction

The design of the prototype system has resulted in a standardized aging health database for data collection, analysis, and sharing. This platform integrates data from various sources, utilizing outlier handling algorithms and offering multidimensional analysis for clear insights. It features secure data sharing with multi-level permissions and watermark technology for traceability. The system includes user and administrator modules, with extensive data storage and large-scale parallel computing for efficient health data processing and visualized analysis.

A scientific committee has been established for the biobank and database to define scientific trajectories

TABLE 1. The PENG ZU cohort flowchart.

Categories	Variables	Baseline	Follow-up
Recruitment		√	
Informed consent		√	
Eligibility criteria checked		√	
Demographic information	Age, sex, education, religion, marital status, occupation	√	
Lifestyle information	Life satisfaction, working and leisure, physical activity, sedentarily time, smoking, alcohol consumption, health production supplementation, food frequency, sleep status, social participation	√	√
Physical condition	Self-health satisfaction, vision loss, hearing loss, tooth loss, appetite, stools and urination, discomfort (fatigue/dysphoria/inattention/impulse/self-reported visceral pain/ allergy), ADL, IADL (*4*–*5*) self-reported disease history, medication, vaccination, and health consciousness	√	√
Physical examination	Body mass index, waist and hip circumference, blood pressure, grip strength, gait speed (comfortable and maximal), TUG, balance test, Chair-stand test, VRT	√	√
Mental condition	TIPI (*6*–*7*), DAP-R (*8*), mental health (*9*), aging attitude (*10*–*11*), mental health for interpersonal communication/self-awareness/emotional experience/cognitive efficacy (*12*), DASS-21 (*13*), Mini-MoCA	√	√
Social economic and environment state	Family relationship, colleagues' relationship, friendship, demand and usage of social services, economic state, insurance, Living environment, housing condition, supporting facilities	√	√
Other examinations*	Clinical laboratory examination (47 indicators): complete blood count, blood biochemistry indexes, blood ions, hormones, tumor biomarkers, etc.; BIA, chest CT electrocardiogram, MRI	√	√

Abbreviation: ADL=activities of daily living; IADL=instrumental activities of daily living; TUG=timed up and go test; VRT=visual reaction test; DAP-R=death attitude profile-revised; TIPI=ten-item personality inventory; DASS-21=depression anxiety stress scales; Mini-MoCA=mini montreal cognitive assessment 5-minute; BIA=body composition; CT=computed tomography; MRI=magnetic resonance imaging.
* Other examinations are proposed for a partial number of participants.

and research priorities. Its responsibilities include evaluating ongoing projects and their progress, addressing ethical or methodological issues arising from the studies, and assessing the relevance, feasibility, and execution of proposed analyses. Additionally, the committee ensures that the transfer of biospecimens is regulated by Material Transfer Agreements (MTAs). Data disclosure will adhere to strict anonymity protocols by utilizing coded and traceable information.

Statistical Methods

A comprehensive statistical analysis plan was developed to address the study's specific aims. To investigate potential significant differences in certain indicators across various age groups and sexes, differential analysis methods, including independent sample t-tests and Kolmogorov-Smirnov tests, will be employed. The multidimensional correlation among indicators will be examined using Pearson's correlation and regression analysis. Machine learning techniques will be considered to handle the extensive and diverse data collected from questionnaire surveys, clinical evaluations, biospecimen multi-omics examinations, and digital assessments. Statistical significance will be determined at $P \leq 0.05$.

Quality Control

To ensure data quality, we established a standardized workflow encompassing subject recruitment, on-site questionnaire surveys, physical examinations, biospecimen collection, biobanking protocols, clinical testing, and data collection.

Recruitment strategies: Baseline recruitment primarily utilizes the following strategies: advertisements at community health service centers, onsite recruitment, personal contact, and dissemination through residential homes. These strategies are monitored and updated as necessary throughout the recruitment period.

Questionnaire design: The team comprised geriatric specialists, psychologists, and sociologists, who collaborated extensively to draft the preliminary version of the questionnaire. A small-scale test involving 150 participants across all age groups was conducted to refine the draft, ensuring all questions were clear, concise, and free from ambiguity, and to confirm the questionnaire's length was suitable to prevent respondent fatigue.

On-site questionnaire survey: All surveyors were recruited from nurses, technicians, and medical students with medical backgrounds. The project team provided standardized training to ensure consistent

data collection. Additionally, supervisors were appointed to regularly visit each site to monitor the survey process and provide feedback to surveyors, ensuring adherence to the prescribed standards for conducting questionnaire interviews.

A specialized data management team oversaw the entire data management process of the study, which included reviewing procedures for data collection, validation, and cleaning. Data encryption technology was utilized in constructing the database to prevent unauthorized access, tampering, or data leakage.

Biospecimen collection: To ensure the quality of biosamples during collection, transportation, division, and storage, corresponding technical specifications were established. Standardized operating procedures for various types of biosamples have been implemented to meet the timeliness requirements of testing projects.

Ethics Approval and Human Genetic Resources

The PENG ZU Cohort Study adhered to the Declaration of Helsinki, embodying the fundamental principles of clinical research ethics. The study protocol received approval from the Beijing Hospital Research Ethics Committee (2019BJYYEC-054-02) in March 2019. In line with the regulations of the People's Republic of China on the Administration of Human Genetics, the collection of biospecimens was conducted under the authorized collection of human genetic resources.

CURRENT PROGRESS OF THE PENG ZU COHORT

Recruitment Status

Baseline recruitment concluded in October 2021. Collaborating with around 1,000 team members from nine cohort recruitment sites across seven major geographical regions in China, this study successfully recruited 26,098 participants. Quantitative and qualitative data, along with biological samples, were collected from 25,016 individuals. All participants consented to biobanking. Detailed baseline information for the participants is provided in Table 2.

The average age of the volunteers was 54.9 years. Among the participants, 11,776 were male (47.07% of the total population) and 13,240 were female (52.93% of the total population). Additionally, 16,448 participants resided in urban areas, while 8,568 lived in rural areas.

TABLE 2. Baseline information of participants in PENG ZU cohort.

Variables	Total (*n*, %)	Male	Female
Age (years)	54.9±17.4	55.0±17.6	54.7±17.2
Total	25,016	11,776 (47.07)	13,240 (52.93)
Area			
Urban	16,448 (65.75)	7,705 (65.43)	8,743 (66.00)
Rural	8,568 (34.25)	4,071 (34.57)	4,497 (34.00)
Education			
Illiteracy	1,889 (7.55)	565 (4.80)	1,324 (10.00)
Primary Education	3,870 (15.47)	1,672 (14.20)	2,198 (16.60)
Secondary Education	11,860 (47.41)	5,982 (50.80)	5,878 (44.40)
Higher Education	7,397 (29.57)	3,557 (30.20)	3,840 (29.00)
Marital Status			
Single	1,980 (7.91)	1,119 (9.50)	861 (6.50)
Married (Living Together)	18,856 (75.38)	9,138 (77.60)	9,718 (73.40)
Married (Separated)	868 (3.47)	471 (4.00)	397 (3.00)
Divorced	778 (3.11)	341 (2.90)	437 (3.30)
Widowed	2,534 (10.13)	707 (6.00)	1,827 (13.80)
Living status			
Living alone	2,250 (9.00)	1,072 (9.10)	1,178 (8.9)
Living not alone	22,766 (91.00)	10,704 (90.90)	12,062 (91.1)

The educational background of the surveyed participants revealed that 1,889 individuals (7.55%) were illiterate, 3,870 (15.74%) had primary education (elementary school), 11,860 (47.41%) had secondary education (middle school, high school, or vocational school), and 7,397 (29.57%) had higher education (junior college, undergraduate, master's, or doctorate degrees).

Of the total surveyed population, 1,980 individuals (7.91%) reported being unmarried; 18,856 (75.38%) reported being married and living together; 868 (3.47%) reported being married but living separately; 778 (3.11%) were divorced, and 2,534 (10.13%) were widowed. Concerning living status, 2,250 individuals (9.0%) reported living alone, while more than 90% lived with others.

Biobanking and Biomarker Mining

The PENG ZU cohort biobank was established to provide a crucial platform for researching molecular biomarkers of aging. Biological samples collected from 25,016 participants were aliquoted and stored at −80 °C. The objective is to identify aging biomarkers that align with the characteristics of aging in the Chinese population.

Data Collection and Analysis

This project has successfully completed data collection, cleaning, and storage, culminating in the automatic generation of reports. A statistical analysis plan for aging data has been developed, including current status descriptions (absolute trend analysis, relative trend analysis, and data visualization). Single-dimensional, single-index analysis has been performed using regression analysis and change-point detection methods to assess aging trends.

PERSPECTIVES

The PENG ZU cohort exhibits a wide geographical distribution and significant diversity in its characteristics. This extensive database encompasses information on physical health, mental well-being, and social adaptation. Unlike other established cohorts such as China Health and Retirement Longitudinal Study (CHARLS), English Longitudinal Study of Ageing (ELSA), and Korean Longitudinal Study of Aging (KLoSA), which typically include participants aged 45 or 50 and above, the PENG ZU cohort includes individuals aged 25 to 89 years. Benoit et al. identified three peaks at ages 34, 60, and 78 in plasma proteome profiles, indicating that aging processes may begin as early as the thirties (*14*). To achieve successful health aging, it is essential to intervene early in life. Furthermore, this study differentiates itself from previous research that predominantly focused on health outcomes by emphasizing the understanding of physical and cognitive functional decline during aging. It aims to elucidate the interrelationships among social, psychological, physiological factors, and lifestyle. The PENG ZU cohort has also developed an extensive biobank and database, offering an ideal research platform for comprehensive analysis and screening of aging biomarkers. Presently, both baseline and laboratory data analyses have been completed. The findings from this study will provide technological support for understanding health changes over time due to aging and offer recommendations for efficient and effective interventions to maintain functional ability and promote healthy aging in China.

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Notifiable Infectious Diseases Reports

Reported Cases and Deaths of National Notifiable Infectious Diseases — China, June 2024*

Diseases	Cases	Deaths
Plague	0	0
Cholera	0	0
SARS-CoV	0	0
Acquired immune deficiency syndrome†	5,201	1,680
Hepatitis	152,225	265
Hepatitis A	1,128	0
Hepatitis B	129,221	24
Hepatitis C	18,600	239
Hepatitis D	16	0
Hepatitis E	2,738	2
Other hepatitis	522	0
Poliomyelitis	0	0
Human infection with H5N1 virus	0	0
Measles	201	0
Epidemic hemorrhagic fever	433	0
Rabies	13	10
Japanese encephalitis	5	0
Dengue	130	0
Anthrax	41	0
Dysentery	4,197	0
Tuberculosis	58,241	291
Typhoid fever and paratyphoid fever	532	0
Meningococcal meningitis	8	0
Pertussis	85,817	1
Diphtheria	0	0
Neonatal tetanus	2	0
Scarlet fever	12,397	0
Brucellosis	7,711	0
Gonorrhea	8,396	0
Syphilis	54,760	5
Leptospirosis	21	0
Schistosomiasis	1	0
Malaria	299	1
Human infection with H7N9 virus	0	0
Monkey pox§	51	0
Influenza	314,709	1
Mumps	9,939	0

Continued

Diseases	Cases	Deaths
Rubella	73	0
Acute hemorrhagic conjunctivitis	2,971	0
Leprosy	26	0
Typhus	131	0
Kala azar	24	0
Echinococcosis	302	0
Filariasis	0	0
Infectious diarrhea[¶]	122,585	0
Hand, foot and mouth disease	275,966	0
Total	1,117,408	2,254

* According to the National Bureau of Disease Control and Prevention, not included coronavirus disease 2019 (COVID-19).
† The number of deaths of acquired immune deficiency syndrome (AIDS) is the number of all-cause deaths reported in the month by cumulative reported AIDS patients.
§ Since September 20, 2023, Monkey pox was included in the management of Class B infectious diseases.
¶ Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever.
The number of cases and cause-specific deaths refer to data recorded in National Notifiable Disease Reporting System in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in the Chinese mainland are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan, China are not included. Monthly statistics are calculated without annual verification, which were usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via National Notifiable Disease Reporting System according to information verification or field investigations by local CDCs.

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