Supplementary METHODS

Plasma CRP and CC16 measurements

Plasma CRP is frequently used as an indicator of systemic inflammatory response. The CC16 can protect the respiratory tract from oxidative damage and inflammation, and is a biomarker of lung epithelium integrity. The plasma CRP and CC16 concentrations were measured by enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA). The assay range was 0.8–50 ng/mL for both CRP and CC16, and sensitivities were 0.022 and 0.217 ng/mL, respectively. Sample concentration below the LOQ (800 pg/mL for CRP and CC16) was replaced with half of the LOQ (n=43 for CRP, and n=222 for CC16). After excluding participants without samples (n=766), 3511 CRP and 3511 CC16 values were used.

Urinary 8-OHdG and 8-isoprostane measurements

We used urinary 8-OHdG and urinary 8-isoprostane as biomarkers of DNA oxidative damage and lipid peroxidation, respectively. Urinary 8-OHdG concentration was measured using high performance liquid chromatography with an electrochemical detector (Waters 2645 HPLC-ECD, Waters Corporation, Milford, MA, USA) as previously described.[1] Valid urinary 8-OHdG concentrations were adjusted by urinary creatinine levels and expressed as μmol/mol Cr. After excluding participants without urinary 8-OHdG or urinary creatinine measurements (n=272), 3645 8-OHdG values were used.

Urinary 8-isoprostane concentration was measured by an ELISA kit (Cayman Chemical, Ann Arbor, MI, USA), with assay range 2.5–1500 pg/mL and sensitivity of

10 pg/mL. Valid urinary 8-isoprostane concentrations were adjusted by urinary creatinine levels and expressed as ng/mmol Cr. After excluding participants without urinary 8-isoprostane or urinary creatinine measurements (n=414), 3503 8-isoprostane values were used.

$PM_{2.5}$-bound zinc measurement

Personal 24-h $PM_{2.5}$ was sampled using personal $PM_{2.5}$ samplers (Model 200 Personal Environmental Monitor, MSP Corporation, Shoreview, MN, USA) and pumps of Gilian 5000 (Sensidyne Company, Petersburg, FL, USA) equipped with micro-quartz fiber filters (MK360, Munktell Filter Ab, Falun, Sweden), at the flow of 2 L/min. The $PM_{2.5}$-bound zinc levels were measured using ICP-MS and adjusted by background zinc levels in blank filters.

Covariate assessment

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with participants wearing light indoor clothing.

Participants were asked about the time spent in traffic per day for four travel modes: walking, biking, taking a bus, and driving an automobile. Traffic exposure time (minutes/day) was calculated as the sum of the time spent on different travel modes.

Diet information, including the intake frequencies of grains, fruits and vegetables, meats, fishes, and milk and eggs in each day or week or month for each participant, was collected from questionnaires. Dietary zinc intake was estimated from food frequency (times/month), food consumption structure in China,[2] and the average

zinc concentrations of Chinese foods,[3] specifically,

$$\text{Dietary zinc intake} = \text{grains} \times \beta_1 \times \gamma_1 + fruits\ \ and\ \ vegetables \times \beta_2 \times \gamma_2 + meats \times \beta_3 \times \gamma_3 + fishes \times \beta_4 \times \gamma_4 + milk\ \ and\ \ eggs \times \beta_5 \times \gamma_5 \quad (1)$$

where β represents average zinc content in each 100 g foods, γ represents food consumption ratio.

Cigarette smoking amount (pack-years) was calculated from packs of cigarettes per day multiplied by years of smoking. Participants were asked "How many hours spend in passive smoking per week and how long dose passive smoking last". Passive smoking amount (hours/week-years) was calculated as hours of passive smoking per week multiplied by years. Alcohol consumption amount (times/week-years) was calculated as drinking times per week multiplied by years of drinking.

Information regarding demographics, heart disease (yes/no), physical exercise (yes/no), cooking meals at home (yes/no), and occupational dust exposure (yes/no) were also collected from the questionnaires.

Statistical analysis

Mediation analyses were performed using models developed by Vanderweele and Vansteelandt[4] to assess the roles of CRP, CC16, 8-OHdG, and 8-isoprostane in the associations between urinary zinc and FVC, as well as FEV1. Specifically, two linear models were fitted as follows:

$$\mathrm{E(M|A = a, C = c)} = \beta_0 + \beta_1 \mathrm{a} + \beta_2 \mathrm{c} \quad (2)$$

$$\mathrm{E(Y|A = a, M = m, C = c)} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a * m + \theta_4 c \quad (3)$$

where A is exposure (urinary zinc), M is mediator (CRP, CC16, 8-OHdG, or 8-

isoprostane), Y is dependent variable (FVC or FEV1), and C represents covariates.

Then controlled direct effect (CDE), natural direct effect (NDE), natural indirect effect (NIE), total effect (TE), and proportion mediated were computed as follows:

$$\mathrm{CDE} = E[Y_{am} - Y_{a^*m}] = \theta_1(\mathrm{a} - a^*) + \theta_3\mathrm{m}(\mathrm{a} - a^*) \quad (4)$$

$$\mathrm{NDE} = \mathrm{E}\left[Y_{aM_{a^*}} - Y_{a^*M_{a^*}}\right] = (\theta_1 + \theta_3\beta_0 + \theta_3\beta_1 a^* + \theta_3\beta_2\mathrm{c})(a - a^*) \quad (5)$$

$$\mathrm{NIE} = \mathrm{E}\left[Y_{aM_a} - Y_{aM_{a^*}}\right] = (\theta_2\beta_1 + \theta_3\beta_1 a)(a - a^*) \quad (6)$$

$$\mathrm{TE} = \mathrm{NDE} + \mathrm{NIE} \quad (7)$$

$$\text{Proportion mediated} = \frac{\mathrm{NIE}}{\mathrm{TE}} \quad (8)$$

The model includes the interaction of A and M allowing for an exposure–mediator interaction; when there is no interaction such that $\theta_3 = 0$, then CDE = NDE. All mediation tests were conducted with the SAS *mediation* macros.[5]

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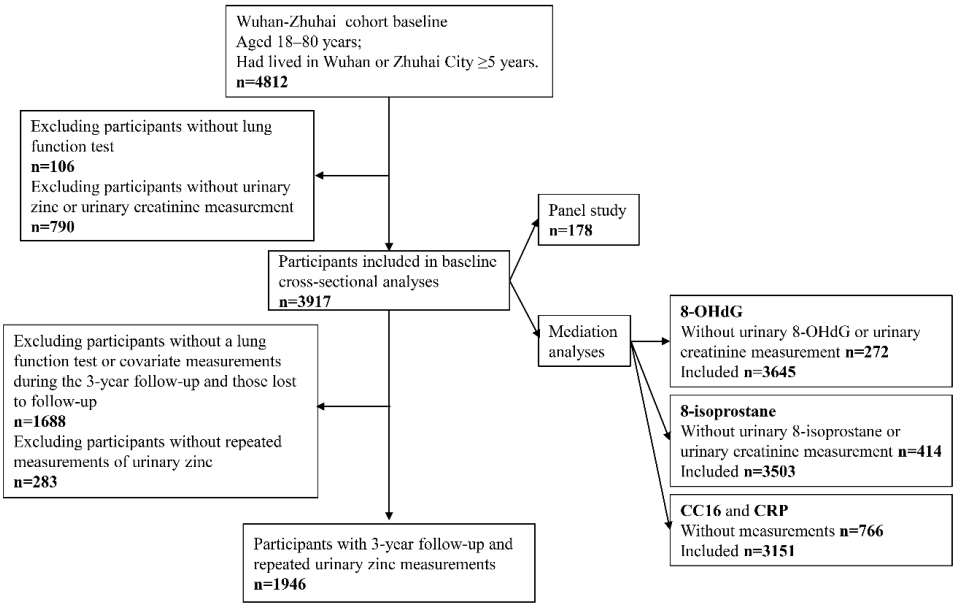


Supplementary Figure 1. Flowchart.

Supplementary Table 1. Baseline basic characteristic of the study population by changes in urinary zinc levels

Variables	3-years follow-up study population						Baseline study population	
	Total (n=1946)	Persistent low (n=196)	Persistent moderate (n=520)	Persistent high (n=195)	Inconsistent (n=1035)	*P* value[#]	Total (n=3917)	*P* value[$]
Age (years, mean ± SD)	54.3±11.4	50.3±12.3	54.1±11.3	56.5±9.5	54.7±11.4	<0.001*	52.5±12.9	<0.001*
Female gender (n, %)	1300(66.8)	146(74.5)	322(61.9)	130(66.7)	702(67.8)	0.798	2656(67.8)	0.440
Height (cm, mean ± SD)	158.7±7.8	159.0±7.7	159.5±7.8	158.5±8.0	158.3±7.8	0.038*	159.2±7.7	0.034*
Weight (kg, mean ± SD)	61.5±10.3	60.8±9.7	61.6±10.3	63.0±10.8	61.2±10.2	0.107	60.9±10.5	0.044*
Smoking amount (pack-years, mean ± SD)	5.1±13.5	3.0±9.2	5.8±14.6	5.1±14.0	5.1±13.5	0.392	4.9±13.7	0.567
Passive smoking amount (hours/week-years, mean ± SD)	55.7±119.5	50.9±99.4	52.1±113.5	64.6±136.3	56.7±122.6	0.316	50.1±112.0	0.083
Alcohol drinking amount (times/week-years, mean ± SD)	18.6±64.1	15.9±53.5	23.6±72.7	19.1±69.5	16.6±60.1	0.258	21.2±71.2	0.170
Physical exercise (n, %)	997(51.2)	87(44.4)	273(52.5)	103(52.8)	534(51.6)	0.320	1873(47.8)	0.014*
Food frequency (times/month, mean ± SD)								
Grains	86.8±12.3	85.5±14.7	86.5±12.7	86.2±14.0	87.3±11.3	0.154	86.2±14.1	0.110
Fruits and vegetables	59.7±18.3	62.0±17.2	59.6±19.1	60.3±16.8	59.3±18.3	0.167	57.9±18.3	<0.001*
Meats	33.6±23.8	33.4±22.0	34.2±24.3	33.7±23.6	33.4±23.9	0.926	34.6±24.2	0.165
Fishes	20.1±20.6	19.3±28.0	20.7±19.9	19.7±18.9	20.1±19.7	0.799	19.7±20.7	0.501
Milk and eggs	19.9±21.5	21.4±16.7	18.8±15.4	17.7±14.3	20.7±25.6	0.074	19.1±19.2	0.133
Heart disease (n, %)	421(21.6)	31(15.8)	106(20.4)	51(26.2)	233(22.5)	0.054	912(23.3)	0.156
Occupational dust exposure (n, %)	503(25.9)	43(21.9)	140(27.0)	47(24.1)	273(26.4)	0.473	1053(26.9)	0.410
Cooking meals at home (n, %)	1483(76.3)	146(74.5)	406(78.2)	153(78.5)	778(75.2)	0.500	2895(73.9)	0.049*
Traffic exposure time (minutes/day, mean ± SD)	64.1±83.7	78.2±113.3	63.1±84.2	64.6±71.2	61.7±78.7	0.442	63.3±83.4	0.753
FVC (mL, mean ± SD)	2525.6±681.5	2655.2±724.8	2593.7±694.9	2438.4±703.1	2483.4±656.3	0.001*	2510.0±669.8	0.403
FEV1 (mL, mean ± SD)	2179.0±586.5	2306.9±602.4	2218.7±590.4	2130.3±588.9	2144.0±577.0	0.002*	2193.5±577.0	0.368
Urinary zinc at baseline (μg/mmol Cr, mean ± SD)	33.6±38.8	12.4±4.0	27.8±6.2	71.1±96.1	33.4±26.5	<0.001*	33.0±33.2	0.580
Urinary zinc at follow-up (μg/mmol Cr, mean ± SD)	47.7±172.1	14.4±5.3	34.9±8.0	86.4±55.3	53.1±233.4	<0.001*	NA	NA

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not applicable; SD, standard deviation.

Persistent low: baseline in Q1 (≤18.05 μg/mmol Cr) and follow-up in Q1 (≤22.42 μg/mmol Cr).

Persistent moderate: baseline in Q2–Q3 (18.06–39.32 μg/mmol Cr) and follow-up in Q2–Q3 (22.43–51.51 μg/mmol Cr).

Persistent high: baseline in Q4 (≥39.33 μg/mmol Cr) and follow-up in Q4 (≥51.52 μg/mmol Cr).

* P <0.05. [#] Comparisons among 3-years follow-up study population. [$] Comparisons between 3-years follow-up and baseline study population.

Supplementary Table 2. The cross-sectional and longitudinal associations between urinary zinc levels and restrictive or obstructive ventilatory impairment

	Restrictive ventilatory impairment			Obstructive ventilatory impairment		
	n (%)	Crude OR or HR (95% CI) ###	Adjusted OR or HR (95% CI) ###	n (%)	Crude OR or HR (95% CI) ###	Adjusted OR or HR (95% CI) ###
Cross-sectional #	1271/3917 (32.4)	1.40(1.26, 1.56)*	1.20(1.07, 1.34)*	71/3917 (1.8)	0.84(0.58, 1.21)	0.75(0.50, 1.13)
Longitudinal $						
Persistent low	5/139 (3.6) ##	Ref	reference	5/192 (2.6) $$	Ref	Ref
Persistent moderate	36/374 (9.6) ##	2.68(1.05, 6.82) ## *	1.99(0.69, 5.76) ##	14/507 (2.8) $$	1.06(0.38, 2.94) $$	0.70(0.24, 2.04) $$
Persistent high	14/135 (10.4) ##	2.88(1.04, 8.00) ## *	1.96(0.61, 6.28) ##	6/192 (3.1) $$	1.20(0.37, 3.93) $$	0.86(0.24, 3.05) $$
Inconsistent	50/748 (6.7) ##	1.86(0.74, 4.66) ##	1.23(0.43, 3.48) ##	30/1001 (3.0) $$	1.15(0.45, 2.97) $$	0.89(0.34, 2.34) $$

HR, hazard ratio; OR, odds ratio.

Adjusted models included age (continuous, years), gender (male/female), height (continuous, cm), weight (continuous, kg), heart disease (yes/no), physical activity (yes/no), smoking amount (continuous, pack-years), passive smoking amount (continuous, hours/week-years), alcohol consumption (continuous, times/week-years), food frequency (continuous, times/month), occupational dust exposure (yes/no), cooking meals at home (yes/no), traffic exposure time (minutes/day), and community (Wuhan/Zhuhai) as covariates.

Cross-sectional analyses were conducted among 3917 participants using linear mixed model with community as a random effect.

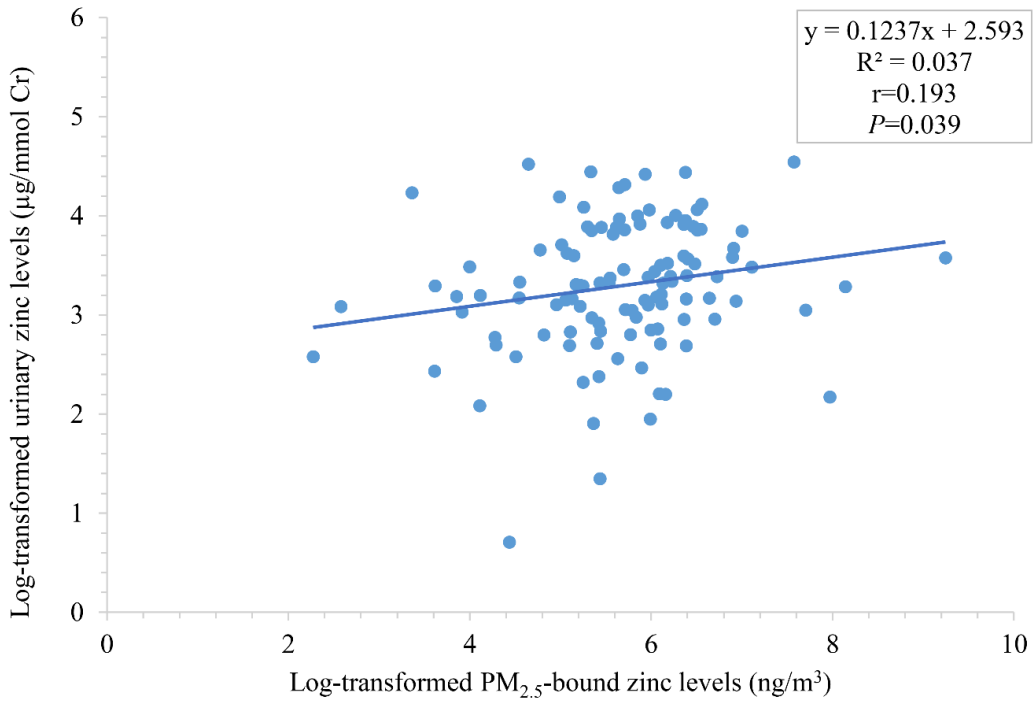
$ Longitudinal analysis conducted among 1946 participants with 3-year follow-up and repeated urinary zinc measurements using COX regression model.

Excluded participants with restrictive ventilatory impairment (FVC <80% predicted and FEV1/FVC ≥70%) at baseline.

$$ Excluded participants with obstructive ventilatory impairment (FEV1/FVC <70%) at baseline.

OR for cross-sectional analyses, and HR for longitudinal analyses.

* P <0.05.



Supplementary Figure 2. Partial Pearson correlation between log-transformed $PM_{2.5}$-bound zinc levels and log-transformed urinary zinc levels in the panel group.
The model was adjusted for age (continuous, years), gender (male/female), height (continuous, cm), weight (continuous, kg), smoking amount (continuous, pack-years), cooking meals at home (yes/no), traffic exposure time (minutes/day), and community (Wuhan/Zhuhai).