Preplanned Studies

A Prospective Cohort Study of Antimony Exposure and Cognitive Impairment in Older Adults — China, 2017–2021

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Summary

What is already known about this topic?

Antimony (Sb) has been identified as a new neurotoxicant that impacts neurological functions in animal studies. However, its effects on the human population remain unknown.

What is added by this report?

The study reveals that there is an association between exposure to Sb and a higher incidence of cognitive impairment in older adults. The dose-response curve demonstrates that the risk of cognitive impairment consistently increased with higher levels of Sb exposure without a discernible threshold.

What are the implications for public health practice?

Reducing exposure to Sb may have a beneficial effect in delaying or preventing the onset of cognitive impairment. This intervention has the potential to significantly decrease the disease burden associated with cognitive impairment, ultimately contributing to social development.

Antimony (Sb) has been identified as a novel neurotoxin that affects neurocognition in previous animal studies. However, there is limited research on the association between Sb exposure and cognitive impairment in humans. Given the increasing aging population, it is crucial to investigate the relationship between Sb and cognitive impairment in older adults. In this study, we utilized data from the Healthy Aging and Biomarkers Cohort Study (HABCS), a prospective cohort study. A total of 1,333 participants aged 65 years and older were recruited in 2017–2018 and followed up in 2020–2021. Blood Sb (B-Sb) and urine Sb (U-Sb) concentrations were measured using inductively coupled plasma mass spectrometry. Cognitive function was assessed using the validated Mini-Mental State Examination. During the follow-up period of 4,972.1 person-years, 241 cases of cognitive impairments were recorded. Cox regression models, adjusted for potential covariates, showed that the risk of cognitive impairment increased by 56.5% for each e-fold increase in U-Sb. Similar results were observed for B-Sb, with a 52.3% increase in the risk of cognitive impairment for each e-fold increase. Our findings suggest that reducing Sb exposure may help mitigate the burden of cognitive impairment, particularly in regions with high Sb pollution.

The participants were selected from the HABCS study (*1*), which was conducted in nine regions known for longevity between 2017 and 2018. Follow-up of participants took place between 2020 and 2021. Detailed information about the nine longevity regions can be found in the Supplementary Material (available at https://weekly.chinacdc.cn/). A total of 3,016 participants were initially recruited, but after excluding those under 65 years old, individuals without blood or urine Sb information, those with missing data on cognitive function, and those who were lost to follow-up or died, a final sample size of 1,333 participants was included (Supplementary Figure S1 and Supplementary Material, available at https://weekly.chinacdc.cn/). Cognitive function was assessed using the Chinese version of the Mini-Mental State Examination (MMSE). Participants completed a face-to-face interview involving 24 items on the MMSE questionnaire, with a maximum score of 30. Cognitive impairment was defined as follows: uneducated individuals with an MMSE score of less than 18, individuals with 1–6 years of education and an MMSE score of less than 20, and individuals with 6 or more years of education and an MMSE score of less than 24 (*2*). Furthermore, standardized questionnaires were used to collect sociodemographic characteristics, frequency of food consumption, and health-related information. Information on exposure to Sb and other metals was obtained through biological sample collection. Please refer to the supplementary material for details on Sb detection and covariate definitions

(Supplementary Table S1 and Supplementary Material, available at https://weekly.chinacdc.cn/). Ethical approval for the study was obtained from the Ethics Review Committee of the National Institute of Environmental Health, Chinese Center for Disease Control and Prevention (No. 2017018).

The study participants were divided into two groups based on their cognitive function. Continuous variables with a normal distribution were presented as mean±standard deviation (SD), while those with a skewed distribution were described as median (P_{25}–P_{75}). The t-test or rank sum test was used to analyze continuous variables, while categorical variables were described as frequencies (percentages) and analyzed using the χ^2-test. A correlation map was used to represent the relationship between the independent variable and the covariable. A strong correlation was defined as |r|>0.7, indicating the possibility of multicollinearity. However, no statistically significant correlations were observed between variables in the correlation map (Supplementary Figure S2, available at https://weekly.chinacdc.cn/). The associations between Sb exposure and the incidence of cognitive impairment were assessed using Cox proportional hazard models. The survival time for participants was calculated from the baseline survey to either the date of cognitive impairment or the end of the survey. Sb exposure levels were modeled as continuous variables using ln-transformed values or categorical variables stratified by high, medium, and low concentrations. Please refer to the Supplementary Material for specific methods used to divide concentration categories. To ensure the accuracy of the study, covariates were included in the Cox proportional hazard models. More details about the models can be found in the eMethods section in the Supplementary Material. The association between Sb exposure and cognitive function was flexibly modeled using restricted cubic splines (RCS). Subgroup analysis was conducted to explore the effects of the association in different populations, and sensitivity analysis was performed to assess the robustness of the observations. Additional information can be found in the supplementary materials. All statistical tests were two-tailed, and P values <0.05 were considered statistically significant. Statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, USA).

A total of 1,333 participants were enrolled in the study from 2020 to 2021, with an average follow-up duration of 3.73±0.21 years. Among these participants, 1,092 (81.9%) had normal cognitive function, while 241 (18.1%) had cognitive impairment. The median (P_{25}–P_{75}) levels of B-Sb and U-Sb exposure were 2.98 (2.45–3.72) μg/L and 0.05 (0.05–0.19) μg/L, respectively (Supplementary Table S2, available at https://weekly.chinacdc.cn/).

After controlling for all covariates, we observed that the risk of cognitive impairment increased by 56.5% with each e-fold increase in U-Sb [hazard ratio (*HR*)=1.565, 95% confidence interval (*CI*): 1.230, 1.991]. Compared to the low U-Sb group, the *HR* (95% *CI*) for cognitive impairment in the high U-Sb group was 2.456 (1.536, 3.927) (Table 1, Model 4). The non-linear relationship between U-Sb and the risk of cognitive impairment in older adults was confirmed by restricted cubic spline analysis ($P_{nonlinear}$<0.05) (Figure 1A). Furthermore, the risk of cognitive impairment in older adults increased linearly with B-Sb exposure, with a 52.3% increased risk for each e-fold increase in B-Sb (*HR*=1.523, 95% *CI*: 1.100, 2.109) (Figure 1B, Table 1).

In the subgroup analysis, we observed a stronger impact of Sb exposure on cognitive impairment in individuals aged 65–79 years, men, and individuals who consume alcohol. Among smokers, the effect of U-Sb on cognitive impairment was higher compared to non-smokers. We found a significant interaction effect between B-Sb and sex, but no significant interactions were observed between age, cigarette smoking, alcohol drinking, and Sb exposure (Table 2). The results of four sensitivity analyses further supported the robustness of our findings (Supplementary Tables S3–S6, available at https://weekly.chinacdc.cn/).

DISCUSSION

To the best of our knowledge, this study represents the first attempt to examine the impact of Sb exposure on cognitive impairment in older adults in China. Using data from the HABCS, a 3-year prospective cohort study, we identified a significant association between Sb exposure and an elevated risk of cognitive impairment.

Previous epidemiological studies have not extensively examined the association between Sb exposure and cognition in older adults. One cross-sectional study (n=631) conducted using National Health and Nutrition Examination Survey (NHANES) data found a non-linear relationship between U-Sb and cognitive function in older adults. Lower doses of U-Sb were associated with better cognitive function, while higher

TABLE 1. Association of antimony with cognitive impairment among Chinese older adults from 2017 to 2021.

Antimony	*HR* (95% *CI*)				
	Crude model	Model 1	Model 2	Model 3	Model 4
Ln-transformed B-Sb[§]	1.189 (0.906, 1.559)	1.179 (0.866, 1.605)	1.121 (0.830, 1.515)	1.235 (0.865, 1.765)	1.523 (1.100, 2.109)*
Categorical by concentration					
Low group	1.000 reference	1.000 reference	1.000 reference	1.000 reference	1.000 reference
Medium group	1.086 (0.789, 1.496)	1.045 (0.752, 1.451)	1.031 (0.735, 1.447)	1.128 (0.788, 1.613)	1.183 (0.822, 1.704)
High group	1.229 (0.891, 1.694)	1.239 (0.890, 1.726)	1.140 (0.810, 1.604)	1.213 (0.844, 1.745)	1.300 (0.890, 1.899)
P for trend	0.209	0.204	0.452	0.296	0.174
Ln-transformed U-Sb[¶]	1.323 (1.127, 1.553)†	1.312 (1.100, 1.565)†	1.309 (1.084, 1.580)†	1.353 (1.105, 1.658)†	1.565 (1.230, 1.991)†
Categorical by concentration					
Low group	1.000 reference	1.000 reference	1.000 reference	1.000 reference	1.000 reference
Medium group	1.476 (1.060, 2.056)*	1.392 (0.970, 1.996)	1.363 (0.932, 1.993)	1.495 (0.989, 2.259)	1.403 (0.913, 2.156)
High group	1.683 (1.216, 2.330)†	1.774 (1.238, 2.542)†	1.708 (1.173, 2.488)†	1.874 (1.243, 2.825)†	2.456 (1.536, 3.927)†
P for trend	<0.001	0.002	0.005	0.002	<0.001

Abbreviation: B-Sb=blood antimony; U-Sb=urine antimony; *HR*=hazard ratio; *CI*=confidence interval.

* Denotes statistical significance at $P<0.05$.

† Denotes statistical significance at $P<0.01$.

§ low group (0.04≤B-Sb≤2.45 μg/L), medium group (2.45<B-Sb≤2.98 μg/L), high group (2.98<B-Sb≤3.72 μg/L); Model 1 was adjusted for age, sex, ethnicity, marriage status, and residence; Model 2 was further adjusted for cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts; Model 3 was further adjusted for BMI, CVD, hypertension, diabetes and CKD; Model 4 was further adjusted for blood As, blood Cd, blood Se, blood Hg, blood Pb and blood Mn.

¶ low group (U-Sb≤0.05 μg/L), medium group (0.05<U-Sb≤0.19 μg/L), high group (0.19<U-Sb≤2.17 μg/L); Model 1 was adjusted for urine creatinine, age, sex, ethnicity, marriage status, and residence; Model 2 was further adjusted for cigarette smoking, alcohol drinking, and the consumption of fruit, fish, milk, and nuts; Model 3 was further adjusted for BMI, CVD, hypertension, diabetes and CKD; Model 4 was further adjusted for urine As, urine Cd, urine Se, urine Hg, urine Pb and urine Mn.

doses may be linked to cognitive impairment (*3*). In contrast, our study is a larger cohort study that considers other cognition-related metals as covariates, in line with previous literature. A 5-year cohort study in Portuguese older adults found no association between Sb levels in fingernails and cognitive decline (*4*). However, the inconsistent findings may be due to the small sample size and different exposure assessment methods. Another case-control study reported higher B-Sb levels in the healthy group compared to the dementia group, suggesting a potential protective effect of Sb on cognitive function (*5*). Differences in study design and adjustments for covariates may explain the inconsistencies between studies. Animal studies support our findings. Tanu et al. demonstrated the toxic effect of Sb on memory changes in mice (*6*). Xu et al. assessed the risk of Sb-associated dementia (AD) and found that Sb contributed to amyloid-beta accumulation and hyperphosphorylation of tau protein in the mouse brain, indicating an association between Sb exposure and AD risk (*7*). Although the exact cellular and molecular mechanisms of Sb-related neurotoxicity remain unclear, there is evidence suggesting that Sb can damage cognitive function. For instance, Sb inhibits protein kinase B (Akt), which leads to abnormal activation of the Wnt/β-catenin pathway, causing neuronal apoptosis and neurotoxicity (*8*). Additionally, Sb induces autophagic cell death by suppressing the Akt/mammalian target of the rapamycin (mTOR) pathway through reactive oxygen species, resulting in cognitive impairment (*9*).

Subgroup analysis revealed a stronger association between Sb exposure and cognitive impairment in men compared to women. This difference in association may be attributed to variations in lifestyle factors, such as higher rates of smoking and alcohol consumption among men, which increase their likelihood of Sb exposure.

There are several limitations in this study. First, the findings of our study may not be generalized to the general population as our research participants consisted exclusively of older adults. Second, the follow-up period of this study was limited to three years, which necessitates further investigation through long-term observational studies to establish a causal relationship between Sb and cognitive impairment. Third, there may be incomplete or inaccurate data regarding the collected covariates. For instance, information on smoking, drinking, diabetes, and cardiovascular disease relied on self-reporting, which

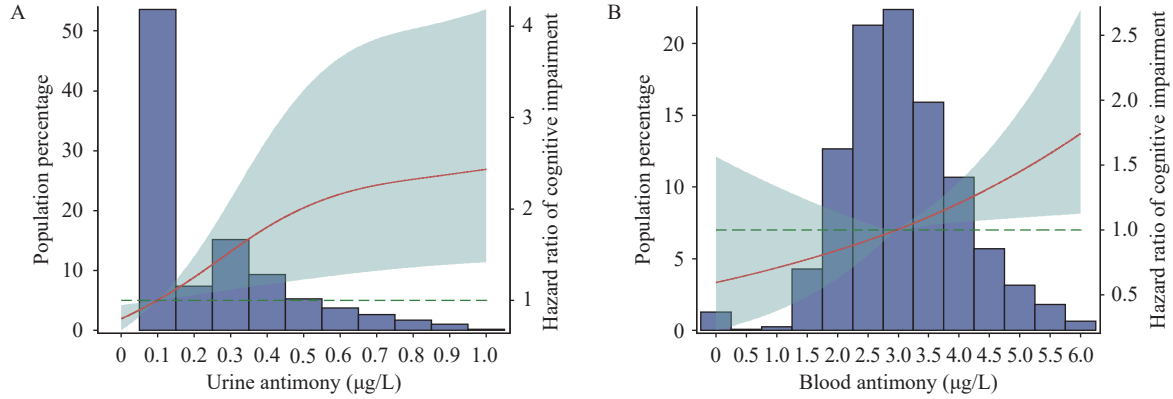

FIGURE 1. Association of antimony with cognitive impairment among Chinese older adults from 2017 to 2021 in Cox models with restricted cubic spline. (A) the dose-response relationship between urine antimony levels and cognitive impairment; (B) the dose-response relationship between blood antimony levels and cognitive impairment.
Note: In Figure 1A, the plot contains three knots located at the 50th, 75th, and 95th centiles; the red line represents the estimated effect of urine antimony on the risk of cognitive impairment, while the green areas indicate the corresponding 95% confidence interval; the effect estimates were adjusted for several covariates, including urine creatinine, age, sex, ethnicity, marital status, residence, cigarette smoking, alcohol drinking, dietary intake of fruit, fish, milk, and nuts, BMI, CVD, hypertension, diabetes, CKD, urine As, urine Cd, urine Se, urine Hg, urine Pb, and urine Mn. In Figure 1B, three knots were observed at the 25th, 50th, and 75th centiles; the estimated effect of blood antimony on the risk of cognitive impairment in older adults is represented by the red line, while the green areas indicate the 95% confidence interval; Adjusted covariates include age, sex, ethnicity, marital status, place of residence, cigarette smoking, alcohol drinking, fruit, fish, milk, and nuts, BMI, CVD, hypertension, diabetes, CKD, blood As, blood Cd, blood Se, blood Hg, blood Pb, and blood Mn.

TABLE 2. Association of antimony with cognitive impairment among Chinese older adults in selected population subgroups from 2017 to 2021.

Subgroup	Ln-transformed B-Sb (*HR*, 95% *CI*)[§]	$P_{interaction}$	Ln-transformed U-Sb (*HR*, 95% *CI*)	$P_{interaction}$
Age, years		0.433		0.072
65–79 (*n*=759)	2.577 (1.235, 5.377)*		1.859 (1.106, 3.125)*	
≥80 (*n*=574)	1.242 (0.829, 1.861)		1.557 (1.174, 2.064)†	
Sex		0.048		0.666
Men (*n*=703)	2.458 (1.416, 4.267)†		1.733 (1.243, 2.416)†	
Women (*n*=630)	1.041 (0.681, 1.592)		1.293 (0.899, 1.860)	
Cigarette smoking		0.375		0.175
Smoker (*n*=423)	2.015 (0.974, 4.169)		2.099 (1.345, 3.278)†	
Non-smoker (*n*=904)	1.445 (0.972, 2.147)		1.536 (1.116, 2.116)†	
Alcohol drinking		0.123		0.653
Drinker (*n*=390)	2.705 (1.075, 6.807)*		1.891 (1.145, 3.123)*	
Non-drinker (*n*=934)	1.346 (0.964, 1.881)		1.431 (1.046, 1.957)*	

Abbreviation: B-Sb=blood antimony; U-Sb=urine antimony; *HR*=hazard ratio; *CI*=confidence interval.
* Denotes statistical significance at $P<0.05$.
† Denotes statistical significance at $P<0.01$.
§ Model was adjusted for age, sex, ethnicity, marriage status, residence, cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts, BMI, CVD, hypertension, diabetes, CKD, blood As, blood Cd, blood Se, blood Hg, blood Pb, and blood Mn.
¶ Model was adjusted for urine creatinine, age, sex, ethnicity, marriage status, residence, cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts, BMI, CVD, hypertension, diabetes, CKD, urine As, urine Cd, urine Se, urine Hg, urine Pb, and urine Mn.

may be subject to recall bias. Additionally, although oxidative stress and psychological stress could potentially act as confounding factors, our study did not measure these indicators. Lastly, the loss of follow-up bias is an unavoidable limitation in this study.

In conclusion, our study findings from a prospective cohort of older adults in China reveal a significant association between Sb exposure and an increased risk

of cognitive impairment, particularly in men. This suggests that Sb may act as a novel neurotoxicant, adversely affecting the neurocognitive function of older individuals. Food, particularly seafood and dairy products, is considered the primary source of Sb intake among the population (*10*). Therefore, reducing Sb exposure could potentially delay or prevent the onset of cognitive impairment in older adults. Future research should include longer follow-up studies to provide a more comprehensive understanding of the relationship between Sb exposure and cognition, allowing for a better exploration of causality.

Conflicts of interest: Xiaoming Shi is a editorial board member of the journal China CDC Weekly. He was not involved in the peer-review or handling of the manuscript. The authors have no other competing interests to disclose.

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SUPPLEMENTARY MATERIAL

eMethods

Information on the Nine Longevity Regions of HABCS in 2017–2018

The nine regions mentioned are as follows: Laizhou City in Shandong Province, Zhongxiang City in Hubei Province, Mayang County in Hunan Province, Rudong County in Jiangsu Province, Sanshui District in Guangdong Province, Yongfu County in Guangxi Autonomous Region, Chengmai County in Hainan Province, Dujiangyan City in Sichuan Province, and Xiayi County in Henan Province.

Sample Size

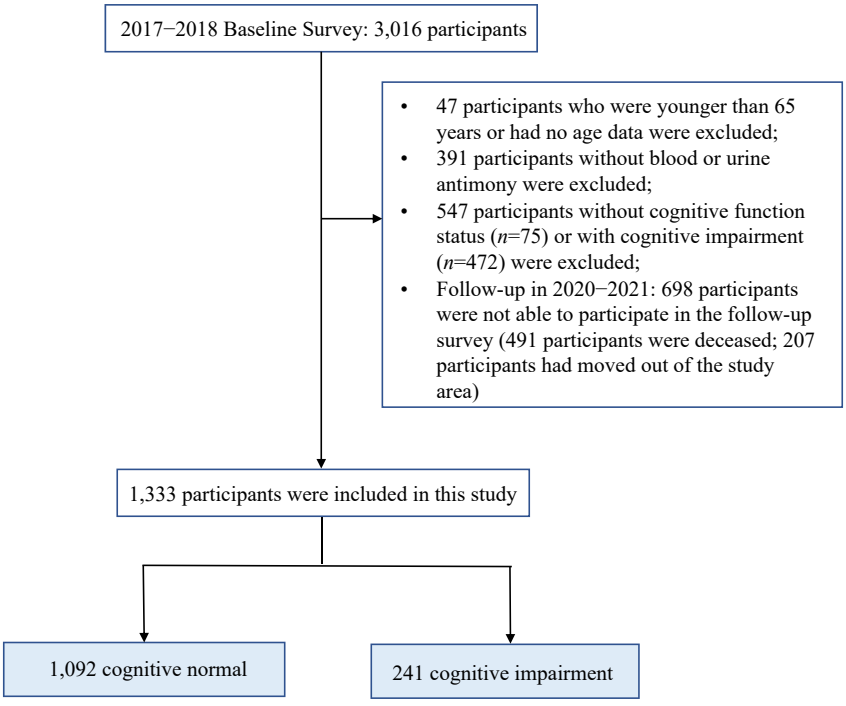
According to the previous cohort study conducted on older adults, the incidence of cognitive impairment over a span of 3 years was approximately 13.5%. The required sample size for the upcoming prospective cohort study was determined as follows:

$$n = \frac{\left(Z_{\alpha/2}\sqrt{2\bar{p}\bar{q}} + Z_{\beta}\sqrt{p_0 q_0 + p_1 q_1}\right)^2}{\left(p_1 - p_0\right)^2} \quad (1)$$

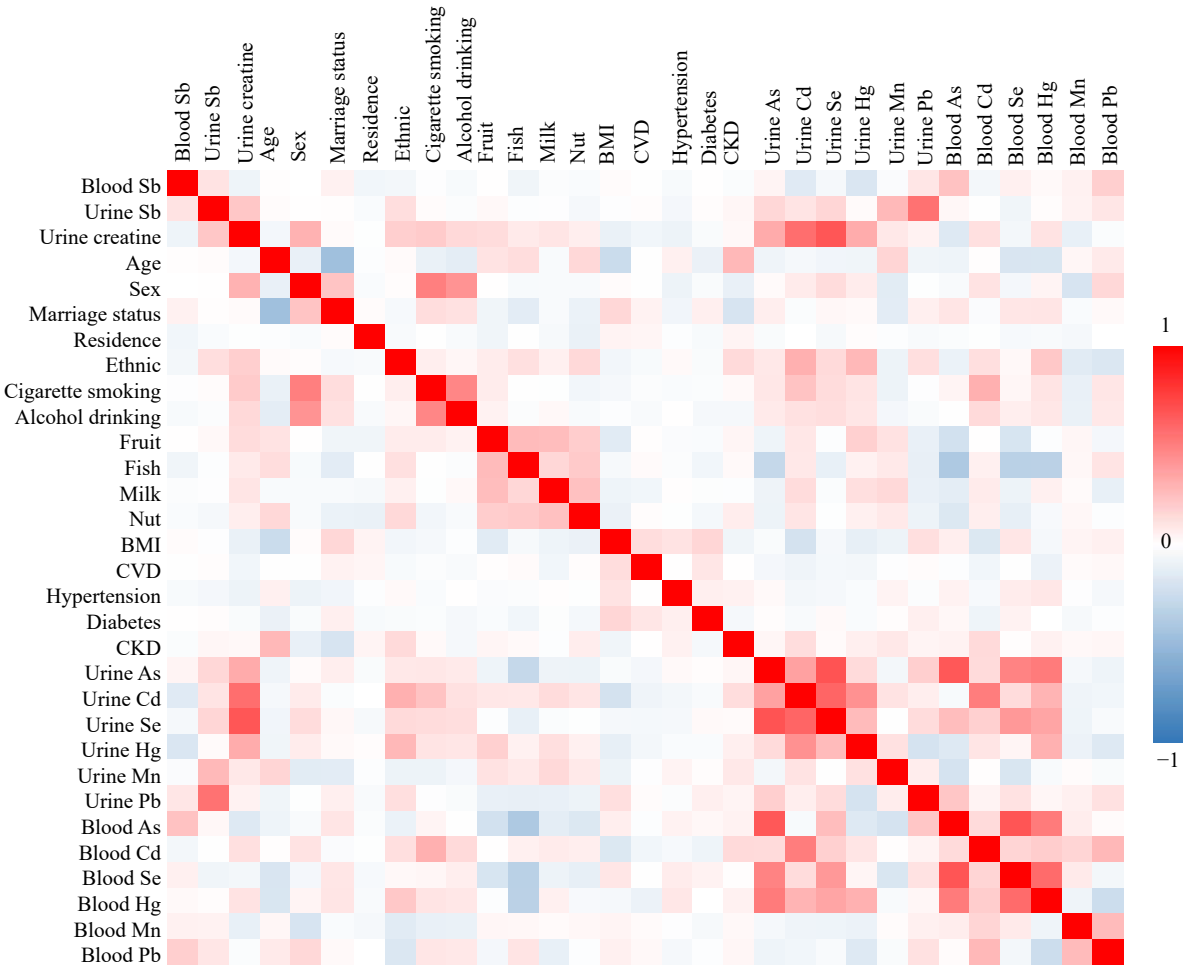
p_0=0.135, q_0=0.865, α=0.05 (bilateral), β=0.10, $Z_{\alpha/2}$=1.960, Z_{β}=1.282. According to existing studies, the *OR* value between Sb exposure and cognitive impairment is estimated to be 0.402 (*1*), $p_1=OR\times p_0\approx 0.054$, $q_1=1-p_1\approx 0.946$. $\bar{p}=(p_1+p_0)/2\approx 0.095$, $\bar{q}=1-\bar{p}=0.905$, substituting into the above formula, the maximum required sample n≈273. Considering a 20% loss of follow-up and death, the total sample size required for prospective cohort studies was 273/(1−20%)×2≈683. This study plans to include 1,333 participants who are adults aged 65 years and older with normal baseline cognitive function. This sample size meets the estimated requirements.

Measurement of Antimony and Other Metals

Antimony and other metals were obtained from blood and urine samples collected from participants at baseline to assess their prior exposure. A trained phlebotomist collected 1 mL of blood with heparin and 4.5 mL of urine in the early morning after a fasting period of at least 12 hours. Blood and urine metal concentrations were measured using



SUPPLEMENTARY FIGURE S1. Flow chart depicting the inclusion of 1,333 participants from HABCS (2017–2021).



SUPPLEMENTARY FIGURE S2. Correlation map of independent variables and covariates among 1,333 Chinese older adults. Note: The values represent the coefficients obtained from Spearman's rank correlation analysis conducted among the covariates.

0.5 mL of blood and 1 mL of urine. For the analysis, 0.5 mL of blood was diluted with a 0.1% nitric acid and 0.01% Triton X-100 solution, while 1 mL of urine was diluted with a 1% nitric acid solution. The metal levels in the resulting supernatants were analyzed using centrifugal inductively coupled plasma mass spectrometry (ICP-MS). The LOD for blood antimony (B-Sb) was 0.07 μg/L, and for urine antimony (U-Sb), it was 0.10 μg/L. The LODs for other metals are provided in Supplementary Table S1. In this study, 1.23% of participants had B-Sb concentrations lower than the LOD, and 51.61% had U-Sb concentrations lower than the LOD. For Sb concentrations below the LODs, the concentrations were considered as half of the LOD.

High, Medium and Low Definition of Sb Exposure Concentration

We categorized the participants into three groups based on their B-Sb levels: tertile 1 (low group) with B-Sb levels ranging from 0.04 to 2.45 μg/L (reference), tertile 2 (medium group) with B-Sb levels ranging from 2.45 to 2.98 μg/L, and tertile 3 (high group) with B-Sb levels ranging from 2.98 to 3.72 μg/L. Since 51.38% of the U-Sb participants had values below the limit of detection (LOD), we considered these participants as the low group with U-Sb levels of 0.05 μg/L or below (reference). The remaining participants were divided into the medium group with U-Sb levels ranging from 0.05 to 0.19 μg/L and the high group with U-Sb levels ranging from 0.19 to 2.17 μg/L, using the P_{75} dividing line.

Covariate Collection and Definitions

The interviewers received formal training and used standardized questionnaires to collect data on

SUPPLEMENTARY TABLE S1. The limit of detections for other metals.

Metals	Limit of detections (μg/L)
Blood arsenic	0.40
Blood cadmium	0.07
Blood selenium	1.20
Blood mercury	0.20
Blood manganese	0.40
Blood lead	0.20
Urine arsenic	0.20
Urine cadmium	0.06
Urine selenium	1.10
Urine mercury	0.04
Urine manganese	0.20
Urine lead	0.10

sociodemographic characteristics, food consumption frequency, health characteristics, and metal exposure. Sociodemographic characteristics encompassed age, sex (men or women), ethnicity (Han or ethnic minorities), marital status (married or unmarried), and residence (urban or rural). Food consumption frequencies were documented for various items such as fruit, fish, milk, and nuts, with options ranging from almost every day to rarely or never. Health characteristics included urine creatine levels, cigarette smoking (yes or no), alcohol drinking (yes or no), body mass index (BMI), self-reported cardiovascular disease (yes or no), hypertension, self-reported diabetes (yes or no), and chronic kidney disease (CKD). BMI was categorized into four groups: underweight (<18.5 kg/m^2), normal weight (18.5–24.0 kg/m^2), overweight (24.0–28.0 kg/m^2), and obese (≥28.0 kg/m^2). BMI was calculated by dividing weight (kg) by the square of height (m^2). Hypertension was defined as diastolic blood pressure measurements exceeding 90 mmHg and/or systolic blood pressure measurements exceeding 140 mmHg, or a diagnosis of hypertension given by a physician or healthcare provider. CKD was defined by an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 or the presence of proteinuria.

Cox Proportional Hazard Models for Blood Antimony and Urine Antimony

Blood Antimony: the crude model did not adjust for any covariates. Model 1 was adjusted for age, sex, ethnicity, marital status, and residence. Model 2 further adjusted for cigarette smoking, alcohol consumption, and dietary factors including fruit, fish, milk, and nut intake. Model 3 additionally adjusted for BMI and the presence of comorbidities such as CVD, hypertension, diabetes, and CKD. Finally, model 4 accounted for potential confounding factors by adding adjustments for blood As, blood Cd, blood Se, blood Hg, blood Pb, and blood Mn.

Urine Antimony: the crude model did not adjust for any covariates. Model 1 included adjustments for urine creatinine, age, sex, ethnicity, marital status, and residence. Model 2 further adjusted for factors such as cigarette smoking, alcohol consumption, and the intake of fruit, fish, milk, and nuts. Model 3 additionally adjusted for BMI, CVD, hypertension, diabetes, and CKD. Lastly, model 4 further adjusted for urine As, urine Cd, urine Se, urine Hg, urine Pb, and urine Mn.

Subgroup Analysis

A subgroup analysis was performed to examine the potential impact of age (65–79 years old *vs.* ≥80 years old), sex (men *vs.* women), cigarette smoking (smoker *vs.* non-smoker), and alcohol drinking (drinker *vs.* non-drinker) on the outcomes. Multiplicative interaction effects were calculated.

Sensitivity Analysis

Four additional sensitivity analyses were conducted to evaluate the robustness of our study findings. First, participants with two or more chronic diseases were excluded from the analysis due to their higher likelihood of experiencing cognitive impairment. Second, given that our study participants consisted of older adults, with over

SUPPLEMENTARY TABLE S2. Characteristics of 1,333 study participants described by cognitive functioning status at baseline.

Characteristics	Normal cognitive function (*N*=1,092)	Cognitive impairment (*N*=241)	Total (*N*=1,333)	*P* value
Age, mean±SD, years	77.2±8.1	86.4±9.4	78.9±9.1	<0.001
Sex, *n* (%)				0.004
Women	496 (45.4)	134 (55.6)	630 (47.3)	
Men	596 (54.6)	107 (44.4)	703 (52.7)	
Rural, *n* (%)	1,057 (97.6)	237 (98.8)	1,294 (97.8)	0.271
Married, *n* (%)	728 (67.2)	98 (41.4)	826 (62.6)	<0.001
Han, *n* (%)	945 (92.0)	198 (83.9)	1,143 (90.5)	<0.001
Cigarette smoking, *n* (%)	357 (32.8)	66 (27.5)	423 (31.9)	0.108
Alcohol drinking, *n* (%)	339 (31.2)	51 (21.3)	390 (29.5)	0.002
Frequency of fruit consumption, *n* (%)				0.049
Almost everyday	210 (19.3)	33 (13.8)	243 (18.3)	
Quite often	327 (30.1)	66 (27.6)	393 (29.6)	
Occasionally	366 (33.7)	85 (35.6)	451 (34.0)	
Rarely or never	184 (16.9)	55 (23.0)	239 (18.0)	
Frequency of fish consumption, *n* (%)				0.019
Almost everyday	87 (8.0)	7 (2.9)	94 (7.1)	
Not every day, but at least weekly	473 (43.5)	96 (39.8)	569 (42.8)	
Not every week, but at least monthly	253 (23.3)	60 (24.9)	313 (23.6)	
Not every month, but occasionally	150 (13.8)	42 (17.4)	192 (14.4)	
Rarely or never	125 (11.5)	36 (14.9)	161 (12.1)	
Frequency of milk consumption, *n* (%)				0.609
Almost everyday	167 (15.3)	33 (13.7)	200 (15.0)	
Not every day, but at least weekly	146 (13.4)	40 (16.6)	186 (14.0)	
Not every week, but at least monthly	112 (10.3)	21 (8.7)	133 (10.0)	
Not every month, but occasionally	147 (13.5)	29 (12.0)	176 (13.2)	
Rarely or never	516 (47.4)	118 (49.0)	634 (47.7)	
Frequency of nut consumption, *n* (%)				<0.001
Almost everyday	64 (5.9)	5 (2.1)	69 (5.2)	
Not every day, but at least weekly	138 (12.7)	26 (10.8)	164 (12.3)	
Not every week, but at least monthly	144 (13.2)	18 (7.5)	162 (12.2)	
Not every month, but occasionally	182 (16.7)	33 (13.8)	215 (16.2)	
Rarely or never	560 (51.5)	158 (65.8)	718 (54.1)	
BMI, *n* (%)				<0.001
Underweight	90 (8.3)	35 (14.9)	125 (9.5)	
Normal weight	527 (48.8)	136 (57.9)	663 (50.4)	
Overweight	353 (32.7)	46 (19.6)	399 (30.3)	
Obesity	110 (10.2)	18 (7.7)	128 (9.7)	
CVD, *n* (%)	192 (17.7)	35 (14.6)	227 (17.1)	0.247
Hypertension, *n* (%)	770 (71.0)	171 (72.8)	941 (71.3)	0.594
Diabetes, *n* (%)	64 (5.9)	8 (3.4)	72 (5.5)	0.121
CKD, *n* (%)	214 (20.2)	73 (31.6)	287 (22.2)	<0.001
Blood Sb, median (P_{25}–P_{75}), μg/L	2.97 (2.46–3.73)	3.01 (2.43–3.68)	2.98 (2.45–3.72)	0.479

Continued

Characteristics	Normal cognitive function (*N*=1,092)	Cognitive impairment (*N*=241)	Total (*N*=1,333)	*P* value
Blood As, median (P_{25}–P_{75}), μg/L	1.70 (0.87–4.90)	1.07 (0.63–2.36)	1.51 (0.80–4.45)	0.001
Blood Cd, median (P_{25}–P_{75}), μg/L	1.31 (0.69–2.89)	1.19 (0.62–2.33)	1.28 (0.68–2.86)	0.014
Blood Se, median (P_{25}–P_{75}), μg/L	112.79 (91.37–139.50)	96.53 (79.74–121.55)	109.38 (88.32–135.37)	<0.001
Blood Hg, median (P_{25}–P_{75}), μg/L	1.72 (0.77–2.93)	1.21 (0.31–2.37)	1.61 (0.72–2.87)	<0.001
Blood Pb, median (P_{25}–P_{75}), μg/L	33.88 (23.19–55.94)	34.27 (22.07–59.53)	33.97 (23.00–56.12)	0.886
Blood Mn, median (P_{25}–P_{75}), μg/L	10.56 (8.45–13.22)	10.42 (8.73–12.94)	10.53 (8.49–13.19)	0.635
Urine Sb, median (P_{25}–P_{75}), μg/L	0.05 (0.05–0.18)	0.11 (0.05–0.20)	0.05 (0.05–0.19)	0.248
Urine As, median (P_{25}–P_{75}), μg/L	35.29 (17.67–78.04)	26.94 (14.26–53.63)	33.44 (16.83–72.26)	0.017
Urine Cd, median (P_{25}–P_{75}), μg/L	0.95 (0.49–1.92)	0.75 (0.42–1.99)	0.91 (0.48–1.94)	0.604
Urine Se, median (P_{25}–P_{75}), μg/L	18.37 (10.77–29.51)	15.37 (9.50–23.61)	18.02 (10.45–27.88)	0.012
Urine Hg, median (P_{25}–P_{75}), μg/L	0.32 (0.06–0.82)	0.36 (0.02–0.81)	0.33 (0.05–0.81)	0.663
Urine Pb, median (P_{25}–P_{75}), μg/L	6.89 (3.10–14.68)	6.42 (3.00–11.56)	6.69 (3.05–14.31)	0.113
Urine Mn, median (P_{25}–P_{75}), μg/L	0.51 (0.10–1.16)	0.83 (0.36–1.94)	0.55 (0.10–1.24)	0.057
Urine creatine, median (P_{25}–P_{75}), mg/dL	0.88 (0.55–1.27)	0.85 (0.57–1.33)	0.87 (0.55–1.28)	0.644

Note: Data were presented as the frequency (percentage) for categorical variables, and mean±SD for age, the metal concentrations, and urine creatine are expressed in terms of median (P_{25}–P_{75}).
Abbreviation: BMI=body mass index; Sb=antimony; As=arsenic; Cd=cadmium; Se=selenium; Hg=mercury; Pb=lead; Mn=manganese; SD=standard deviation; IQR=interquartile range.

SUPPLEMENTARY TABLE S3. Sensitivity analysis: Association of antimony with cognitive impairment among Chinese older adults from 2017 to 2021 (Excluding individuals with comorbidities, *n*=940).

Antimony	*HR* (95% *CI*)				
	Crude model	Model 1	Model 2	Model 3	Model 4
Ln-transformed B-Sb[§]	1.373 (0.929, 2.028)	1.686 (1.047, 2.717)*	1.562 (0.987, 2.472)	1.525 (0.963, 2.413)	1.797 (1.193, 2.709)*
Categorical by concentration					
Low group	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference
Medium group	0.829 (0.556, 1.234)	0.915 (0.611, 1.370)	0.953 (0.629, 1.442)	0.998 (0.658, 1.515)	1.085 (0.707, 1.664)
High group	1.178 (0.803, 1.729)	1.483 (1.000, 2.199)*	1.335 (0.893, 1.998)	1.291 (0.857, 1.944)	1.371 (0.897, 2.096)
P for trend	0.421	0.060	0.176	0.236	0.152
Ln-transformed U-Sb[¶]	1.418 (1.168, 1.721)[†]	1.385 (1.114, 1.722)[†]	1.403 (1.109, 1.776)[†]	1.437 (1.129, 1.829)[†]	1.504 (1.138, 1.990)[†]
Categorical by concentration					
Low group	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference
Medium group	1.961 (1.320, 2.915)[†]	1.740 (1.135, 2.666)*	1.590 (1.010, 2.502)*	1.695 (1.064, 2.699)*	1.498 (0.922, 2.434)
High group	1.956 (1.300, 2.942)[†]	1.972 (1.257, 3.094)[†]	1.980 (1.229, 3.189)[†]	2.047 (1.256, 3.337)[†]	2.245 (1.316, 3.830)[†]
P for trend	<0.001	0.002	0.004	0.003	0.003

Abbreviation: B-Sb=blood antimony; U-Sb=urine antimony; *HR*=hazard ratio; *CI*=confidence interval.
* Denotes statistical significance at $P<0.05$;
[†] Denotes statistical significance at $P<0.01$.
[§] low group ($0.04 \leq$ B-Sb ≤ 2.45 μg/L), medium group ($2.45 <$ B-Sb ≤ 2.98 μg/L), high group ($2.98 <$ B-Sb ≤ 3.72 μg/L); Model 1 was adjusted for age, sex, ethnicity, marriage status, and residence; Model 2 was further adjusted for cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts; Model 3 was further adjusted for BMI, CVD, hypertension, diabetes, and CKD; Model 4 was further adjusted for blood As, blood Cd, blood Se, blood Hg, blood Pb, and blood Mn.
[¶] low group (U-Sb ≤ 0.05 μg/L), medium group ($0.05 <$ U-Sb ≤ 0.19 μg/L), high group ($0.19 <$ U-Sb ≤ 2.17 μg/L); Model 1 was adjusted for urine creatinine, age, sex, ethnicity, marriage status, and residence; Model 2 was further adjusted for cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts; Model 3 was further adjusted for BMI, CVD, hypertension, diabetes, and CKD; Model 4 was further adjusted for urine As, urine Cd, urine Se, urine Hg urine Pb, and urine Mn.

SUPPLEMENTARY TABLE S4. Sensitivity analysis: Association of antimony with cognitive impairment (MMSE<18) among Chinese older adults from 2017 to 2021 (*n*=1,491).

Antimony	*HR* (95% *CI*)				
	Crude model	Model 1	Model 2	Model 3	Model 4
Ln-transformed B-Sb[§]	1.393 (0.996, 1.949)	1.325 (0.916, 1.916)	1.314 (0.907, 1.904)	1.334 (0.892, 1.995)	1.535 (1.055, 2.232)*
Categorical by concentration					
Low group	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference
Medium group	0.930 (0.657, 1.316)	0.919 (0.644, 1.312)	0.953 (0.658, 1.380)	1.041 (0.702, 1.544)	1.082 (0.726, 1.613)
High group	1.317 (0.946, 1.835)	1.244 (0.882, 1.756)	1.274 (0.893, 1.816)	1.375 (0.946, 1.998)	1.479 (0.997, 2.195)
P for trend	0.098	0.196	0.172	0.092	0.052
Ln-transformed U-Sb[¶]	1.398 (1.180, 1.657)[†]	1.358 (1.123, 1.641)[†]	1.306 (1.068, 1.597)[†]	1.325 (1.071, 1.640)[†]	1.482 (1.138, 1.929)[†]
Categorical by concentration					
Low group	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference
Medium group	1.374 (0.953, 1.983)	1.206 (0.816, 1.783)	1.127 (0.739, 1.718)	1.356 (0.861, 2.137)	1.306 (0.820, 2.079)
High group	1.885 (1.343, 2.645)[†]	1.866 (1.282, 2.715)[†]	1.708 (1.150, 2.536)[†]	1.796 (1.169, 2.757)[†]	2.162 (1.297, 3.603)[†]
P for trend	<0.001	0.002	0.010	0.007	0.004

Abbreviation: B-Sb=blood antimony; U-Sb=urine antimony; *HR*=hazard ratio; *CI*=confidence interval.
* denotes statistical significance at *P*<0.05.
[†] denotes statistical significance at *P*<0.01.
[§] low group (0.04≤B-Sb≤2.45 μg/L), medium group (2.45<B-Sb≤2.98 μg/L), high group (2.98<B-Sb≤3.72 μg/L); Model 1 was adjusted for age, sex, ethnicity, marriage status, residence, and education; Model 2 was further adjusted for cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts; Model 3 was further adjusted for BMI, CVD, hypertension, diabetes, and CKD; Model 4 was further adjusted for blood As, blood Cd, blood Se, blood Hg, blood Pb, and blood Mn.
[¶] low group (U-Sb≤0.05 μg/L), medium group (0.05<U-Sb≤0.19 μg/L), high group (0.19<U-Sb≤2.17 μg/L); Model 1 was adjusted for urine creatinine, age, sex, ethnicity, marital status, residence, and education. Model 2 was further adjusted for cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts. Model 3 was further adjusted for BMI, CVD, hypertension, diabetes, and CKD. Model 4 was further adjusted for urine As, urine Cd, urine Se, urine Hg, urine Pb, and urine Mn.

SUPPLEMENTARY TABLE S5. Sensitivity analysis: Association of urine antimony with cognitive impairment among Chinese older adults from 2017 to 2021 (excluding individuals below the limit of detection).

Antimony	*HR* (95% *CI*)				
	Crude model	Model 1	Model 2	Model 3	Model 4
Ln-transformed U-Sb	1.157 (0.820, 1.633)	1.149 (0.810, 1.629)	1.179 (0.818, 1.700)	1.110 (0.740, 1.666)	1.515 (0.955, 2.402)
Categorical by concentration					
Tertile 1	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference
Tertile 2	1.573 (0.974, 2.541)	1.535 (0.932, 2.527)	1.783 (1.058, 3.005)*	1.639 (0.941, 2.852)	1.623 (0.919, 2.866)
Tertile 3	1.433 (0.873, 2.353)	1.608 (0.954, 2.711)	1.765 (1.014, 3.073)*	1.680 (0.917, 3.078)	2.790 (1.410, 5.519)[†]
P for trend	0.177	0.078	0.044	0.088	0.003

Note: Model 1 was adjusted for urine creatinine, age, sex, ethnicity, marriage status and residence; Model 2 was further adjusted for cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts; Model 3 was further adjusted for BMI, CVD, hypertension, diabetes and CKD; Model 4 was further adjusted for urine As, urine Cd, urine Se, urine Hg, urine Pb, and urine Mn.
Abbreviation: U-Sb=urine antimony; HR=hazard ratio; *CI*=confidence interval.
* denotes statistical significance at *P*<0.05.
[†] denotes statistical significance at *P*<0.01.

half of them being illiterate, we redefined cognitive impairment by using a different criterion. Specifically, a rrMMSE score ≥18 was considered indicative of normal cognitive function, while an MMSE score <18 denoted cognitive impairment. Third, to address the issue of a substantial proportion of the population having U-Sb levels below the LOD, these individuals were excluded from the analysis, and the analysis focused only on those with U-Sb levels above the LOD. Finally, recognizing that death can act as a competing event for cognitive impairment, a competitive risk model was employed to investigate the relationship between Sb exposure and cognitive impairment.

SUPPLEMENTARY TABLE S6. Sensitivity analysis: Association of antimony with cognitive impairment among Chinese older adults from 2017 to 2021 (using a competitive risk model, *n*=1,824).

Antimony	*HR* (95% *CI*)				
	Crude model	Model 1	Model 2	Model 3	Model 4
Ln-transformed B-Sb[†]	1.058 (0.793, 1.411)	1.028 (0.762, 1.385)	1.001 (0.767, 1.305)	1.075 (0.774, 1.492)	1.157 (0.873, 1.532)
Categorical by concentration					
Low group	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference
Medium group	0.974 (0.714, 1.329)	0.903 (0.657, 1.241)	0.835 (0.603, 1.156)	0.857 (0.607, 1.21)	0.886 (0.623, 1.26)
High group	1.088 (0.799, 1.482)	1.073 (0.777, 1.481)	1.016 (0.734, 1.408)	1.105 (0.782, 1.561)	1.085 (0.753, 1.562)
P for trend	0.599	0.671	0.919	0.578	0.671
Ln-transformed U-Sb[§]	1.164 (1.006, 1.347)*	1.119 (0.955, 1.311)	1.143 (0.958, 1.364)	1.171 (0.966, 1.419)	1.317 (1.053, 1.648)*
Categorical by concentration					
Low group	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference	1.000 Reference
Medium group	1.363 (0.991, 1.873)	1.313 (0.935, 1.844)	1.252 (0.881, 1.78)	1.317 (0.902, 1.925)	1.372 (0.932, 2.018)
High group	1.348 (0.98, 1.856)	1.233 (0.877, 1.733)	1.271 (0.883, 1.829)	1.337 (0.892, 2.005)	1.595 (0.983, 2.588)
P for trend	0.036	0.164	0.164	0.129	0.046

Abbreviation: B-Sb=blood antimony; U-Sb=urine antimony; *HR*=hazard ratio; *CI*=confidence interval.

* Denotes statistical significance at $P<0.05$.

[†] low group ($0.04\leq$B-Sb≤ 2.64 μg/L) ,medium group ($2.64<$B-Sb≤ 3.46 μg/L), high group ($3.46<$B-Sb≤ 13.77 μg/L); Model 1 was adjusted for age, sex, ethnicity, marriage status, residence, and education; Model 2 was further adjusted for cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts; Model 3 was further adjusted for BMI, CVD, hypertension, diabetes, and CKD; Model 4 was further adjusted for blood As, blood Cd, blood Se, blood Hg, blood Pb, and blood Mn.

[§] low group (U-Sb≤ 0.05 μg/L), medium group ($0.05<$U-Sb≤ 0.20 μg/L), high group ($0.20<$U-Sb≤ 2.17 μg/L); Model 1 was adjusted for urine creatinine, age, sex, ethnicity, marriage status, residence, and education; Model 2 was further adjusted for cigarette smoking, alcohol drinking, the consumption of fruit, fish, milk, and nuts; Model 3 was further adjusted for BMI, CVD, hypertension, diabetes, and CKD; Model 4 was further adjusted for urine As, urine Cd, urine Se, urine Hg, urine Pb, and urine Mn.

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