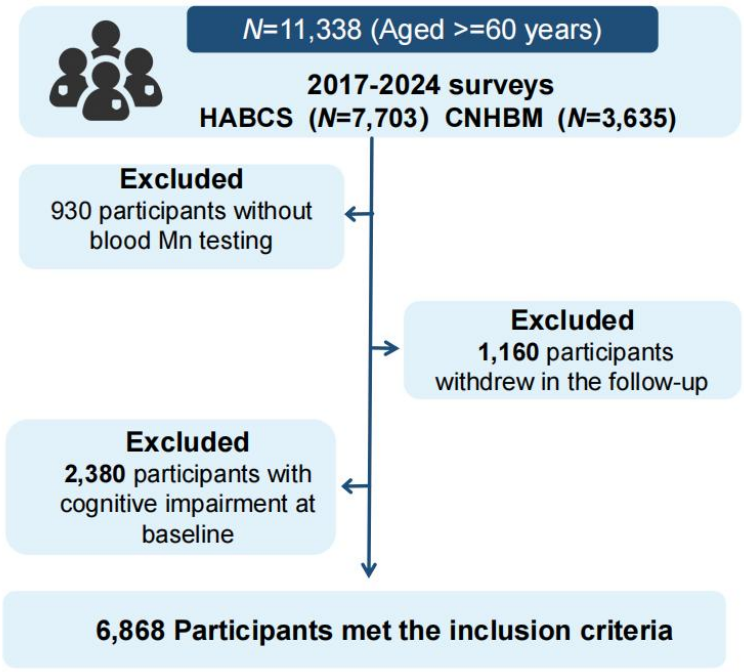


Supplementary Figure S1. Flowchart of participant selection for blood manganese analyses. HABCS, Healthy Ageing and Biomarkers Cohort Study; CNHBM, China National Human Biomonitoring; Mn, manganese; *N*, number of participants.

Supplementary Table S1. Comparison of baseline characteristics between participants included in the final analysis and those excluded due to loss to follow-up

Characteristic	Overall	Exclusion	Inclusion	*P* value
Participants, *n*	8,028	1,160	6,868	
Age, years	76.35 ± 11.84	76.09 ± 13.10	76.39 ± 11.61	0.414
Blood Mn (μg/L)	11.32 ± 3.89	11.47 ± 4.58	11.30 ± 3.76	0.172
MMSE	28.00 (25.00–30.00)	26.00 (26.00–26.00)	28.00 (25.00–30.00)	0.511
Sex				< 0.001
Female	4,121 (51.33%)	681 (58.71%)	3,440 (50.09%)	
Male	3,907 (48.67%)	479 (41.29%)	3,428 (49.91%)	
Residence				< 0.001
Urban	1,958 (24.39%)	496 (42.76%)	1,462 (21.29%)	
Rural	6,070 (75.61%)	664 (57.24%)	5,406 (78.71%)	
Ethnicity				< 0.001
Other	511 (6.37%)	117 (10.09%)	394 (5.74%)	
Han	7,517 (93.63%)	1,043 (89.91%)	6,474 (94.26%)	
Education level				0.005
Illiteracy	3,015 (37.56%)	392 (33.79%)	2,623 (38.19%)	
Educated	5,013 (62.44%)	768 (66.21%)	4,245 (61.81%)	
Marital status				0.432
Unmarried	2,787 (34.72%)	415 (35.78%)	2,372 (34.54%)	
Married	5,241 (65.28%)	745 (64.22%)	4,496 (65.46%)	
Economic level				< 0.001
Poor	1,112 (13.85%)	166 (14.31%)	946 (13.77%)	
Average	5,029 (62.64%)	631 (54.40%)	4,398 (64.04%)	
Rich	1,887 (23.51%)	363 (31.29%)	1,524 (22.19%)	
Body mass index				0.112
Underweight (< 18.5 kg/m²)	640 (7.97%)	104 (8.97%)	536 (7.80%)	
Normal (18.5–23.9 kg/m²)	3,790 (47.21%)	511 (44.05%)	3,279 (47.74%)	
Overweight (24.0–27.9 kg/m²)	2,515 (31.33%)	379 (32.67%)	2,136 (31.10%)	
Obesity (≥ 28.0 kg/m²)	1,083 (13.49%)	166 (14.31%)	917 (13.35%)	
Smoking status				0.070
No	6,241 (77.74%)	926 (79.83%)	5,315 (77.39%)	
Yes	1,787 (22.26%)	234 (20.17%)	1,553 (22.61%)	
Alcohol consumption				0.018
No	6,016 (74.94%)	902 (77.76%)	5,114 (74.46%)	
Yes	2,012 (25.06%)	258 (22.24%)	1,754 (25.54%)	
Hypertension				0.016

Characteristic	Overall	Exclusion	Inclusion	*P* value
No	2,374 (29.57%)	378 (32.59%)	1,996 (29.06%)	
Yes	5,654 (70.43%)	782 (67.41%)	4,872 (70.94%)	
Diabetes				0.039
No	6,605 (82.27%)	929 (80.09%)	5,676 (82.64%)	
Yes	1,423 (17.73%)	231 (19.91%)	1,192 (17.36%)	
Chronic kidney disease				0.033
No	6,385 (79.53%)	895 (77.16%)	5,490 (79.94%)	
Yes	1,643 (20.47%)	265 (22.84%)	1,378 (20.06%)	
Dyslipidemia				0.002
No	5,399 (67.25%)	733 (63.19%)	4,666 (67.94%)	
Yes	2,629 (32.75%)	427 (36.81%)	2,202 (32.06%)	
Meat consumption				0.544
No	549 (6.84%)	74 (6.38%)	475 (6.92%)	
Yes	7,479 (93.16%)	1,086 (93.62%)	6,393 (93.08%)	
Vegetable consumption				0.192
No	220 (2.74%)	39 (3.36%)	181 (2.64%)	
Yes	7,808 (97.26%)	1,121 (96.64%)	6,687 (97.36%)	
Fruit consumption				< 0.001
No	1,938 (24.14%)	224 (19.31%)	1,714 (24.96%)	
Yes	6,090 (75.86%)	936 (80.69%)	5,154 (75.04%)	

Note. Continuous variables are presented as mean ± standard deviation (*SD*) or median (interquartile range [*IQR*]), as appropriate; categorical variables are presented as number of participants (*n*) and percentage (%). Mn, manganese; MMSE, Mini-Mental State Examination; *SD*, standard deviation; *IQR*, interquartile range; *n*, number of participants; *P*, probability value.

Supplementary Table S2. Spiked recoveries and relative standard deviations for blood manganese

Analyte	> LOD (%)	Background (μg/L)	2.5 μg/L		5 μg/L		10 μg/L	
			Recovery (%)	RSD (%)	Recovery (%)	RSD (%)	Recovery (%)	RSD (%)
Blood Mn	99.8	7.26	99.8	3.2	97.1	2.3	99.5	1.9

Note. Mn, manganese; RSD, relative standard deviation; LOD, limits of detection.

Supplementary Table S3. Components of mini-mental state examination

Dimensions	Questions	Maximum score
Orientation	What is the year?	1
	What is the month?	1
	When is Mid-Autumn Festival?	1
	What season of the year is it?	1
	What county, city or town are we in?	1
Attention and calculation	20-3=?	1
	20-3-3=?	1
	20-3-3-3=?	1
	20-3-3-3-3=?	1
	20-3-3-3-3-3=?	1
Visual construction	Copy the design shown.	1
Language	Can name a 'pencil'?	1
	Can name a 'watch'?	1
	Repeat a sentence.	1
	Take paper in right hand.	1
	Folds paper in half.	1
	Put paper down on lap.	1
Naming	Naming as many kinds of food as possible in one minute.	7
Recall	Remembered 'table'?	1
	Remembered 'apple'?	1
	Remembered 'clothes'?	1
	Can repeat 'table' immediately?	1
	Can repeat 'apple' immediately?	1
	Can repeat 'clothes' immediately?	1

Supplementary Table S4. Distribution of blood manganese concentrations by gender and age groups

Subgroup	*N*	Mean ± SD	Statistical value	*P* value
Total	6,868	11.297 ± 3.763		
Female	3,440	11.694 ± 3.75	8.821	< 0.001
Male	3,428	10.898 ± 3.735		
60–70 year	2,378	10.95 ± 3.738	26.980	< 0.001
70–80 year	2,026	11.186 ± 3.664		
≥ 80 year	2,464	11.723 ± 3.828		

Note. Mn, manganese; N, number of participants; SD, standard deviation; *P*, probability value.

Supplementary Table S5. Associations of blood manganese levels with MMSE and cognitive domain scores

Cognitive scores	Model 1 *β* (95% *CI*)	Model 2 *β* (95% *CI*)	Model 3 *β* (95% *CI*)	Model 4 *β* (95% *CI*)
MMSE	-0.029 (-0.045, -0.014)*	-0.030 (-0.045, -0.014)*	-0.030 (-0.045, -0.014)*	-0.033 (-0.048, -0.018)*
Orientation score	-0.019 (-0.029, -0.008)*	-0.019 (-0.029, -0.008)*	-0.018 (-0.029, -0.008)*	-0.013 (-0.024, -0.002)*
Attention and calculation score	-0.018 (-0.034, -0.002)*	-0.018 (-0.034, -0.003)*	-0.018 (-0.034, -0.003)*	-0.022 (-0.038, -0.007)*
Visual construction score	-0.018 (-0.044, 0.007)	-0.018 (-0.044, 0.007)	-0.017 (-0.043, 0.009)	-0.017 (-0.042, 0.009)
Language score	-0.033 (-0.047, -0.018)*	-0.033 (-0.048, -0.018)*	-0.033 (-0.047, -0.018)*	-0.029 (-0.044, -0.014)*
Naming score	-0.045 (-0.072, -0.017)*	-0.045 (-0.072, -0.017)*	-0.043 (-0.071, -0.016)*	-0.043 (-0.070, -0.015)*
Recall score	-0.044 (-0.061, -0.027)*	-0.044 (-0.061, -0.028)*	-0.044 (-0.061, -0.028)*	-0.047 (-0.064, -0.030) *

Note. Blood manganese concentrations were modeled per interquartile range (*IQR*) increase. The cognitive scores were standardized to *Z*-scores. Model covariate adjustments: Model 1 adjusted for age, gender, cohort, area. Model 2 further adjusted for ethnicity, marital status, residence, education level, economic level. Model 3 further adjusted for smoking status, drinking status, as well as vegetable, fruit and meat intake. Model 4 further adjusted for body mass index, hypertension, diabetes, chronic kidney disease, dyslipidemia. Mn, manganese; MMSE, Mini-Mental State Examination; *β*, regression coefficient; *CI*, confidence interval; *IQR*, interquartile. *$P < 0.05$.

Supplementary Table S6. Sensitivity analysis of the association between blood manganese levels and incident cognitive impairment

Mn	Remove values below LOD	Remove values above P_{99}	Adjust for Hg and Pb
	***HR* (95% *CI*)**	***HR* (95% *CI*)**	***HR* (95% *CI*)**
Q_1	Reference	Reference	Reference
Q_2	1.107 (0.934-1.311)	1.108 (0.935-1.314)	1.120(0.946-1.327)
Q_3	1.120 (0.941-1.334)	1.140 (0.957-1.359)	1.173 (0.985-1.397)
Q_4	1.285 (1.082-1.527)*	1.275 (1.072-1.518)*	1.378 (1.157-1.640)*
Per *IQR*	1.131 (1.051-1.218)*	1.139 (1.053-1.232)*	1.168 (1.084-1.258)*

Note. Models adjusted for age, gender, cohort, area, ethnicity, marital status, residence, education level, economic level, smoking status, drinking status, vegetable, fruit and meat intake, body mass index, hypertension, diabetes, chronic kidney disease and dyslipidemia. Three sensitivity analyses were performed: (1) Remove values below the LOD. (2) Remove values above P_{99}. (3) Further adjust for mercury (Hg) and lead (Pb) levels. Results are presented by quartiles (Q_1–Q_4; $Q1$ as reference) and per interquartile range (*IQR*). limit of detection; P_{99}, 99th percentile; *IQR*, interquartile range; Mn, manganese; Hg, mercury; Pb, lead; *HR*, hazard ratio; *CI*, confidence interval; *LOD*, limits of detection. *$P < 0.05$.

Supplementary Table S7. Associations of blood manganese levels with incident cognitive impairment using competing risk model analysis

Blood Mn (μg/L)	Model 1	Model 2	Model 3	Model 4
	***HR* (95% *CI*)**	***HR* (95% *CI*)**	***HR* (95% *CI*)**	***HR* (95% *CI*)**
Q_1	Reference	Reference	Reference	Reference
Q_2	1.119 (0.953-1.314)	1.122 (0.955-1.318)	1.119 (0.953-1.315)	1.145 (0.973-1.347)
Q_3	1.065 (0.903-1.255)	1.064 (0.903-1.254)	1.063 (0.902-1.253)	1.095 (0.926-1.293)
Q_4	1.156 (0.984-1.359)	1.154 (0.981-1.357)	1.155 (0.982-1.358)	1.212 (1.026-1.431)*
Per *IQR*	1.078 (1.005-1.156)*	1.077 (1.004-1.155)*	1.074 (1.002-1.152)*	1.075 (1.002-1.152)*

Note. Quartiles (Q_1–Q_4) are defined by the study-specific distribution (Q_1 as reference). "Per *IQR*" denotes the *HR* per interquartile-range increase in manganese. Model covariate adjustments: Model 1 adjusted for age, gender, cohort, area; Model 2 further adjusted for ethnicity, marital status, residence, education level, economic level; Model 3 further adjusted for smoking status, drinking status, as well as vegetable, fruit and meat intake; Model 4 further adjusted for body mass index, hypertension, diabetes, chronic kidney disease, dyslipidemia. *Q*, quartile; *IQR*, interquartile range; Mn, manganese; *HR*, hazard ratio; *CI*, confidence interval. *$P < 0.05$.