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A bayesian benchmark dose–based assessment of the neuro-safety reference of urinary fluoride: implications for revising current Chinese standards

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ABSTRACT

Background: High fluoride exposure has been linked to neurological impairment; however, evidence on the safety threshold for fluoride-induced neurotoxicity remains limited.
Methods: A cross-sectional study was undertaken in a fluorosis-affected area with drinking water in Jishan County, Shanxi Province. Urinary fluoride was used as the biomarker of fluoride exposure and measured using an ion-selective electrode method. Cognitive function was assessed with the Mini-Mental State Examination (MMSE). Multivariable linear regression and binary logistic regression were employed to examine the dose–response relationship between urinary fluoride and cognitive performance. The Bayesian Benchmark Dose (BBMD) system was used to estimate the safety reference for urinary fluoride.
Results: Higher urinary fluoride levels were significantly associated with cognitive impairment. Upon controlling for possible confounders, each 1 mg/L increment in urine fluoride correlated with a 5% elevated risk of cognitive impairment (OR = 1.05, 95% CI: 1.01–1.09). At a benchmark response (BMR) of 5%, the benchmark dose (BMD) was 3.12 mg/L, with a 95% lower bound (BMDL) of 1.18 mg/L.
Conclusion: Elevated urinary fluoride is an independent associated factor for cognitive dysfunction. The neuroprotective safety reference value of 1.0 mg/L for urinary fluoride estimated in this study is lower than the current Chinese reference standard, indicating that more rigorous regulations may be necessary to safeguard the nervous system from excessive fluoride exposure. These findings offer novel scientific information to guide measures for reducing fluoride-induced neurotoxicity.

1. Introduction

Endemic fluorosis is a biogeochemical disease that results from long-term, excessive fluoride intake through drinking water, food, or air, leading to systemic, chronic, cumulative toxicity in humans(Bibi, et al.,2024). According to the predominant exposure pathway, fluorosis is classified into drinking-water-type, coal-burning-type, and tea-drinking-type forms(Li, et al.,2021). Among these, drinking-water-type fluorosis, caused by the prolonged consumption of high-fluoride water, is the most prevalent and widely distributed subtype(Taher, et al.,2024). Globally, more than 25 countries face challenges related to high fluoride in drinking water, and the health of approximately 200 million people is threatened as a consequence(Lavalle-Carrasco, et al.,2021; Mosiman, et al.,2021; Solanki, et al.,2022). China is one of the countries severely endemic for drinking water-borne fluorosis, which affects 28 provincial-level administrative divisions (PLADs) and approximately 70 million people at risk(Zhao, et al.,2024). The classic pathological manifestations of fluorosis involve hard tissues, leading to skeletal fluorosis and dental fluorosis(Everett,2011; Hung, et al.,2023; Veneri, et al.,2023). Nonetheless, mounting evidence indicates that

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fluoride possesses systemic toxicity that transcends the skeletal and dental systems, adversely affecting several soft organs, including the neurological system, musculature, kidneys, liver, blood vessels, and endocrine glands(Perumal, et al.,2013; Wei, et al.,2019; Manoharan, et al.,2024).

The blood–brain barrier (BBB) is a highly specialized interface between the cerebral microvasculature and brain parenchyma that tightly regulates the passage of substances into the central nervous system (CNS)(Kadry, et al.,2020; Chagnot and Montagne,2025). Due to its small radius and distinctive chemical characteristics, the fluoride ion can cross BBB through many transport routes(Agalakova and Nadei,2020; Ottappilakkil, et al.,2023). Upon entering the CNS, excessive fluoride tends to accumulate in brain regions essential for cognition, such as the hippocampus and cortex, instigating a series of pathological processes, including neuronal structural damage, impaired synaptic plasticity, and disrupted neurotransmitter homeostasis, ultimately resulting in cognitive decline and deficits in learning and memory(Ren, et al.,2022). Numerous animal studies have shown that chronic fluoride exposure significantly hinders learning and memory in mice(Zhang, et al.,2020; Ran, et al.,2023; Du, et al.,2024; Nadei and Agalakova,2024). Rats exposed to fluoride exhibit substantial deficiencies in spatial learning and memory in the Morris water maze, as evidenced by a markedly increased escape latency to locate the hidden platform and reduced time spent in the target quadrant. Complementary epidemiological evidence in humans has demonstrated that prolonged exposure to high fluoride (e.g., long-term consumption of high-fluoride drinking water) negatively impacts children's IQ, cognitive ability, and memory(Duan, et al.,2018; Wang, et al.,2020; Taylor, et al.,2025). In a study conducted in Xuzhou, Jiangsu Province, Ren et al. reported elevated abnormal rates on the AD8 and MoCA-B cognitive screening scales among elder adults residing in high-fluoride regions compared to those in areas with drinking water meeting national standards, indicating that chronic exposed to high-fluoride water may adversely affect cognitive function in the elderly population(Ren, et al.,2021). Collectively, these findings highlight the neurotoxicity of fluoride and its potential implications to public health.

To safeguard public health, several countries and international organizations have formulated guideline values for fluoride levels in drinking water and reference ranges for urine fluoride. For instance, the World Health Organization (WHO) advises that fluoride level in drinking water should not exceed 1.5 mg/L(World Health Organization,2011). The United States Environmental Protection Agency (EPA) has set a maximum contaminant level of 4.0 mg/L to avert skeletal fluorosis and a secondary standard of 2.0 mg/L to reduce the risk of dental fluorosis(U.S. Environmental Protection Agency,2011). In China, the National Standard for Drinking Water Quality (GB 5749–2022) stipulates that fluoride concentration in drinking water should not exceed 1.0 mg/L(China NHCo,2022), and WS/T 10023–2024 defines the normal urinary fluoride reference values for the Chinese population, with geometric means not exceeding 1.4 mg/L in children and 1.6 mg/L in adults(China NDCaPAo,2024). Nonetheless, the established guideline values for fluoride in drinking water and urinary were primarily designed to avert skeletal and dental issues and have not adequately considered the potential neurotoxicity of fluoride; neurobehavioral endpoints and data on cognitive impairment have largely been omitted from the current risk assessment framework. A cross-sectional study in rural Tianjin, China, demonstrated that even modest fluoride concentrations in drinking water (< 1.0 mg/L) were correlated with a significant decrease in the likelihood of children attaining very high IQ scores (IQ ≥ 130)(Yu, et al.,2018). Considering the heightened sensitivity of neurological system to environmental toxicants(Camacho, et al.,2024), it is plausible to hypothesize that fluoride concentrations in drinking water or urine within the scope of current regulatory limits may nevertheless induce neurotoxic consequences and cognitive deficits. This raises critical concerns regarding the inadequacy of existing guidelines in safeguarding against fluoride-induced neurotoxicity and underscores the urgent necessity to reassess and potentially amend these standards to strengthen neurological health protection.

Accurately determining protective exposure thresholds is a crucial step in safeguarding public health in the larger subject of health risk assessment. The benchmark dose (BMD), the lowest observed adverse effect level (LOAEL), and the no observed adverse effect level (NOAEL) are examples of traditional threshold derivation techniques(Dourson, et al.,1986; Shao and Shapiro,2018). NOAEL is the maximum tested dosage at which no detrimental health effects are detected under specific exposure circumstances, whereas LOAEL is the minimum tested dose at which harmful effects are identified. Both methods, however, possess notable limitations: they rely on data from a singular dose group, neglect the complete profile and variability of the dose–response curve, lead to information loss, and fail to offer confidence intervals corresponding to specific risk levels, thus constraining formal uncertainty analysis.

To rectify these deficiencies, the BMD approach has been established and extensively applied in environmental health risk assessment(Li, et al.,2020; EFSA Scientific Committee, et al.,2022). Specifically, the BMD is determined by fitting a statistical model to the full dose–response dataset and pinpointing the dose corresponding a specified benchmark response (BMR). The BMR denotes a predetermined threshold for enhanced response, typically established at a 5% or 10% increase in the effect, which represents a minimally acceptable or tolerable risk level within risk management frameworks(Auton,1994; Gaylor and Kodell,2002). The BMD approach offers a more efficient and statistically robust foundation for deriving health-based guidance values by incorporating the complete dose–response curve and its variability. The Statistical Lower Bound of BMD (BMDL) serves as a reference point for protective thresholds, providing a clear quantitative boundary for risk assessment(Corbett,2003).

The Bayesian Benchmark Dose (BBMD) system is an online platform for BMD analysis that employs a Bayesian statistical framework utilizing Markov Chain Monte Carlo (MCMC) methods to estimate model parameters and derive BMD values(Shao and Shapiro,2018; Ji, et al.,2022). This system facilitates probabilistic risk assessment and synthesizes results from various candidate models through Bayesian model averaging (BMA)(Forbes, et al.,2023), resulting in more dependable estimates of BMD and BMDL. In evaluating the correlation between fluoride exposure and neurotoxicity, the BBMD system may concurrently analyze many model types, encompassing both linear and nonlinear dose–response models, and allocate weights to each model based on its goodness-of-fit to the data. This produces a composite BMD estimate that more accurately reflects model uncertainty and data structure. This technique facilitates a comprehensive and precise assessment of the risks linked to fluoride exposure and offers a solid scientific foundation for determining health-based exposure limits that specifically consider neurotoxic consequences.

This research comprised two interrelated components, designed to establish a scientific basis for updating fluoride exposure guidelines concerning neurological safety. The first component investigated the dose–response association between urine fluoride levels and cognitive performance among residents in drinking water fluorosis-endemic areas. The second component utilized the BBMD system to derive a neurotoxicity-based BMD for urinary fluoride. Collectively, these findings aim to address the insufficient protection against neurological impairments offered by the existing standards.

2. Methods

2.1. Study population

This cross-sectional study was performed from March to April 2023 in Jishan County, Yuncheng City, Shanxi Province, a region endemic for drinking-water-type fluorosis. Using a cluster sampling method, we initially recruited 3,492 residents from 11 endemic villages and 1 non-endemic village. Participants qualified if they: (1) were at least 18

years old, and (2) had resided in the research area for over 10 years. The following criteria were used to exclude people: (1) a history of traumatic brain damage; (2) a history of psychiatric illnesses; (3) a history of stroke; or (4) the absence of important information (such as urine fluoride, MMSE score, or basic demographic data). A total of 3,126 participants were incorporated into the final analysis after applying these criteria (Fig. 1).

All participants provided written informed consent prior to enrolment. The study protocol was approved by the Ethics Committee of the Endemic Disease Center, Harbin Medical University (HRBMUECDC20210303). Trained investigators performed in-person interviews utilizing a structured questionnaire to gather demographic information (age, sex, education), medical history (hypertension, diabetes, coronary heart disease), lifestyle factors, and physical examination data. A random urine sample was collected from each participant into a 15-mL centrifuge tube, aliquoted into 2-mL cryovials, and preserved at − 80 °C until analysis. 5 mL of fasting peripheral blood samples were collected from each participant. Centrifugation was performed at 3000 r/min (2 h after blood collection) for 10 min, and serum was divided into 1.5 mL EP tubes for detection of kidney function-related indicators.

2.2. Assessment of cognitive function

Cognitive function was assessed utilizing the Chinese adaptation of the Mini-Mental State Examination (MMSE), modified to reflect the cultural and socioeconomic setting of China(Katzman, et al.,1988; Dufouil, et al.,2000). The Chinese MMSE assesses five cognitive domains: orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language and praxis (9 points). Total scores range from 0 to 30, with lower scores indicating poorer cognitive function (treated as a continuous variable). Due to the significant impact of educational attainment on MMSE performance (Crum, et al.,1993), we additionally categorized cognitive state as normal or impaired utilizing education-specific thresholds(Zhang, et al.,1990; Li, et al.,2016; Chen, et al.,2023). Cognitive impairment was characterized by an MMSE score of $\leq$ 17 for illiterate individuals, $\leq$ 20 for those with $\leq$ 6 years of education (primary school), and $\leq$ 24 for those with $>$ 6 years of education (junior high school or higher). Accordingly, MMSE scores exceeding 17, 20, and 24 in these three educational categories were designated as indicative of normal cognition. All evaluations were conducted through in-person interviews, with participants responding to all items autonomously.

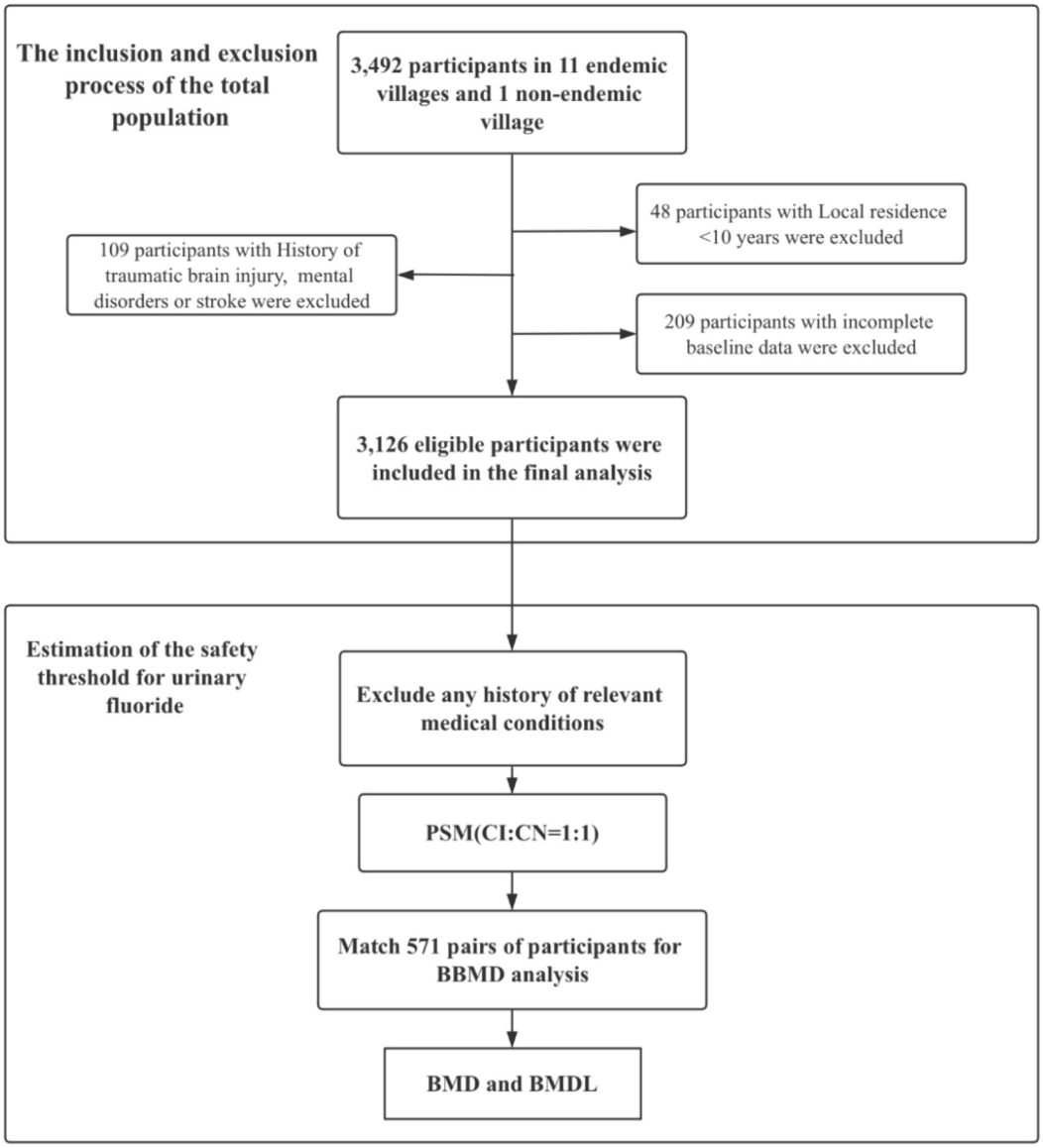

Fig. 1. Flowchart of inclusion and exclusion of population in Shanxi.

2.3. Covariates

Baseline potential confounders were demographic characteristics, lifestyle factors, and health status. Demographic characteristics included sex, age, education level (primary school or less versus junior high school or above), yearly household income ($\leq$ 2,0000 against $>$ 2,0000 CNY), and marital status (married versus unmarried, the latter encompassing never married, separated, divorced, or widowed). Lifestyle factors including tobacco use, alcohol intake, and sleep length. Smoking status was determined based on cumulative intake, categorizing people who had smoked over 100 cigarettes throughout their lifetime as smokers(He, et al.,2022). Alcohol consumption was classified as either non-drinker or drinker. Night-time sleep duration was self-reported and categorized into short sleep ($<$ 6 h), normal sleep (6–8 h), and long sleep ($>$ 8 h)(Li, et al.,2022; Ding, et al.,2024). Health status was assessed based on self-reported physician-diagnosed histories of hypertension, diabetes, coronary heart disease and kidney disease. Blood pressure was measured using a portable electronic sphygmomanometer. In accordance with the 2023 Chinese Guidelines for the Prevention and Treatment of Hypertension, hypertension was defined as either a self-reported history of hypertension or a measured systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg. The body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) and categorized into two categories: normal weight (BMI $<$ 24.0 kg/m^2) and overweight/obesity (BMI $\geq$ 24.0 kg/m^2). Due to the limited number of underweight participants (BMI $<$ 18.5 kg/m^2) (n = 45), they were amalgamated with the normal BMI cohort.

2.4. Measurement of fluoride concentrations

Urinary fluoride concentrations were measured using ion-selective electrode methodology (Shanghai Weiye Instrument Co., China). Sample preparation and analytical procedures followed the Chinese national standard "Determination of fluoride in urine—Ion-selective electrode method" (WS/T 89–2015).

2.5. Determination of biomarkers for kidney function

In this study, serum uric acid (UA) and serum blood urea nitrogen (BUN) were determined using an Automatic Biochemical Analyzer 3100 (Hitachi High-Technologies Corporation, Japan) for the evaluation of renal function(Wu, et al.,2021, 2023).

2.6. Quality assurance and quality control

Urine samples were stored at − 80 °C immediately after collection and processing, and the interval from sample collection to fluoride analysis did not exceed one month. Calibration was performed using a series of fluoride standard solutions ranging from 0.1 to 10.0 mg/L (0.1, 0.2, 0.5, 1.0, 2.0, 5.0, and 10.0 mg/L). To monitor instrument stability in real time, a midpoint calibration with 1.0 mg/L fluoride standard solution was conducted after every 20 samples. The calibration curve was constructed with the logarithm of fluoride concentration (mg/L) on the x-axis and the corresponding electric potential values on the y-axis (Fig. S1), yielding a linear regression equation of $y = -59.655x + 267.59$ with a determination coefficient (R^2) of 0.9999. The limit of detection (LOD) of the method was 0.1 mg/L.

For batch quality control and to mitigate temporal drift, each analytical batch included blank controls (deionized water), duplicate samples (one duplicate per 20 samples), and certified reference materials (GSB 04–1771-2004). Only batches meeting all quality criteria—blank control results below the LOD, relative deviation of duplicate samples $\leq \pm$10%, and certified reference material values within the certified acceptable ranges—were accepted for data analysis. The coefficients of variation (CV) for repeated measurements of urinary fluoride were less than 10%. Each sample was analyzed in duplicate, and the average fluoride concentration was used for subsequent data analysis.

2.7. Bayesian benchmark dose estimation

To mitigate potential confounding in the benchmark dosage study, we initially excluded people having a history of significant chronic illnesses (hypertension, coronary heart disease, or diabetes; n = 936), as illustrated in Fig. 1. We subsequently employed propensity score matching (PSM) in a 1:1 ratio between participants with cognitive impairment and those with normal cognition (cognitive impairment: normal cognition = 1:1), aligning on age, sex, household income, and marital status. This procedure yielded 571 matched pairs (571 participants with cognitive impairment and 571 cognitively normal participants). BMD estimation was conducted using the web-based platform BBMD (https://benchmarkdose.com). The MCMC parameters were as follows: 30,000 iterations, 1 Markov chain, a burn-in (preheating) proportion of 50%, and a random seed of 2025. We fitted eight dichotomous dose–response models to the data: Logistic, Log-Logistic, Probit, Log-Probit, Quantal-Linear, Multistage (2nd order), Weibull, and Dichotomous Hill. The model fit was evaluated using the posterior predictive p-value (PPP); with values ranging from 0.05 to 0.95 deemed indicative of satisfactory model fit. To address model uncertainty, we applied Bayesian model averaging, weighting each model by its posterior support. On this basis, we calculated BMDs and BMDLs corresponding to extra risk levels (benchmark response, BMR) of 1%, 2%, and 5%.

2.8. Statistical analysis

Categorical variables were summarized as counts and percentages, and group differences were assessed using the chi-square test. Continuous variables were expressed as median (P25–P75) and compared between groups using the Wilcoxon rank-sum test, given their non-normal distributions. Initially, we employed Spearman rank correlation to analyze the relationships between urine fluoride concentrations and overall MMSE scores, as well as the five cognitive domains of the MMSE. The urinary fluoride levels of participants were subsequently classified into quartiles to investigate exposure–response relationships, with Q1 ($<$ 1.79 mg/L) defined as the reference ("control") group, Q2 as the low-fluoride group (1.80–2.91 mg/L), Q3 as the medium-fluoride group (2.92–4.53 mg/L), and Q4 as the high-fluoride group ($>$ 4.53 mg/L). We analyzed the prevalence of cognitive impairment across these quartiles utilizing the chi-square test, performed pairwise comparisons with Bonferroni correction for multiple testing, and employed the Cochran–Armitage trend test to evaluate linear trends in cognitive impairment prevalence across ascending urinary fluoride categories. We used binary logistic regression models using urine fluoride as the primary exposure and cognitive impairment (yes/no) as the dependent variable in order to better quantify relationships. Simultaneously, we employed linear regression models to assess the relationships between urine fluoride and (i) overall MMSE score and (ii) domain-specific MMSE scores, considering these as continuous variables. Due to the non-normal distribution of urine fluoride levels, we implemented a base-10 logarithmic adjustment before doing regression analysis. In the regression framework for trend testing, we assigned the median urinary fluoride value of each quartile, treated it as a continuous variable, and analyzed linear trends across exposure levels. We employed restricted cubic spline (RCS) functions to adeptly model and illustrate the dose–response relationship between urine fluoride and cognitive impairment, enabling the evaluation of potential non-linear correlations.

We performed subgroup analyses to examine the association between urinary fluoride levels and cognitive function across sex and age groups ($<$60 years and $\geq$ 60 years). In addition, to evaluate the potential effect modification by sex and age, we introduced interaction terms into the multivariable regression models and calculated the corresponding p-values for interaction. To assess the robustness of our primary findings, we performed two sensitivity analyses: (i) Excluding 45 participants

with BMI < 18.5; (ii) Cognitive impairment was reclassified based on education-adjusted MMSE cut-offs (≤ 19 for illiterate persons; ≤ 22 for those with ≤ 6 years of schooling; ≤ 26 for individuals with > 6 years of schooling)(Yin, et al.,2016).

All statistical analyses were performed using R software (version 4.4.1), with a $P < 0.05$ considered statistically significant.

3. Results

3.1. General characteristics of the study population and urinary fluoride concentrations

The baseline characteristics of the study population are summarized in Table 1. A total of 3,126 participants were enrolled in this analysis, with a median age of 61 years (interquartile range [IQR]: 53–68). The cohort comprised 63.6% women, 93.7% married individuals, and 50.4% who had attained an education level of junior high school or above. The overall prevalence of cognitive impairment (CI) was 28.41% (888/3,126). Participants were stratified by cognitive status into CI and cognitively normal (CN) groups for comparative analysis. As shown in Table 1, participants in the CI group were significantly older than those in the CN group ($p < 0.001$). Significant differences were also observed between groups regarding sex distribution, education level, annual household income, marital status, alcohol consumption, night-time sleep duration, BMI, and history of hypertension and coronary heart disease (all $p < 0.05$). Conversely, no significant differences were found in smoking status, physical activity levels, or history of diabetes (all $p > 0.05$). The median urine fluoride content in the general population was 2.91 mg/L (IQR: 1.79–4.53). Individuals in the CI group exhibited markedly elevated urinary fluoride concentrations compared to those in the CN group, with median values of 3.18 mg/L (IQR: 1.95–4.83) and 2.81 mg/L (IQR: 1.73–4.37).

3.2. Dose–response relationship between urinary fluoride and cognitive function

Urinary fluoride concentration was negatively correlated with MMSE score, with a Spearman correlation coefficient of − 0.17 ($p < 0.01$; Fig. 2A). Similar inverse associations were observed across all five MMSE cognitive domains (Fig. 2B–F). As shown in Fig. 2G, the prevalence of cognitive impairment increased progressively across higher categories of urinary fluoride concentration (p for trend < 0.05). Multiple comparisons indicated that both the medium-fluoride group and the high-fluoride group had significantly higher prevalences of cognitive impairment than the reference group (all $p < 0.05$). We further examined the dose–response relationship using RCS models (Fig. 2H–I). The results showed a monotonic pattern: as urinary fluoride levels increased, the risk of cognitive impairment rose steadily, whereas MMSE scores declined correspondingly. These findings provide visual and statistical support for a graded, dose–response association between fluoride exposure and impaired cognitive function.

3.3. Regression analyses of urinary fluoride and cognitive function

Binary logistic regression analyses showed that higher urinary fluoride levels were positively associated with the odds of cognitive impairment (Table 2). In the fully adjusted model (Model 3), each 1 mg/L increase in urinary fluoride was associated with a 5% higher risk of cognitive impairment (OR = 1.05; 95% CI: 1.01, 1.09). When urinary fluoride was modeled in quartiles, participants in the highest quartile had a 35% higher risk of cognitive impairment compared with those in the lowest quartile (OR = 1.35; 95% CI: 1.07, 1.71), with a significant linear trend (p for trend < 0.05).

Subsequently, we employed multivariable linear regression models to evaluate the relationships between urinary fluoride and the overall MMSE score and the five MMSE cognitive domains (Table 3). In general,

Table 1
Characteristics of the study population according to cognitive function.

Characteristic	Overall, N = 3,126	CN, N = 2,238	CI, N = 888	*p*-value [c]
Age [a], Median (IQR)	61.00 (53.00, 68.00)	59.00 (52.00, 66.00)	65.00 (57.00, 72.00)	**<0.001**
Age Categorical [b], n (%)				**<0.001**
< 60	1,443 (46.2%)	1,158 (51.7%)	285 (32.1%)	
≥ 60	1,683 (53.8%)	1,080 (48.3%)	603 (67.9%)	
Sex [b], n (%)				**0.019**
Male	1,139 (36.4%)	787 (35.2%)	352 (39.6%)	
Female	1,987 (63.6%)	1,451 (64.8%)	536 (60.4%)	
Educational status [b], n (%)				**<0.001**
Primary or below	1,549 (49.6%)	1,153 (51.5%)	396 (44.6%)	
Above primary	1,577 (50.4%)	1,085 (48.5%)	492 (55.4%)	
Annual household income [b], n (%)				**<0.001**
< 2,0000 CNY	1,812 (58.0%)	1,231 (55.0%)	581 (65.4%)	
≥ 2,0000 CNY	1,314 (42.0%)	1,007 (45.0%)	307 (34.6%)	
Marital status [b], n (%)				**0.003**
Married	2,930 (93.7%)	2,116 (94.5%)	814 (91.7%)	
Unmarried	196 (6.3%)	122 (5.5%)	74 (8.3%)	
Smoking [b], n (%)				0.786
Never	2,502 (80.0%)	1,794 (80.2%)	708 (79.7%)	
Current and Former	624 (20.0%)	444 (19.8%)	180 (20.3%)	
Drinking [b], n (%)				**0.037**
No	2,685 (85.9%)	1,904 (85.1%)	781 (88.0%)	
Yes	441 (14.1%)	334 (14.9%)	107 (12.0%)	
Body mass index [b], n (%)				**0.011**
< 24	1,124 (36.0%)	774 (34.6%)	350 (39.4%)	
≥ 24	2,002 (64.0%)	1,464 (65.4%)	538 (60.6%)	
Nocturnal sleep duration (hour) [b] n (%)				**<0.001**
6 – 8	1,999 (63.9%)	1,471 (65.7%)	528 (59.5%)	
< 6	361 (11.5%)	259 (11.6%)	102 (11.5%)	
> 8	766 (24.5%)	508 (22.7%)	258 (29.1%)	
Physical exercise [b], n (%)				0.570
No	2,244 (71.8%)	1,613 (72.1%)	631 (71.1%)	
Yes	882 (28.2%)	625 (27.9%)	257 (28.9%)	
Hypertension [b], n (%)				**<0.001**
No	1,000 (32.0%)	756 (33.8%)	244 (27.5%)	
Yes	2,126 (68.0%)	1,482 (66.2%)	644 (72.5%)	
History of diabetes [b], n (%)				0.344
No	2,955 (94.5%)	2,121 (94.8%)	834 (93.9%)	
Yes	171 (5.5%)	117 (5.2%)	54 (6.1%)	
History of coronary heart disease [b], n (%)				**0.030**

(continued on next page)

Table 1 (*continued*)

Characteristic	Overall, N = 3,126	CN, N = 2,238	CI, N = 888	*p*-value [c]
No	2,912 (93.2%)	2,071 (92.5%)	841 (94.7%)	
Yes	214 (6.8%)	167 (7.5%)	47 (5.3%)	
UF (mg/L) [a], Median (IQR)	2.91 (1.79, 4.53)	2.81 (1.73, 4.37)	3.18 (1.95, 4.83)	**<0.001**

Abbreviations: CI, cognitively impaired group; CN, cognitively normal group; UF, Urine fluoride.

[a] Data were presented as median (P25-P75) for continuous variables.

[b] Number (percentage/proportion) for categorical variable.

[c] Wilcoxon test was applied to compare the difference of continuous variables, and the Chi-square test was used to compare the difference of categorical variables.

urinary fluoride concentrations exhibited a negative correlation with MMSE scores. In Model 3, each one-unit increase in $\log_{10}$-transformed urinary fluoride was associated with a 1.31-point reduction in MMSE score ($\beta = -1.31$; 95% CI: −2.00, −0.64). In comparison to the lowest quartile of urinary fluoride, MMSE scores were diminished by 0.60 points (95% CI: −1.16, −0.05) in the third quartile and by 1.17 points (95% CI: −1.74, −0.61) in the highest quartile, exhibiting a significant linear trend (p for trend < 0.05). Consistent inverse correlations were noted for four of the five MMSE domains, except the language and praxis domain (Table S1). These findings strengthen the validity of the inverse correlation between urine fluoride exposure and various dimensions of cognitive performance.

3.4. Benchmark dose estimation for urinary fluoride

Urinary fluoride levels and cognitive status for the 571 PSM-matched pairs (Table S2) are entered into the BBMD platform in order to estimate the neurotoxicity BMD of fluoride. Eight dichotomous Bayesian models were calibrated, and the BMD along with BMDL were calculated at BMR of 1%, 2%, and 5% (Table 4).The incidence of cognitive impairment escalated with increasing urine fluoride levels across all models (Fig. 3). PPP varied between 0.05 and 0.95, signifying an adequate model fit. Logistic and Probit models contributed the greatest posterior weights (26.72% and 26.30%, respectively). At a BMR of 5%, the BMD/BMDL values for the two models were 2.07/1.22 mg/L and 2.05/1.21 mg/L, respectively, while the model-averaged estimations were 2.44 mg/L (BMD) and 1.18 mg/L (BMDL). At a BMR of 2%, the model-averaged BMD/BMDL values were 0.97/0.47 mg/L, and at a BMR of 1%, they were 0.49/0.24 mg/L. Overall, lower BMR levels corresponded to

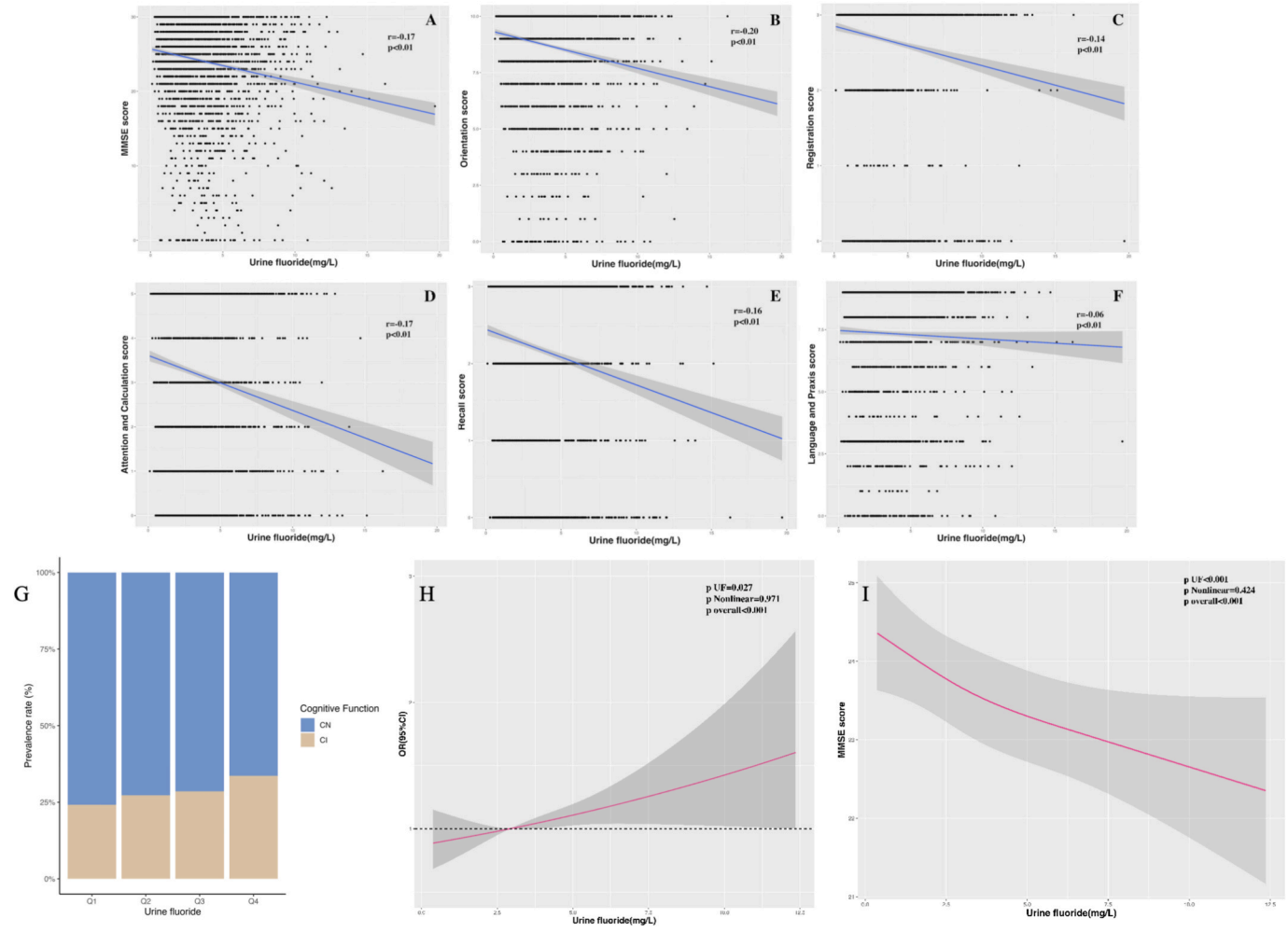

Fig. 2. Association between Urine fluoride concentration and cognitive function. (A)MMSE scores; (B)orientation scores; (C)registration scores; (D)attention and calculations scores; (E)recall scores; (F)language and praxis scores. (G)The prevalence of cognitive impairment at different UF concentrations. Q1:UF ≤ 1.79 mg/L; Q2:1.79 mg/L < UF ≤ 2.91 mg/L; Q3:2.91 mg/L < UF ≤ 4.53 mg/L; Q4:UF > 4.53 mg/L. RCS curves of Urine fluoride concentrations and cognitive function. (H)The relationship between Urine fluoride concentrations and cognitive function based on logistic regression model; (I)The relationship between Urine fluoride concentrations and MMSE scores based on linear regression model. Adjusted for gender, age,Educational status, Annual household income stratification, Marital status, Drinking, BMI, Nocturnal sleep duration, Hypertension and History of coronary heart disease.

Table 2
Relationship between UF concentration (mg/L) and cognitive function.

urinary fluoride	crude *OR* (95% *CI*)	model1 *OR* (95% *CI*)	model2 *OR* (95% *CI*)	model3 *OR* (95% *CI*)
Continuous	**1.07 (1.04, 1.11)**	**1.06 (1.02, 1.10)**	**1.05 (1.01, 1.09)**	**1.05 (1.01, 1.09)**
Quartile 1 (≤ 1.79 mg/L)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Quartile 2 (1.80 – 2.91 mg/L)	1.18 (0.94, 1.48)	1.07 (0.85, 1.36)	1.07 (0.84, 1.36)	1.08 (0.85, 1.37)
Quartile 3 (2.92 – 4.53 mg/L)	**1.25 (1.00, 1.57)**	1.15 (0.91, 1.46)	1.13 (0.89, 1.44)	1.13 (0.89, 1.43)
Quartile 4 (> 4.53 mg/L)	**1.59 (1.28, 1.98)**	**1.39 (1.10, 1.77)**	**1.34 (1.06, 1.70)**	**1.35 (1.06, 1.71)**
p for trend	**< 0.001**	**0.003**	**0.010**	**0.009**

Abbreviation: UF, Urine fluoride; OR, odds ratio, the risk of cognitive function; CI, confidence interval.
model1 adjustments: sex, age, annual household income, education level and marital status.
model2 adjustments: On the basis of model1, add drinking, BMI and Nocturnal sleep duration.
model3 adjustments: On the basis of model2, add Hypertension and history of coronary heart disease.

Table 3
Relationship between UF concentration (mg/L) and MMSE score.

urinary fluoride	crude **β**(95% CI)	model1 **β**(95% CI)	model2 **β**(95% CI)	model3 **β**(95% CI)
Continuous	**−3.55 (−4.26, −2.85)**	**−1.56 (−2.25, −0.88)**	**−1.37 (−2.05, −0.68)**	**−1.31 (−2.00, −0.64)**
Quartile 1 (≤ 1.79 mg/L)	0.00 (Ref.)	0.00 (Ref.)	0.00 (Ref.)	0.00 (Ref.)
Quartile 2 (1.80–2.91 mg/L)	**−1.31 (−1.90, −0.71)**	−0.47 (−1.02, 0.09)	−0.46 (−1.01, 0.09)	−0.44 (−0.99, 0.11)
Quartile 3 (2.92–4.53 mg/L)	**−1.89 (−2.49, −1.30)**	**−0.70 (−1.26, −0.14)**	**−0.62 (−1.18, −0.06)**	**−0.60 (−1.16, −0.05)**
Quartile 4 (> 4.53 mg/L)	**−2.91 (−3.51, −2.32)**	**−1.36 (−1.92, −0.79)**	**−1.20 (−1.77, −0.64)**	**−1.17 (−1.74, −0.61)**
p for trend	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**

Abbreviation: UF, Urine fluoride; β, regression coefficient; CI, confidence interval.
model1 adjustments: sex, age, annual household income, education level and marital status.
model2 adjustments: On the basis of model1, add drinking, BMI and Nocturnal sleep duration.
model3 adjustments: On the basis of model2, add Hypertension and history of coronary heart disease.

substantially lower BMD and BMDL values, suggesting a heightened risk of neurotoxicity even at relatively low urinary fluoride concentrations.

3.5. Subgroup and sensitivity analyses

We found no evidence of effect modification by sex or age in the association between urinary fluoride and cognitive function; the interaction terms for urinary fluoride with sex and age group were not statistically significant (all p for interaction > 0.05, Table S3). Sensitivity analyses further supported the robustness of these findings. Excluding 45 participants with BMI < 18.5 did not materially change the associations (Table S4). The reclassification of cognitive impairment utilizing education-specific MMSE thresholds demonstrated consistent inverse correlations between urine fluoride levels and cognitive performance (Table S5).

4. Discussion

In this study, cognitive function was assessed using the Chinese version of the MMSE, a validated, efficient and practical assessment tool. Its utility lies in its design, which allows for both a global cognitive score and a nuanced analysis across five core domains: orientation, registration, attention and calculation, recall, and language and praxis(Folstein, et al.,1975). Our results revealed a negative correlation between urine fluoride levels and the total MMSE score, with this adverse correlation was consistently observed across all cognitive domains except for language and praxis. Moreover, multiple linear regression analysis indicated that each unit rise in urine fluoride corresponded to a reduction of 1.31 points in the total MMSE score. Specifically, scores in the domains of orientation, registration, attention and calculation, and recall diminished by 0.73, 0.24, 0.37, and 0.25 points, respectively (Table S1). These findings closely correspond with the recognized objectives about fluoride's neurotoxicity. From a toxicological mechanism standpoint, the hippocampus and prefrontal cortex are pivotal brain areas for cognitive function(Zhao, et al.,2026): the hippocampus is essential for memory storage and retrieval, with structural damage leading to deficits in both immediate and delayed recall(Sun, et al.,2019), while the prefrontal cortex regulates attention and orientation, whose impairment often manifests as cognitive dysfunction. This mechanistic insight aligns with our quantitative findings that urinary fluoride elevation is associated with domain-specific cognitive decline; accumulating evidence has shown that fluoride can penetrate the BBB and accumulate in these brain regions, causing neuronal structural damage (e.g., sparse hippocampal neurons and loss of Nissl bodies in rat models) and reduced synaptic plasticity, thereby resulting in deficits in specific cognitive domains (Dec, et al.,2020; Zhou, et al.,2021; Qiu, et al.,2025). Collectively, our findings not only corroborate these mechanistic insights but also illustrate a domain-specific pattern of cognitive impairment associated with fluoride exposure, thereby addressing a critical gap in previous studies that lacked detailed functional assessment.

In a dose–response perspective, both binary logistic regression and restricted cubic spline analyses confirmed a distinct exposure–response gradient. Participants in the highest quartile of urine fluoride (> 4.53

Table 4
Estimated UF BMDs and BMDLs (mg/L) based on BMR of 1%,2% and 5% for Cognitive impairment.

Model	Weight (%)	PPP	BMR = 1%		BMR = 2%		BMR = 5%	
			BMD	BMDL	BMD	BMDL	BMD	BMDL
Logistic	26.72	0.546	0.42	0.25	0.83	0.49	2.07	1.22
LogLogistic	6.56	0.621	7.27	3.94	7.70	4.70	8.37	5.91
Probit	26.30	0.545	0.41	0.24	0.82	0.49	2.05	1.21
LogProbit	11.74	0.689	8.70	6.63	8.90	7.05	9.22	7.70
Quantal linear	23.96	0.556	0.37	0.20	0.75	0.40	1.91	1.02
Multistage 2	1.30	0.593	0.70	0.27	1.28	0.53	2.65	1.31
Weibull	3.35	0.603	3.02	0.83	3.82	1.36	5.20	2.58
Dichotomous Hill	0.07	0.532	6.61	1.62	7.14	2.14	7.94	3.37
Model average			0.49	0.24	0.97	0.47	2.44	1.18

Abbreviations: UF, Urine fluoride; BMD, benchmark dose; BMDL, benchmark dose lower bound;
BMR, benchmark response; PPP, posterior prediction P-value.

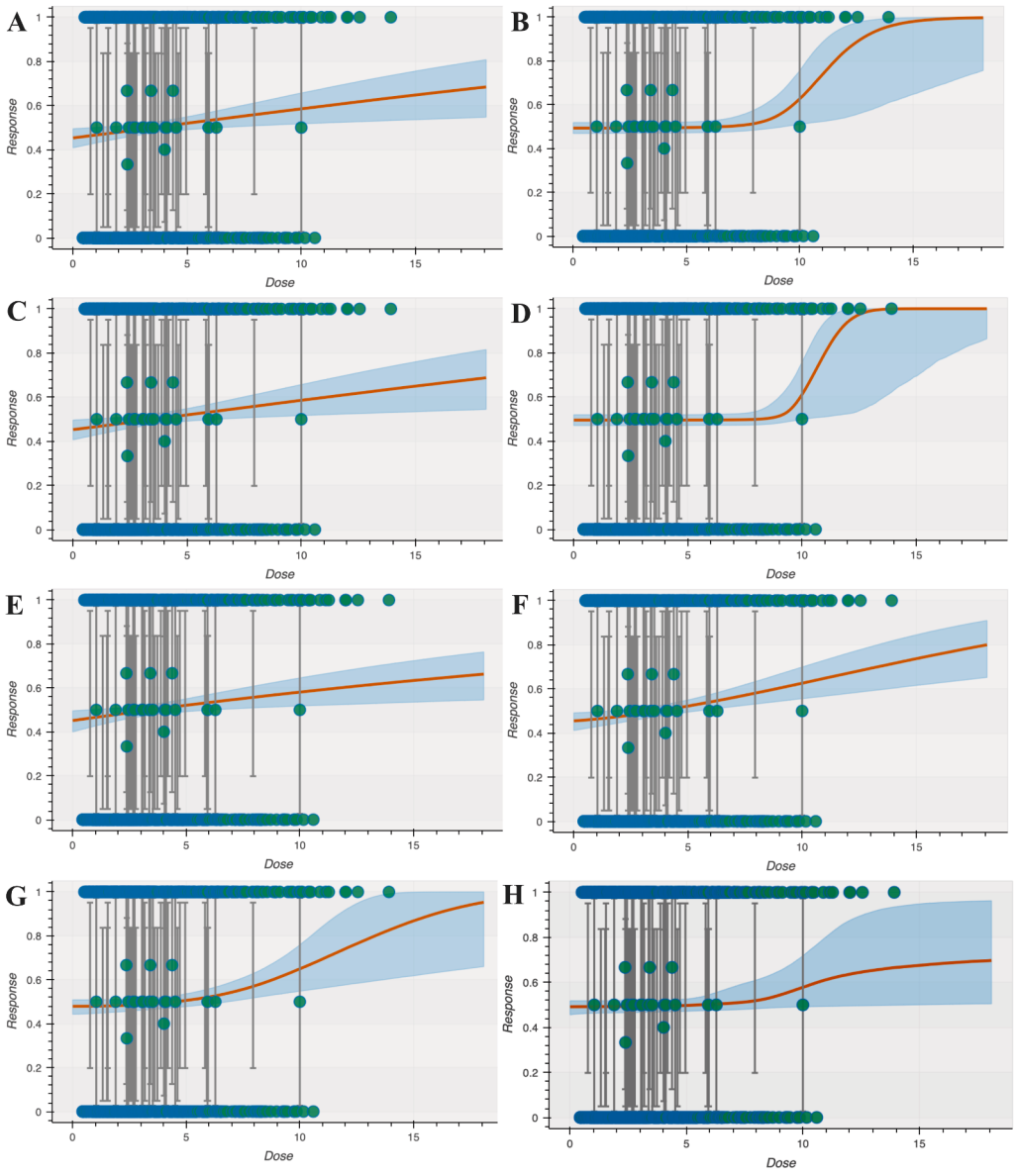

Fig. 3. The dose–response relationship between Urine fluoride concentration (mg/L) and cognitive fuction, (A) Logistic model; (B) LogLogistic model; (C) Probit model; (D) LogProbit model; (E) Quantal linear model; (F) Multistage 2 model; (G) Weibull model;(H) Dichotomous Hill model.

mg/L) exhibited a 35% elevated risk of cognitive impairment (OR = 1.35) compared to those in the lowest quartile, with a consistent rise in risk corresponding to greater urinary fluoride concentrations (p for trend < 0.05). Most previous studies have concentrated on either children's intelligence or cognitive decline in the elderly, whereas our study included an adult population aged 18 years and older (median age 61 years). Stratified analyses further demonstrated that the correlation between urinary fluoride and cognitive impairment was consistent across age groups (e.g., $<$ 60 years and $\geq$ 60 years; Table S3), suggesting that fluoride neurotoxicity may represent a prolonged cumulative process rather than being limited to a particular age range. Consequently, our findings fill a significant gap in the literature and offer stronger evidence for a complete evaluation of the neurohealth concerns associated with fluoride exposure at the population level.

Furthermore, we employed urinary fluoride as an internal exposure biomarker, which more accurately reflects individual fluoride intake than drinking-water fluoride concentration alone(Khan, et al.,2025), thereby reducing exposure misclassification arising from discrepancies between water fluoride levels and actual ingestion. By excluding individuals who had resided in the study area for fewer than 10 years, we ensured chronic fluoride exposure and minimized the potential for reverse causation, strengthening the plausibility of the observed association between excessive fluoride exposure and cognitive impairment. As drinking water was the primary and stable fluoride exposure source for our study population, urinary fluoride levels were relatively consistent within this population, which to some extent supports that a single spot urinary fluoride sample can reasonably reflect participants' long-term fluoride burden. Previous studies have confirmed that, among populations with stable fluoride exposure, single-spot urinary fluoride concentrations are moderately correlated with long-term cumulative fluoride exposure and satisfy the requirements of epidemiological association analyses(Eskandari, et al.,2023). Further analysis showed that daily water intake was weakly correlated with urinary fluoride concentration (Fig. S2, $r_s = -0.05$, $p = 0.06$), and after adjusting for daily water intake as a covariate, the direction and significance of the association between fluoride exposure and cognitive impairment remained unchanged (Table S6), suggesting that hydration status has no significant interference with exposure assessment and further validates the

reliability of our exposure evaluation.

The BMD methodology has been extensively utilized as a substitute for the conventional NOAEL/LOAEL technique in toxicological dose–response assessment and health risk assessments(Shao and Shapiro,2018). Conventional BMD computation tools (e.g., BMDS, PROAST) have inherent limitations in integrating prior knowledge and generating probabilistic BMD distributions. The BBMD system is an online BMD analysis platform constructed within a Bayesian statistical framework that offers distinct advantages over frequentist tools such as BMDS: BBMD utilizes MCMC sampling to produce posterior distributions for both BMD and BMDL, instead of providing single-point estimates. This trait enhances its suitability for probabilistic risk assessment. Furthermore, BBMD uses the BMA method to synthesize outcomes from many models, producing more reliable estimates of BMD and BMDL that explicitly incorporate model uncertainty(Shao and Shapiro,2018; Ji, et al.,2022).

In the present work, we adopted a progressive analytical strategy of "full-sample exploration and subset-based precise validation". A regression analysis was first conducted in the full sample (N = 3,126) to preliminarily identify the positive association between urinary fluoride and cognitive impairment, laying the foundation for subsequent BMD estimation. To further control for confounding bias, prior to BMD modeling, 571 pairs of participants with cognitive impairment and normal cognition were matched at a 1:1 ratio using PSM to balance key baseline characteristics including age, sex, household income, and marital status between the two groups. Finally, an analytical subset of 1,142 participants was established for core association verification and BMD estimation, minimizing the interference of non-exposure factors at the source. Based on this PSM-matched subset, the BBMD software was used to fit the dose–response relationship between urinary fluoride and cognitive impairment, and to estimate the BMD and BMDL for urinary fluoride. Cognitive impairment was treated as a binary endpoint for BMD calculation, justified by BMD estimation principles and practical risk assessment needs. Binary outcomes clarify BMR by defining it as an increased incidence of cognitive impairment, avoiding the ambiguity of continuous MMSE scores with potential measurement error. Using epidemiologically validated education-adjusted MMSE cut-offs for Chinese populations converts abstract scores into epidemiologically meaningful classifications and reduces interference from confounding factors and measurement variability in continuous cognitive assessment tools(Zhang, et al.,1990; Li, et al.,2016). In all eight dichotomous models, the predicted probability of cognitive impairment increased with rising urinary fluoride concentrations. All models had PPP between 0.05 and 0.95, signifying an adequate model fit. Among the candidate models, the Logistic and Probit models had the highest posterior weights (26.72% and 26.30%, respectively), indicating that they best represented the connection between urinary fluoride and cognitive impairment in our data. At a BMR of 5%, the BMDLs from the Logistic and Probit models were 1.22 mg/L and 1.21 mg/L, respectively, closely aligning with the model-averaged BMDL of 1.18 mg/L. When study participants with chronic diseases were not excluded and modeling was re-performed after only matching core characteristics via PSM, the BMDL was 1.15 mg/L at a BMR of 5% (Table S7), which was highly consistent with the primary BBMD analysis result (1.18 mg/L) and confirmed the robustness of the core BBMD findings.

Our BBMD-derived BMDL estimates for urinary fluoride align with the trends reported in a previous fluoride neurotoxicity study in a coal-burning fluorosis area in Guizhou, China(Jin, et al.,2024), while offering notable methodological and population-specific advantages. The larger sample size (N = 1,142) enhances the stability of our estimates, while the use of PSM effectively controlled for key confounding biases. Furthermore, by focusing on the water-borne exposure pathway predominant in most Chinese endemic areas, our findings possess stronger generalizability to similar regions across the country.

In a public health perspective, the BMDL is a critical reference value for establishing safety thresholds, with its value directly influencing the stringency of health standards. This study derived urinary fluoride BMDLs based on two distinct endpoints: first, a model-averaged BMDL of 1.18 mg/L corresponding to a BMR of 5%; and second, a BMDL of 0.84 mg/L (Table S8), derived by defining a clinically meaningful cognitive decline as a MMSE score reduction of $\geq$ 4 points, consistent with previous studies(Tombaugh,2005; Hensel, et al.,2007). Notably, both estimated BMDLs are substantially lower than the current geometric mean limit for adult urinary fluoride (1.6 mg/L) specified in the Chinese industry standard WS/T 10023–2024, "Safe Guidance Value for Population Urinary Fluoride". This notable discrepancy between our neurotoxicity-based BMDL and the current Chinese national standard highlights the urgent need to revise the existing urinary fluoride reference value by incorporating neurological health protection into the regulatory framework, thereby laying a foundation for the proposed revision framework below. This discrepancy is further accentuated when more conservative BMRs are applied; at BMRs of 2% and 1%, the model-averaged BMDLs decreased to 0.47 mg/L and 0.24 mg/L, respectively.

This neurotoxicity-driven evidence base leads us to propose a "neuroprotection-oriented" revision of the urinary fluoride standard, establishing a dual-reference-value system that addresses both skeletal/dental protection and nervous system protection in parallel. Specifically, we recommend preliminarily setting the neurohealth protection reference value for adult urinary fluoride at 1.0 mg/L. This value is a conservative derivation from our study's BMDL of 1.18 mg/L (at a BMR of 5%), which represents a risk-based reference point rather than a strict toxicological threshold, enabling differentiated management from the existing population urinary fluoride normal value of 1.6 mg/L. Our choice of a 5% BMR as the core for deriving this neurohealth safety reference value balances academic convention, public health practice, and the characteristics of cognitive endpoints. First, most previous benchmark dose studies on neurotoxicity endpoints have used this level, ensuring the comparability of our findings with existing academic consensus(Kullar, et al.,2019; Huang, et al.,2024); Second, from the perspective of balancing health protection and health economics, the BMDL values derived from 1% and 2% BMR (0.24 mg/L and 0.47 mg/L, respectively) are overly stringent, making the corresponding control measures infeasible in endemic fluorosis areas with drinking water as the exposure source. In contrast, the BMDL corresponding to 5% BMR (1.18 mg/L) can effectively prevent the risk of cognitive impairment while aligning with the actual public health resource conditions in the region.

The implementation of this dual-reference-value system requires three targeted and actionable components. First, a graded risk-warning system could be implemented. In places affected by drinking-water-type fluorosis, a mean urine fluoride level exceeding 1.0 mg/L should activate a "neurotoxicity risk warning," necessitating targeted actions such as improved cognitive screening and expedited safe-water or defluoridation initiatives. When the average urine fluoride concentration surpasses 1.6 mg/L, a corresponding "bone/teeth toxicity risk warning" should be initiated, along with enhanced prevention and management of dental and skeletal fluorosis. Second, the scope and substance of current standards could be augmented. We propose the inclusion of a distinct "neurological health protection" section in WS/T 10023–2024, explicitly delineating the target demographics (e.g., inhabitants of endemic fluorosis regions and chronic consumers of high-fluoride water), the neurohealth protection reference value, and the suggested monitoring frequency (e.g., population-based urinary fluoride and cognitive evaluations biennially to triennially). Third, extra safeguards for vulnerable populations, especially the elderly, should be taken into account. Due to age-related deterioration of blood–brain barrier integrity, the elderly may exhibit increased vulnerability to fluoride-associated neurotoxicity effects(Bowman, et al.,2018). In our investigation, the BMDL for individuals aged $\geq$ 60 years at a BMR of 5% was 0.83 mg/L (Table S9), indicating a diminished tolerance reference point. We propose tentatively reducing the neurohealth protection reference value for older

persons to 0.8 mg/L to enhance the margin of protection.

This study possesses numerous significant strengths. First, the study population encompassed the entire adult age spectrum. Instead of concentrating exclusively on children or the elderly, we investigated the correlation between overall fluoride exposure and cognitive function in adults aged 18 years and older. Our stratified analyses confirmed that the association between urinary fluoride and cognitive impairment was consistent across various age groups (<60 and ≥ 60 years), thereby filling a significant gap in previous age-specific research. Second, our technique was stringent. Utilising the BBMD system with BMA to obtain BMDs and BMDLs diminished the uncertainty linked to dependence on a singular model. The implementation of PSM further accounted for significant confounders, enhancing the validity of the observed correlations. Furthermore, we utilized a substantial sample size and employed many supplementary methodologies—including Spearman correlation, restricted cubic splines, and multivariable regression—to delineate the dose–response connection, so enhancing the robustness of our conclusions.

Nevertheless, several limitations should be acknowledged. First, given the cross-sectional design of this study, our findings reflect associations rather than causal relationships between urinary fluoride and cognitive impairment. The BMDL-derived reference values established herein serve as risk-based benchmarks for public health guidance, rather than definitive toxicological thresholds, and thus warrant cautious interpretation pending future longitudinal investigations or toxicological validation. Although we comprehensively adjusted for covariates, applied PSM method, and conducted supplementary analyses confirming no significant group differences in renal function (serum UA, BUN) or nutritional status indicators (calcium supplement use, dairy intake), factors known to modulate urinary fluoride levels (Table S2 and S10), residual and unmeasured confounding (e.g., co-exposure to other neurotoxicants) cannot be entirely ruled out, which may introduce bias into the derived neuroprotective reference values. Furthermore, the study population was confined to a single drinking-water fluorosis area, which restricts the generalizability of our findings to other fluorosis subtypes or non-endemic regions. Finally, the MMSE exhibits ceiling effects and limited sensitivity in detecting mild cognitive impairment, which may underestimate subtle neurotoxic effects of fluoride and compromise the accuracy of BMDL estimation at low exposure levels. Collectively, these limitations do not negate the core association observed in this study but underscore the need for prudent interpretation of the results, and future research is warranted to address these issues to improve the reliability and generalizability of evidence regarding fluoride-related neurotoxicity risks.

5. Conclusion

This study illustrates a positive association between urinary fluoride concentrations and cognitive impairment in individuals residing in an area affected by drinking-water fluorosis. A 1 mg/L rise in urinary fluoride was associated with a 5% higher likelihood of cognitive impairment. The neurohealth protection reference value, as determined by the BBMD methodology (BMDL = 1.18 mg/L for BMR = 5%), is inferior to the existing Chinese reference value for adults (1.6 mg/L), indicating that more rigorous urinary fluoride regulations may be necessary to mitigate fluoride-induced neurotoxicity in populations subjected to elevated fluoride levels in drinking water. Our findings provide critical scientific evidence for the revision of existing urinary fluoride standards to incorporate neurological health protection, and support the establishment of a dual-reference-value system to address both skeletal/dental and nervous system risks associated with fluoride exposure.

CRediT authorship contribution statement

Shuaifei Yang: Writing – original draft, Visualization, Methodology, Conceptualization. **Meichen Zhang:** Visualization, Formal analysis. **Yue Gao:** Writing – review & editing. **Xirui Feng:** Investigation. **Xin Wang:** Investigation. **Jianguo Feng:** Investigation. **Mengyuan Li:** Investigation. **Xinhua Shao:** Investigation. **Yanmei Yang:** Writing – review & editing. **Yanhui Gao:** Supervision, Project administration, Funding acquisition.

Ethics approval

The study was proved by the Harbin Medical University, Center for Endemic Disease Control Ethics Committee (HRBMUECDC 20210303).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2026.110190.

Data availability

Data will be made available on request.

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