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ORIGINAL PAPER

Relatively low fluoride in drinking water increases risk of knee osteoarthritis (KOA): a population-based cross-sectional study in China

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Abstract Previous studies indicate that fluoride in drinking water has a toxic effect on cartilage and skeleton, which triggers osteoarthritis (OA) of which the most frequent is knee OA (KOA). A cross-sectional study was conducted to assess the association between fluoride exposure and KOA among 1128 subjects. Water fluoride (WF) and urinary fluoride (UF) were chosen as external exposure (internal exposure) of fluoride. Logistic regression analysis showed that an increased fluoride exposure was a risk factor for KOA (WF: OR = 1.318, 95% CI 1.162–1.495, $p < 0.001$; UF: OR = 1.210, 95% CI 1.119–1.310, $p < 0.001$). After adjusting for covariates, the risk of KOA in the 4th quartile (Q) of WF was twice that of the 1st Q (OR = 2.079, 95% CI 1.448–2.986, $p < 0.001$). The risks of KOA in the 2nd Q, 3rd Q and 4th Q of UF were 1.6, 1.5, and 2.9 times higher than in the 1stQ (OR = 1.597, 95% CI 1.066–2.393, $p = 0.023$; OR = 1.560, 95% CI 1.043–2.333, $p = 0.030$; OR = 2.897, 95% CI 1.957–4.288, $p < 0.001$). The population aged < 60 exposed to the 4th Q of WF (or UF) had a higher risk than the population exposed to the 1st Q of WF (or UF) ($OR_{WF} = 1.958$, 95% CI 1.249–3.070, $p = 0.003$; $OR_{UF} = 2.923$, 95% CI 1.814–4.711, $p < 0.001$). With increasing UF by Q, the male had a risk of KOA. In conclusion, excessive fluoride dose in drinking water could increase the risk of KOA. Especially, the population with aged < 60, male and obesity more likely to having KOA when they exposed to same higher fluoride.

Keywords Knee osteoarthritis · Fluoride · Drinking water · Urine · Fluorosis · Cross-sectional study

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Introduction

Osteoarthritis (OA) is a prevalent chronic degenerative joint disease with unknown etiology, which involve cartilage and surrounding tissues. The predilection sites are knee joint, hip joint, etc. (Brandt et al., 2006; Hunter & Bierma-Zeinstra, 2019). X-ray examination is the first choice for the diagnosis (Hunter et al., 2014; Santy-Tomlinson, 2015). The disease manifests by pain, stiffness, swelling, disability and can lead to important body burden. According to the literature reports, there are over 300 million patients with OA worldwide, with approximately 61.2 million in China (Safiri et al., 2020). The prevalence of OA is continuously increasing as the global life expectancy rises (Woolf & Pfleger, 2003). As a chronic, disabling and high economic burden disease, OA has attracted the worldwide attention (Center for Disease Control & Prevention., 2020; Cross et al., 2014; United States Bone & Joint Initiative, 2018), but its etiology is still unclear.

Fluoride is widely distributed in nature and is an important environmental pollutant (Qingguang et al., 2022). Fluoride is sourced from drinking water, air, food, skin contact (He et al., 2022), special living habits such as drinking high-fluoride brick tea (Fan et al., 2016) and burning high-fluoride coal (Qin et al., 2009), fluoride products which include: toothpastes, fluoride varnishes, fluoride containing whitening agents, and other fluoride containing cleaning products (Carey, 2014), etc. Fluoride in drinking water is the leading exposure of fluoride, which causes skeletal fluorosis (SF) in the population exposed to excessive fluoride (Sharma et al., 2017; Srivastava & Flora, 2020).

SF is the most serious consequence of excessive fluoride exposure and manifests by chronic joint pain, backache, stiffness and rigidity of the spine, physical limitations, inadequate labor capacity, and disability (Sellami et al., 2020). These symptoms similar to OA are related to articular damage and calcification of ligaments caused by excessive fluoride accumulation in bone tissue (Cui et al., 2012). It clues that fluoride maybe link with the risk of having OA. The scholars in India, Turkey and China conducted the smaller sample size of ecological studies to explore the link between fluoride and OA. In 2001, Turkish scholars reported that endemic fluorosis may increase the severity of KOA in an ecological study with 56 endemic fluorosis patients and 40 non-endemic control patients (Savas et al., 2001). An ecological study conducted in Gaomi City, China, in 2006 found that the more frequency of OA symptoms was reported in the population living in the areas with higher water fluoride (Ge et al., 2006). A observational study in a total of 80 OA patients in an Indian hospital in 2020 showed that elevated serum fluoride levels increased the risk of KOA, and linked with more severe symptoms (Singh et al., 2020). A frequency-matched case–control study (186 OA patients and 186 healthy participants) conducted by our group found excessive exposure of water fluoride could have more impact on the specific population such as non-obese, and adult aged $\leq$ 60 years (Sowanou et al., 2022). The above studies indicate higher fluoride in drinking water linked with a higher risk of OA. However, the epidemiological evidence on the association between fluoride and OA is not very strong, because of study design, smaller sample size, lower statistical power, unclear dose–response relationship, confounding factors without controlling, self-report symptom, etc.

To address the weakness, a cross-sectional study was strictly conducted by our group to explore the dose–response relationship between fluoride in water and urine and KOA in 1128 adults with controlling confounding factors, X-ray diagnosis, and advanced statistical analysis.

Materials and methods

Study population and design

A cross-sectional study was conducted in Zhaodong city of Suihua city, Dumeng county and Zhaozhou county of Daqing city, Baiquan county, Yi 'an county, Tailai county and Longjiang county of Qiqihar city, Heilongjiang province, People's Republic of China. Sample size was calculated from an online open source epidemiologic statistics for public health (Dean et al., 2013), with 59.03% as OA prevalence from the fluorosis-afflicted area in China (Jia et al., 2022), and with the desired CI of 95%.

Inclusion criteria: The subjects enrolled in this study were older than 18 years, and born and bred in the named villages. A participant is selected as OA case only if he meets the defined criteria and is diagnosed by both radiologists. A participant is selected

as a control only if he meets the criteria for being a healthy participant.

Exclusion criteria: Subjects with incomplete data, rheumatoid arthritis, prior joint injury, and trauma were excluded. The participant's selection flowchart was as shown in Fig. 1

Collection of data and biological samples

All participants received written information sheets for the study and provided informed consent. The data were collected using questionnaire, administered to all subjects by specially trained investigators. The questionnaire was used to collect the participant's information including age, gender, height, weight, education level (level 5), economic level (level 5), smoking (level 5), drinking frequency (level 4), BMI (according to the Chinese BMI standard division (ChineseStandard.net., 2013)).

Drinking water and urine samples from each subject were collected with a labeled polyethylene tube (50 ml) and stored at − 20 ℃ for laboratory testing.

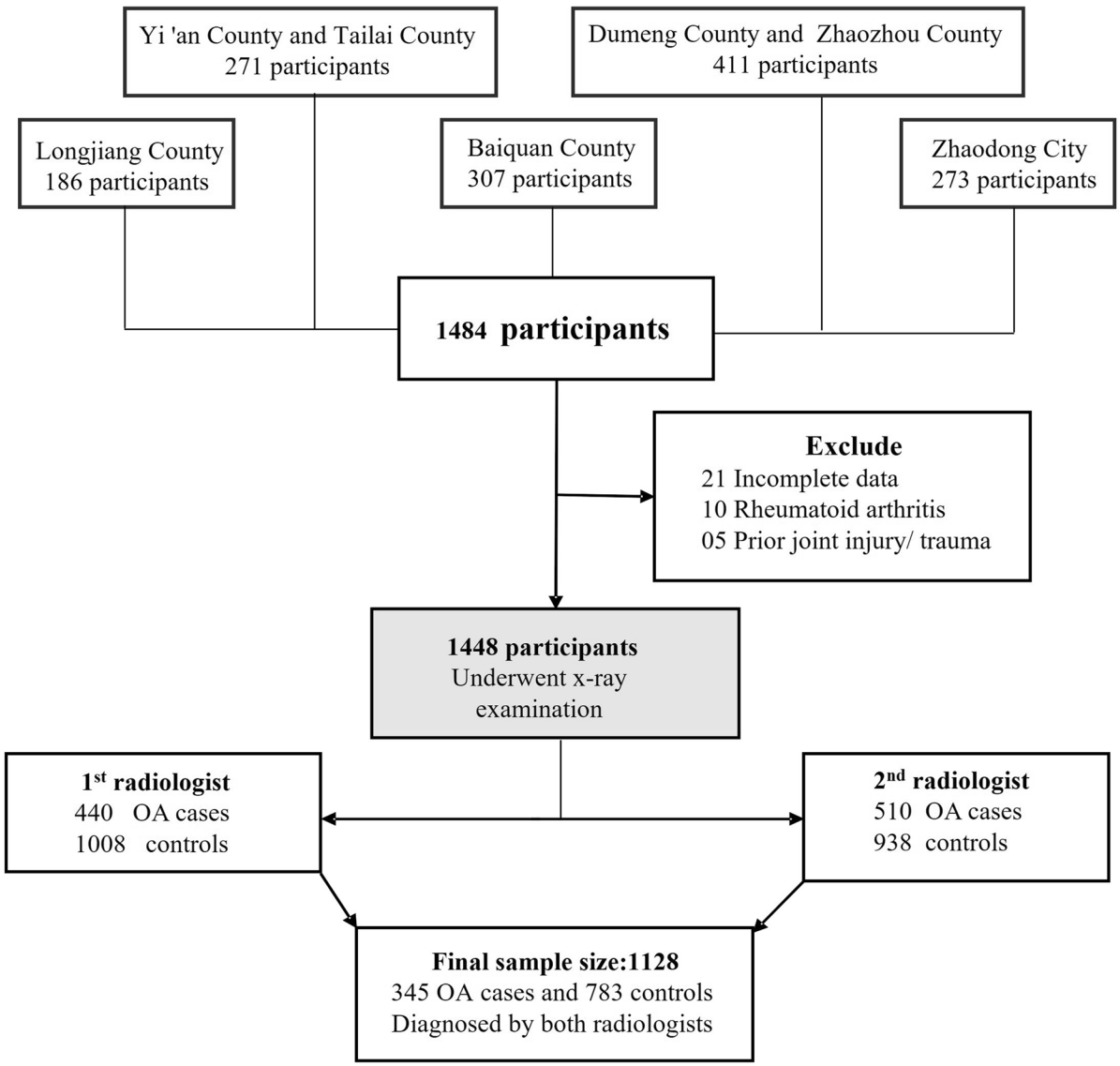

Fig. 1 Participant's selection flowchart

Fluoride concentration analysis

All samples of the study for fluoride analysis were stored at − 20 ℃ until analyzed. Fluoride content was detected by a fluoride ion selective electrode. (Shanghai Yidian scientific instrument co., LTD). The operating procedure of fluoride analysis in water and urine was separately performed according to the standard examination methods for drinking water–Nonmetal parameters (GB 5750.5-2006, China), and the determination of fluoride in urine-ion selective electrode method (WS/T 89-2015, China).

According to the national standard《GB 5749-2022》of the People's Republic of China (ChineseStandard.net., 2022), the fluoride content in drinking water is less than 1.0 mg/L; according to the health industry standard 《WS/T 256-2005》of the People's Republic of China (ChineseStandard.net., 2005), the geometric mean of UF in adults is not more than 1.6 mg/L. Using WF as external exposure and UF as internal exposure.

X-ray examination

High frequency portable digital Medical Diagnostic X-ray imaging DR system (Beijing Lang'an Imaging Technology Co., LTD.) was applied. Forward X-ray examination was applied to the elbow and knee joint of all the subjects. The diagnosis was made according to the Chinese OA diagnosis and treatment guidelines (2018 edition) (Joint Surgery Branch of the Chinese Orthopaedic Association, 2021).

To guarantee the accuracy of the diagnosis, all films were not only evaluated by field investigator, but also brought to the radiological unit of the 2nd affiliated hospital outpatient's department of Harbin Medical University. They were then read by an experienced, academically based bone and joint radiologist using the same criteria. Only the films with OA diagnosis from both radiologists were accepted and considered for this study.

Ethics statement

The study was approved by the Ethical Review Board of Harbin Medical University (HMUIRB20120021). The study has obtained the necessary approvals from relevant authorities in the city. Each participant of the study population signed a written informed consent.

Statistical analysis

EpiData 3.1 and Excel 2007 were used for data entry. R 4.0.3 was used for statistical analysis. Two-tailed $p \leq 0.05$ was used for all tests as significance level.

Body mass index (BMI (kg/m^2) = weight/height^2). Data were expressed as mean ± SD or P50 (P25–P75). Quantitative variables were evaluated by Student's t test and Kruskal–Wallis H test; qualitative variables were compared using Chi-square test. The correlation between fluoride exposure concentration and the prevalence of knee OA (KOA) was analyzed, and the exposure response curve was drawn. Different logistic regression models were used to calculate OR and 95% CI, and the relationship between fluoride exposure and the risk of KOA was analyzed and evaluated. In order to explore the independent effect of fluoride exposure, interaction analysis was performed, and to limit the influence of confounding factors, stratified analysis was conducted.

Results

Fluoride exposure and KOA prevalence

A total of 1128 subjects were investigated, including 345 cases (KOA patients) aged 58 ± 10 years and 783 controls (healthy people) aged 50 ± 12 years. The fluoride concentration in the water samples ranged from 0.013 to 5.10 mg/L knowing that the China's national standard limit is 1.0 mg/L. The fluoride concentration in the urine samples ranged from 0.049 to 15.88 mg/L knowing that the China's national standard limit is 1.6 mg/L.

The subjects were equally grouped by the percentiles of WF and UF concentration, and the percentage chart was drawn according to the concentration of fluoride and the prevalence of KOA in the group. As shown in Fig. 2, with the increase in fluoride exposure (external exposure: WF, internal exposure: UF), the prevalence of KOA showed an increasing trend.

Chi-square test was performed, suggesting that there was a dose–response relationship between

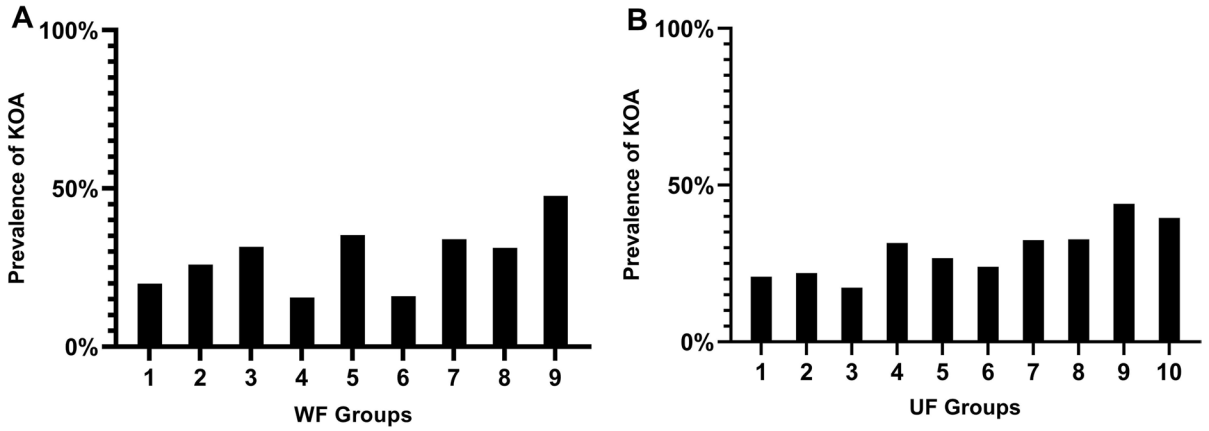

Fig. 2 KOA prevalence in the groups with different fluoride exposure. WF, water fluoride intake; UF, urine fluoride; KOA, knee osteoarthritis. *Note*: The prevalence of KOA in each group was calculated, all the subjects were equally grouped by the percentiles of WF (**A**) and UF (**B**) concentration. **A** WF Groups (mg/L), Group 1 (0–0.1649), Group 2 (0.1649–0.1944), Group 3 (0.1944–0.3000), Group 4 (0.3000–0.3855), Group 5 (0.3855–0.4600), Group 6 (0.4600–0.6837), Group 7 (0.6837–1.0841), Group 8 (1.0841–2.0620), Group 9 (> 2.0620). **B** UF Groups (mg/L), Group 1 (0–0.4190), Group 2 (0.4190–0.6100), Group 3 (0.6100–0.8000), Group 4 (0.8000–1.0200), Group 5 (1.0200–1.3226), Group 6 (1.3226–1.6600), Group 7 (1.6600–2.0640), Group 8 (2.0640–2.6180), Group 9 (2.6180–3.5535), Group 10 (> 3.5535)

fluoride exposure concentration and KOA (WF: $\chi^2 = 44.89$, $p < 0.001$; UF: $\chi^2 = 34.66$, $p < 0.001$). Rank correlation test showed that there was a positive correlation (WF: $r_s = 0.688$, $p = 0.041$; UF: $r_s = 0.677$, $p = 0.032$). A nonlinear model was used to plot the exposure response curve between fluoride exposure and KOA prevalence, as shown in Fig. 3, fluoride exposure (WF and UF) was both positively correlated with KOA prevalence (WF: $R^2 = 0.30449$, $p = 0.00751$; UF: $R^2 = 0.68932$, $p = 0.002262$).

Demographic information for the case–control study

The fluoride exposure level, gender, age, smoking, drinking, BMI, education and income were statistically analyzed between the cases and the control group. As shown in Table 1, older age and female sex increased the risk of KOA; higher income and education levels reduced the risk of KOA; BMI > 24 and above increased risk of KOA; WF and urinary fluoride (UF) in the cases were both significantly higher than those in the controls.

Logistics analysis predicts KOA risk with different fluoride exposure

In conclusion, fluoride exposure (WF or UF) is a risk factor for KOA, in order to further clarify the role between fluoride exposure and the risk of KOA, different regression models were used for correction analysis.

As shown in Table 2, in model 1(WF was a continuous variable), the increased concentration of WF was significantly correlated with the occurrence of KOA, for every 1 mg/L increase in WF level, the risk of KOA increased by 31.8%. In model 2 (WF was a categorical variable), the risk of KOA increased with increasing WF concentration. In order to reduce the influence of confounding factors, the binary logistic regression model was used to substitute different influencing factors into the correction analysis. The results of different correction analyses all showed that the risk of KOA increased with the increase of WF, after adjusting with the confounders, the risk of KOA in the 4th quartile (Q) of WF was twice than that in the 1st Q of WF.

To further evaluate the association between fluoride exposure and the risk of KOA, UF was selected as a proxy for internal exposure. As shown in Table 3, in the unconditional logistic regression analysis, in model 1 (UF as a continuous variable), increased UF concentration was significantly correlated with the occurrence of KOA (OR = 1.210, 95% CI 1.119–1.310, $p < 0.001$). In other words, for every 1 mg/L increase in UF level, the risk of KOA increased by 21%. In Model 2 (UF as an ordinal

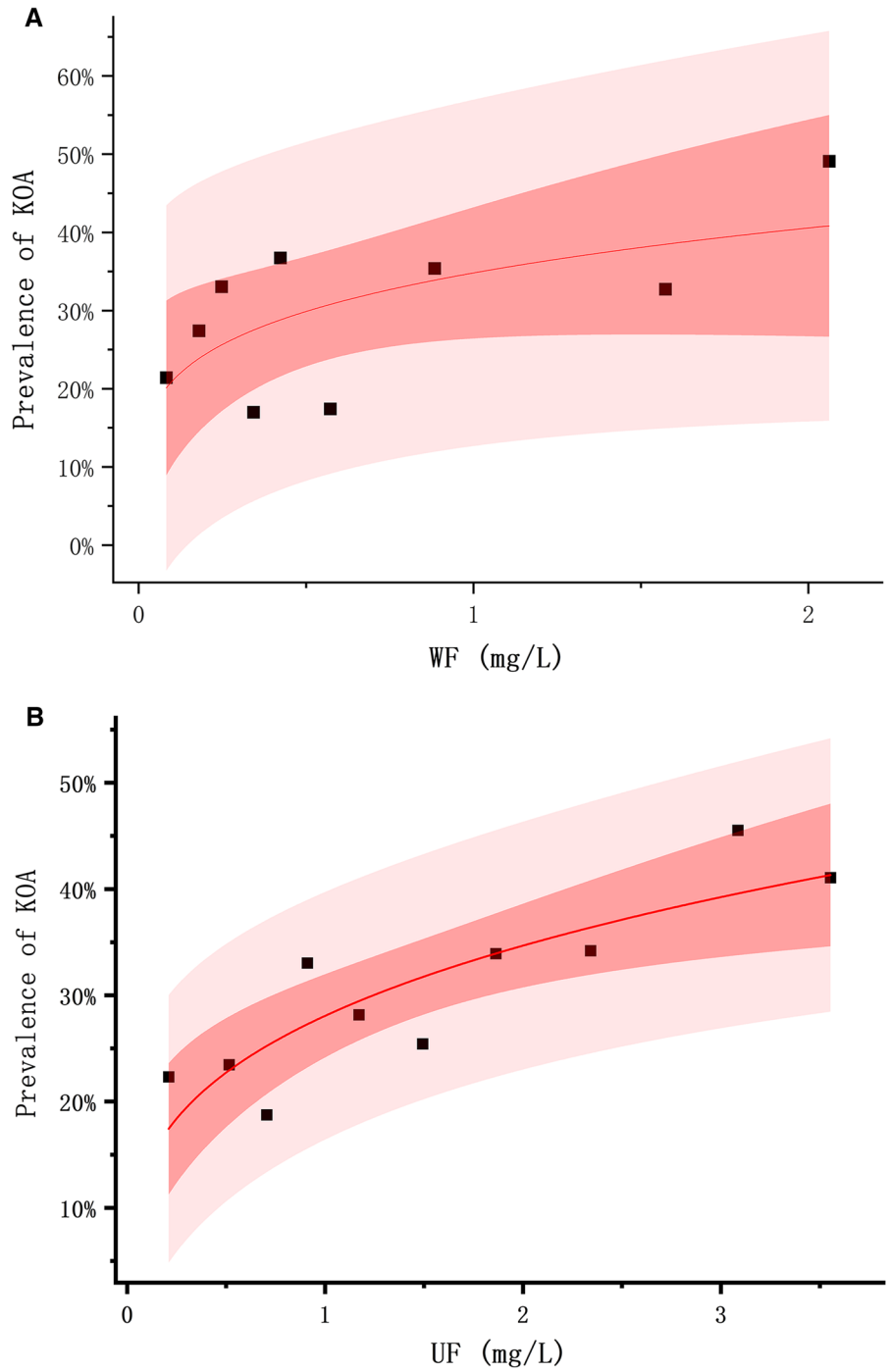

Fig. 3 Exposure–response association curve between fluoride exposure and KOA prevalence. ▪ : Prevalence of KOA : Prevalence of KOA; ——: the mean estimate : the mean estimate; ▭: 95% confidence interval : 95% confidence interval; ▭: 95% prediction interval : 95% prediction interval. WF, water fluoride intake; UF, urine fluoride; KOA, knee osteoarthritis. *Note*: Correlation analysis and prediction analysis were performed between the median of WF (**A**) and UF (**B**) concentration in each group and the prevalence of KOA

variable), the risk of KOA increased with increasing UF concentration. The analysis results of different models all showed that the risk of KOA increased with the increase of UF content. In order to reduce the influence of confounding factors, binary logistic regression model was used to substitute different influencing factors into correction analysis, after adjusting with the confounders, the risks of KOA in the 2nd Q, 3rd Q and 4th Q of UF were 1.6, 1.5, and 2.8 times higher than those in the 1st Q of UF.

Table 1 Comparisons of variables between case and control in KOA

Characteristics	Category	Control $n=783$ n (%)	Case $n=345$ n (%)	OR (95% CI)[a]	p	p-trend
Age (year)					**< 0.001**	**< 0.001**
	Mean age	50 ± 12	58 ± 10			
	< 45	281 (35.9)	37 (10.7)	1 (reference)		
	45 ~	335 (42.8%)	175 (50.7)	**3.967 (2.960, 5.851)**		
	60 ~	167 (21.3)	133 (38.6)	**6.048 (4.008, 9.128)**		
Gender					**0.039**	**0.040**
	Male	235 (30)	125 (36.2)	1 (reference)		
	Female	548 (70)	220 (62.8)	**1.325 (1.014, 1.731)**		
Education					**0.005**	**0.001**
	Illiteracy	123 (15.7)	81 (23.5)	1 (reference)		
	Primary school	360 (46.0)	161 (46.7)	**0.679 (0.485, 0.951)**		
	Middle school	217 (27.7)	77 (22.3)	**0.539 (0.368,0.790)**		
	High school and above	83 (10.6)	26 (7.5)	**0.476 (0.282, 0.802)**		
Income (RMB)					**< 0.001**	**< 0.001**
	< 3000	92 (11.7)	63 (18.3)	1 (reference)		
	3000 ~	57 (7.2)	41 (11.9)	1.609 (0.639, 1.786)		
	5000 ~	120 (15.3)	62 (18.0)	0.754 (0.484, 1.176)		
	10,000 ~	318 (40.4)	120 (34.8)	**0.555 (0.378, 0.814)**		
	30,000 ~	199 (25.4)	59 (17.1)	**0.433 (0.281, 0.667)**		
Smoking					0.207	0.660
	Don't smoke	502 (64.1)	225 (65.2)	1 (reference)		
	< 10	72 (9.2)	25 (7.2)	0.775 (0.479, 1.254)		
	10 ~	96 (12.3)	33 (9.6)	0.767 (0.501, 1.174)		
	19 ~	113 (14.4)	62 (18.0)	1.224 (0.865, 1.733)		
Drinking					0.094	0.145
	Don't drink	561 (71.6)	243 (70.4)	1 (reference)		
	Occasionally	90 (11.5)	27 (7.8)	0.693 (0.439, 1.092)		
	Frequently	38 (4.9)	20 (5.8)	1.215 (0.693, 2.131)		
	Everyday	94 (12.0)	55 (15.9)	1.351 (0.938, 1.946)		
BMI (kg/m^2)					**< 0.001**	**< 0.001**
	< 18.5	42 (5.4)	10 (2.9)	1 (reference)		
	18.5 ~	379 (48.4)	127 (36.8)	1.407 (0.686, 2.887)	0.351	
	24 ~	263 (33.6)	138 (40.0)	**2.204 (1.073, 4.526)**	**0.031**	
	27.9 ~	99 (12.6)	70 (20.3)	**2.970 (1.396, 6.315)**	**0.005**	
WF (mg/L)		0.34 (0.23, 0.76)	0.44 (0.30, 1.17)		**< 0.001**	
UF (mg/L)		1.17 (0.66, 2.12)	1.67 (0.87, 2.81)		**< 0.001**	

Age was represented as Mean ± SD; WF and UF were represented as median (P25, P75)

KOA, knee osteoarthritis; WF, water fluoride intake; UF, urine fluoride

[a]Univariate logistic regression analysis; bold fonts, $p < 0.05$

Table 2 Association between WF and KOA in full sample

Models	Sample size	Category	OR (95% CI)	*p* value	*p*-trend	Adjusted OR (95% CI)[a]	*p* value	*p*-trend	Adjusted OR (95% CI)[b]	*p* value	*p*-trend
Mode1	1128	Each 1 mg/L increase	**1.318 (1.162, 1.495)**	**< 0.001**		**1.386 (1.211, 1.586)**	**< 0.001**		**1.328 (1.169, 1.508)**	**< 0.001**	
Mode2	282	1st Q	1 (reference)		**< 0.001**	1 (reference)		**< 0.001**	1 (reference)		**< 0.001**
	282	2nd Q	1.220 (0.840, 1.773)	0.296		1.055 (0.710, 1.566)	0.792		1.241 (0.853, 1.806)	0.296	
	282	3rd Q	1.220 (0.840, 1.773)	0.296		1.120 (0.755, 1.661)	0.573		1.235 (0.848, 1.799)	0.296	
	282	4th Q	**2.025 (1.413, 2.903)**	**< 0.001**		**1.801 (1.228, 2.641)**	**0.003**		**2.079 (1.448, 2.986)**	**< 0.001**	

Q of WF (mg/L), 1st Q (≤ 0.248), 2nd Q (0.248–0.358), 3rd Q (0.358–0.889), 4th Q (> 0.889)

WF, water fluoride intake; KOA, knee osteoarthritis; Q, quartiles; bold fonts, $p < 0.05$

[a]Adjusted for age, gender, education, income and BMI. [b]Adjusted for smoking and drinking

Table 3 Association between UF and KOA in full sample

Models	Sample size	Category	OR (95% CI)	*p* value	*p*-trend	Adjusted OR (95% CI)[a]	*p* value	*p*-trend	Adjusted OR (95% CI)[b]	*p* value	*p*-trend
Mode1	1128	Each 1 mg/L increase	**1.210 (1.119, 1.310)**	**< 0.001**		**1.211 (1.114, 1.316)**	**< 0.001**		**1.223 (1.128, 1.326)**	**< 0.001**	
Mode2	282	1st Q	**1 (reference)**		**< 0.001**	**1 (reference)**		**< 0.001**	**1 (reference)**		**< 0.001**
	282	2nd Q	**1.517 (1.033, 2.227)**	**0.033**		**1.576 (1.051, 2.363)**	**0.028**		**1.529 (1.041, 2.245)**	**0.03**	
	282	3rd Q	**1.588 (1.084, 2.327)**	**0.018**		**1.505 (1.002, 2.261)**	**0.049**		**1.618 (1.102, 2.375)**	**0.014**	
	282	4th Q	**2.679 (1.849, 3.881)**	**< 0.001**		**2.765 (1.857, 4.117)**	**< 0.001**		**2.730 (1.880, 3.962)**	**< 0.001**	

Q of UF (mg/L), 1st Q (≤ 0.697), 2nd Q (0.697–1.326), 3rd Q (1.326–2.330), 4th Q (> 2.330)

UF, urine fluoride; KOA, knee osteoarthritis; Q, quartiles; bold fonts, $p < 0.05$

[a]Adjusted for age, gender, education, income and BMI. [b]Adjusted for smoking and drinking

Stratified analysis on the link between fluoride exposure and KOA

Interactions between potential risk factors (age, sex, and BMI) and fluoride exposure (WF and UF) were analyzed; there was no interaction between them (see supplemental Table 1). The association of WF and UF concentrations with KOA risk was further stratified by subgroups of potential risk factors (age, sex, and BMI). (OR values of the stratified analyses are shown in supplemental Tables 2, 3.)

As shown in Fig. 4, the population aged < 60 exposed to the 4th Q of WF had a higher risk than the 1st Q of WF (OR = 1.958, 95% CI 1.249–3.070, $p = 0.003$). The KOA risks of male and female in the 4thQ WF were both higher than those in the 1st Q of WF (OR = 2.013, 95% CI 1.097–3.758, $p = 0.024$; OR = 1.887, 95% CI 1.206–2.952, $p = 0.005$, respectively), and the $OR_{male} > OR_{female}$. In the obese population, the risk of KOA in the 4th Q of WF was significantly higher than that in the 1st Q of WF (OR = 2.137, 95% CI 1.314–3.474, $p = 0.002$).

A similar association was also found between UF and KOA. Regardless of age, the KOA risk of the UF 4th Q was higher than that in the UF 1st Q ($OR_{aged < 60} = 2.923$, 95% CI 1.814–4.711, $p < 0.001$; $OR_{aged > 60} = 2.338$, 95% CI 1.256–4.350, $p = 0.007$, respectively), and the $OR_{aged < 60} > OR_{aged > 60}$. The male had an increased risk of KOA with the increase of UF ($OR_{2nd\ UF} = 2.163$, $OR_{3rd\ UF} = 2.336$, $OR_{4th\ UF} = 2.784$). Non-obese and obese participants exposed to the UF 4th Q were more likely to having KOA compared to those in the UF 1st Q (OR = 3.327, 95% CI 2.016–5.492, $p < 0.001$; OR = 2.078, 95% CI 1.184–3.649, $p = 0.011$, respectively), and the $OR_{obese} > OR_{non\text{-}obese}$ (see Fig. 5). In conclusion, fluoride in drinking water could increase the risk of KOA. Especially, the population with aged < 60, male and obesity more likely to having KOA when they exposed to higher fluoride.

Discussion

As a degenerative disease with joint pain as the main symptom, OA is one of the main causes of chronic disability in many developed countries (Bitton, 2009), and the economic burden of patients is heavy, especially in disadvantaged and marginalized groups (Peat & Thomas, 2021). In our study, a cross-sectional study was carried out first to analyze the association between water fluoride and the prevalence of KOA, and then, a case–control study was conducted to analyze the factors that may affect the prevalence of OA, different analysis models were used to evaluate the risk association between fluoride exposure and KOA from different perspectives.

Exposure to fluoride through drinking water is the main way of fluoride intake for local residents, and it has been proven that UF is an accurate assessment of fluoride intake on the basis of the population (Zipkin et al., 1956), therefore, in our study, the content of WF and UF was selected to represent the fluoride exposure level. Through the correlation test of fluoride concentration and KOA prevalence rate within the group, it was found that with the increase in fluoride exposure, the prevalence rate of KOA also showed an increasing trend, and the two were significantly positive correlation. A cross-sectional survey of 80 patients with KOA was consistent with our findings (Singh et al., 2020).

In order to further clarify the relationship between fluoride exposure and the risk of KOA, different regression models were used for adjustment analysis. WF was included in the analysis as a continuous variable, for every 1 mg/L increase in WF level, the risk of KOA increased by 31.8%. After grouping by Q of WF, the risk of KOA in the 4th Q group was twice that in the 1st Q group. When UF was used as a representative of fluoride exposure, the above phenomenon was also found: For every 1 mg/L increase in UF level, the risk of KOA increased by 21%; After grouping by Q of UF, the risk of KOA in 2nd Q, 3rd Q and 4th Q groups was 1.6, 1.5 and 2.9 times that in 1st Q group, respectively. The above statistical results are consistent with the previous investigation results of our research group, that is, fluoride in drinking water can increase the risk of KOA (Sowanou et al., 2022). The same findings were found in a case–control study conducted in Turkey (Savas et al., 2001), which, more notably, found strong evidence of an association between fluoride and OA in individuals without signs of skeletal fluorosis. In our study, the proportion of patients with skeletal fluorosis is relatively small, and the confounding influence of skeletal fluorosis is basically excluded. Many other studies have suggested that not only patients with skeletal fluorosis have skeletal changes similar to OA, but also skeletal

fluorosis itself can cause OA (Bao et al., 2003; Luo et al., 2012; Su et al., 2012; Tartakovskaia et al., 1994). In conclusion, it may be shown that fluoride is not only a risk factor for OA, but also directly leads to KOA through skeletal fluorosis-related pathways.

The association of WF and UF concentrations with KOA risk was further stratified by potential risk factor subgroups (age, sex, and BMI). The results suggested that in each stratified analysis, the 4th Q group had a higher risk of KOA than the 1st Q group after grouping by Q of WF, and the male population had a higher risk of KOA than the female population. Similar association was found between UF and KOA. In each stratified analysis, the 4th Q group had a higher risk of KOA than the 1st Q group after grouping by Q of UF. In addition, people younger than 60 years old, male and obese people were more likely to suffer from KOA under the same UF exposure level. It is worth noting that the fluoride exposure level in this study was not much higher than the various standards(Liu & Yu, 2018; National standard for Drinking water hygiene of the People's Republic of China, 2007), indicating that the risk of KOA will also increase when exposed to relatively low fluoride in water and urine.

The world health organization (WHO) recommends the concentration of WF to be less than 1.5 mg/L, while China and U.S. environmental protection agencies (EPA) set their limit at 1 mg/L, and 4 mg/L, respectively(Liu et al., 2022; US Standard of National Primary Drinking Water Regulations, 2002; Taghipour et al., 2016). Although the standards are not identical, they are based on the common occurrence of dental and skeletal fluorosis caused by excessive fluoride consumption(Craig et al., 2015; US Department of Health and Human Services Federal Panel on Community Water Fluoridation, 2015), as well as other parameters such as climatic and local conditions. The national primary drinking water regulations (NPDWR) of the United States, for example, are explicitly meant to prevent health impacts such as bone disease (skeletal and dental fluorosis) (national primary drinking water regulations). Current standards do not take into account the effects of long-term fluoride exposure on cartilage and skeleton damage. However, many adults with WF intake close to the standard were at risk of OA, notably the population

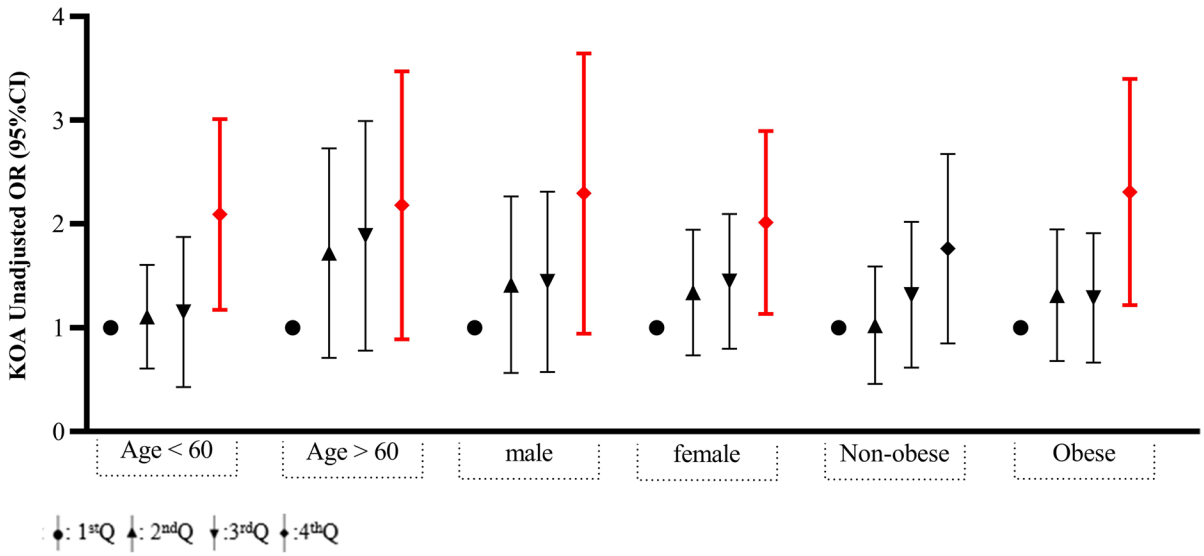

Fig. 4 Association between KOA and WF. : 1stQ: 1st Q; : 2ndQ: 2nd Q; :3rdQ: 3rd Q; :4thQ: 4th Q. KOA, knee osteoarthritis; WF, water fluoride intake; Q, quartiles. Red, $p < 0.05$. *Note*: After stratified by age, sex and BMI (Obese: BMI ≥ 24.0), logistic analysis was performed according to the Q of WF and the prevalence of KOA. OR and 95% CI were calculated. Q of WF (mg/L), 1st Q (≤ 0.248), 2nd Q (0.248–0.358), 3rd Q (0.358–0.889), 4th Q (> 0.889)

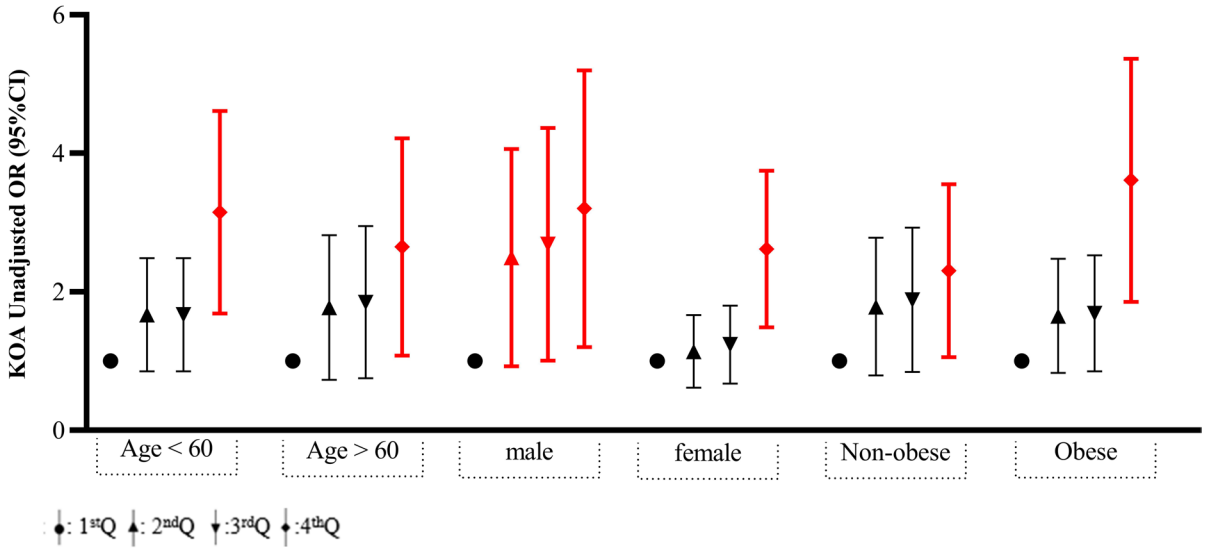

Fig. 5 Association between KOA and UF. : 1stQ: 1st Q; : 2ndQ: 2nd Q; :3rdQ: 3rd Q; :4thQ: 4th Q. KOA, knee osteoarthritis; UF, urine fluoride; Q, quartiles. Red, $p < 0.05$. *Note*: After stratified by age, sex and BMI (Obese: BMI ≥ 24.0), logistic analysis was performed according to the Q of UF and the prevalence of KOA. OR and 95% CI were calculated. Q of UF (mg/L), 1st Q (≤ 0.697), 2nd Q (0.697–1.326), 3rd Q (1.326–2.330), 4th Q (> 2.330)

with aged < 60, male and obesity. As a result, the findings of our study can be seen as evidence of the need to review current WF standards.

The strengths of this study compared to previous studies are: In terms of study content, we incorporated more confounding factors that may affect the relationship between water fluoride exposure and KOA, further adding epidemiological evidence for the determination of causality. Our study observed and analyzed the association between lower water fluoride exposure and KOA, which is more realistic and instructive. Stratified analysis proposed the risk population of KOA in the same fluoride exposure environment. In terms of research methods, the cross-sectional part had a larger sample size; a rigorous case–control study was also conducted to further verify the causal association between water fluoride exposure and KOA. The combination of cross-sectional study and case–control study also draws on the mature research experience in other fields (Roemer et al., 2015; Walther et al., 2022), which ensures the credibility of the research results; cases were detected radiographically rather than by self-report; personal internal and external exposure to fluoride provides a more accurate estimate of the association between fluoride and the disease; multiple models were used to analyze the data to make the conclusions more reliable. Of course, the study has some limitations. Firstly, our study was a case–control analysis based on a cross-sectional study, and a cohort study or matched case–control study should be considered as the next step. Second, individual level fluoride intake estimates, even if the primary source of exposure is community-derived water, there may be some other sources of exposure (toothpaste, tea consumption, food), this would affect the assessment of the relationship between external fluoride exposure and OA.

Conclusions

Taken together, our study found that excessive fluoride dose in drinking water could increase the risk of KOA. The risk of having KOA increases at relatively low fluoride exposure. Especially, the population with aged < 60, male and obesity more likely to having KOA when they exposed to same higher fluoride.

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Author contributions Conceived and designed the experiments: JP and YG. Performed the experiments: XM, JW, YL, ML, ZG, AS, JP, DY and YG. Contributed reagents/materials/analysis tools: JP and DY. Wrote the paper: JP, XM, JW, YL, ML and ZG. XM and JW contributed equally to this work.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest No conflict of interest is associated with this work.

Ethical approval This work received ethical approval from Harbin Medical University.

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