Association Between Osteoarthritis and Water Fluoride Among Tongyu Residents, China, 2019: a Case-Control of Population-Based Study

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Abstract
Fluoride is an environmental chemical that has adverse effects on articular cartilage, probably increasing osteoarthritis (OA) risk. However, this association still needs more epidemiological evidence to clarify. The aim of this study was to determine the relationships between chronic fluoride exposure and OA risk among the residents living in Tongyu County, China, 2019, with a frequency-matched case-control study (186 OA patients and 186 healthy participants). The results showed that urinary fluoride (UF) (2.73 ± 1.18 mg/L) was significantly higher in OA patients compared to the controls (2.35 ± 1.24 mg/L) (p < 0.002). After adjustment, the odds ratios (ORs) with 95% confidence intervals (95% CIs) between the OA risk and fluoride were calculated by the unconditional logistic regression. In full sample analysis, a 1 mg/L increase in UF level was associated with a 27% higher risk of OA (1.06–1.52, p = 0.008), and 4th quarter’s participants were associated with higher risk when compared to 1st quarter (OR: 2.46, 95% CI: 1.34–4.57, p = 0.003). In stratified analysis, compared to 1st quarter, 4th quarter’s participants were 4 times more likely to have OA (1.86–8.82, p < 0.001) in the non-obese group and 7.7 times more likely to have OA (2.58–25.05, p < 0.001) among adults ≤ 60 years. In conclusion, excessive exposure of water fluoride may increase OA risk, and could have more impact on the specific population such as non-obese, and adult aged ≤ 60 years.

Keywords Arthritis · Knee osteoarthritis · Urine fluoride · Fluorosis · Community-based study

Introduction
Osteoarthritis (OA) is the most chronic and prevalent ageing joint disease which does not have an effective treatment proven to delay disease progression. Individual with OA experiences pain, stiffness, swelling, and disability [1, 2]. According to the findings from the Global Burden of Disease Study 2017, approximately 61.2 million individuals were suffering from OA in China [3]. However, the cause of OA remains unclear until now.

Fluoride is a compound that can be found in the air, rocks, soil, and water, and it is both beneficial and harmful to bone health [4, 5]. Fluoride in ground water is a leading source of fluoride exposures to people, which causes skeletal fluorosis (SF) in the population when consumed excessively [6–8]. SF is mainly the manifestation of fluorosis, and a crippling disease induced by excessive accumulation of fluoride in the bone tissues which is caused by excess intake of fluoride through drinking water/food products/industrial pollutants over a long period [9–12]. SF manifests by chronic joint pain, backache, stiffness and rigidity of the spine, calcification of ligaments, physical limitations, inadequate labor capacity, and disability according to the stage of evolution [13–16]. These symptoms are very similar to OA, making differential diagnosis more difficult. As Roschger’s team concluded in 1995, SF can be a very sneaky disease highlighting the difficulty of its diagnostic [17]. The observations made in the endemic areas suggest that fluoride can damage articular cartilage...
and even worsen OA’s symptoms [18, 19]. Several studies have provided clues to a probable link between fluoride and OA. The works including radiological analysis studies and total arthroplasty studies for the treatment of hip and knee severe OA due to fluorosis which have shown that extensive degenerative changes in articular cartilage could occur in a patient with fluorosis [18, 20–22]. An ecological study in fluorosis-affected area (China) found that the incidence of OA in the fluorosis area was remarkably higher than in either the adjacent non-endemic area or the nation as a whole [23]. Additionally, another ecological study in which 56 endemic fluorosis patients were matched in age and sex to 40 non-endemic control patients suggested that endemic fluorosis may increase the severity of knee OA and cause OA before SF is obvious. And the radiological severity of knee OA and osteophytes sign were significantly higher in endemic fluorosis group than in control group [19]. In conversely, US health authorities still assume that fluoride does not cause arthritis symptoms before the traditional bone changes (osteosclerosis) of fluorosis are evident on X-ray [24]. Moreover, the US National Research Council review concluded that only fluoride at high therapeutic doses can cause nodules in articular cartilage and not at environmental doses [25]. Additionally, the above conflicting was also showed in two reports of fluoride at therapeutic doses in rheumatoid patients. One of them reported that fluoride exacerbated rheumatoid arthritis symptoms [26], but it was well tolerated in the other case [27]. Taken together, the present results give clue of the possible link between fluoride and OA; however, the conclusions are not consistent and still need further the evidence of epidemiological studies.

At present, the evidence for the association between fluoride and OA is not very strong, because the few works on the topic found in literature are only ecologic and case-report studies. Therefore, to address this weakness, we conducted a population-based case–control study in 2019 with purpose of evaluating whether fluoride chronic exposure is associated with the risk of OA in population in order to strengthen epidemiological evidence.

Materials and Methods

Study Population and Design

A population-based frequency-matched case–control study with two-step recruitment was carried out in Tongyu County (Baicheng city), Jilin province, as one of endemic fluorosis areas in China. In the first stage of the recruitment, four towns in Tongyu County were investigated from November 2019 to January 2020 using cluster sampling. The stratified random sampling was used to recruit 26–86 years old permanent residents at least 10 years (640 participants). All participants were born and raised in the local area. Subjects with incomplete data, rheumatoid arthritis, prior joint injury, and trauma (22 participants) were excluded. In the second stage, the OA patients (cases) were diagnosed from the remaining 618 participants by two independent evaluators according to the X-ray examination. To remove any selection bias, 186 consecutive and identical OA patients diagnosed by both radiologists were selected and then matched in sex to 186 healthy participants (see additional file, Figure 1). The frequency of sex was the same in the two groups (115 females and 71 males). Finally, the fluoride analysis of the 372 subjects was done in order to avoid any selection bias due to fluoride status at individual level. Sample size was calculated from an online Open Source Epidemiologic Statistics for Public Health [28], with 59.03% as OA prevalence from the fluorosis-afflicted area in China [23] and with the desired CI of 95%.

Collection of Data, Biological, and Radiological Samples

Participants were investigated through face-to-face interview using a structured questionnaire administered uniformly by trained investigators. The questionnaire included demographic information, anthropometric measures, drinking water information, medical history, diet and behaviors, and calcium and vitamin D supplementation information.

For all the 618 consenting participants, a single standing, anteroposterior radiograph of both the knee and elbow was performed in the Baicheng central hospital. The knee and elbow OA subtypes were selected in this study because both joints sites are the most frequently reported in the endemic area [19, 29]. Also, knee OA is the most frequent in normal situation and again with severe complications [30, 31].

About 50-mL spot urine samples (non-standard collection and first-catch urine in the morning) were collected from each participant in precleaned, labelled polythene tubes. All samples were kept in a cooled ice box and then sent immediately to laboratory. Samples were stored at –20 °C until analysis.

Fluoride Exposure Analysis

The 2019 national surveillance analysis of endemic fluorosis showed that fluoride concentration for Tongyu communities’ water samples ranged from 0.94 to 2.30 mg/L (1.49 mg/L as mean) while China’s national standard limit is 1.2 mg/L (GB5749-2006). The population of the study is mainly supplied by 5 water sources, namely 2 public tap water, 1 public shaft water, personal wells, and bottled water. An individual’s fidelity to a single water source is very rare and residents arbitrarily change their water source up to 3 in the same year or after a period of time. Hence, we considered UF as
the consistent and reliable parameter for measuring fluoride exposure at the individual level. UF has been shown to be an accurate evaluation of fluoride ingestion on a population basis [32].

Urine fluoride content was measured at the Key Lab of Etiology and Epidemiology, Center for Endemic Disease Control, Harbin Medical University, by fluoride ion-selective electrode. The operating process was performed according to the China standard for determination of fluoride in urine [33]. We added 5-mL ionic strength adjustment buffer to each urine sample (5 mL) for controlling the pH of the solution at 5.0–5.5 to optimize the determination conditions. Samples were retested twice and the mean value of each sample was used for analysis.

Community water fluoride concentration 2019 data was obtained from the local Center for Endemic Disease Control of Baicheng city, Jilin province, China, and served as an ecologic measure of exposure.

**X-Ray Examination**

Each knee and elbow was evaluated for the presence of lateral or medial osteophytes, joint space narrowing, sclerosis, and cysts. Both joints were also graded for overall evidence of radiographic OA according to the Kellgren and Lawrence criteria (grade 0 to 4, where 0 = none; 1 = possible osteophytes only; 2 = definite osteophytes and possible joint space narrowing; 3 = moderate osteophytes and or definite joint space narrowing; and 4 = large osteophytes, severe joint space narrowing, and or bony sclerosis) [34]. The OA patient (case) was defined as radiographic OA if they had a Kellgren/Lawrence grade of ≥2 in at least one knee or one elbow, and the healthy participant (control) when the Kellgren/Lawrence grade was <2. The X-ray films were independently evaluated by two experienced radiologists. The radiologists had no knowledge about the participants’ ages and their names.

To ensure the reliability of the diagnosis, all films were 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 Kellgren and Lawrence criteria. Only the films with OA diagnosis from both radiologists were accepted and considered for this study.

**Potential Confounders and Effect Modifiers**

Several studies have found age, gender, and obesity to be clearly associated with the occurrence of OA as person level risk factor including a recent systematic and meta-analysis study which included 88 studies [30, 35–37]. They reported that OA risk increases in female group, obese group, and with age. Some dietary factor such as calcium and vitamin D has been suspected to be associated with OA [37].

To eliminate the interference of sex factor among the two groups, controls were selected according to the proportion of female and male sex in cases. Stratified and multivariable analyses were performed in data analysis stage to control the other factors (see the “Statistical Analysis” section). Calcium and vitamin D supplementation information were collected by the questionnaire.

**Ethics Statement**

This study was approved by the Ethical Review Board of Harbin Medical University (HMUIRB20120021). The study has obtained the necessary approvals from the authorities of Baicheng city. Written informed consent was obtained from each participant of the study population.

**Statistical Analysis**

All statistical analyses were performed using R software version 4.0.3 [38]. Two-tailed p < 0.05 was used for all tests as significance level.

The body mass index (BMI) was calculated according to height and weight by the formula: BMI (kg/m²) = weight/height². Population characteristics of cases and controls were compared applying Student’s t test for continuous variables and Pearson chi-squared test (age, gender, medical history, sport, smoking, alcohol, filter use, and education) and Fisher’s exact test (supplementation, ethnicity, and occupation) for qualitative variables. We presented the results as mean with standard deviation (SD) and number and percent as appropriate. ORs along with their 95% CIs were derived from all logistic regression models and presented. Based on the characteristics of the study population and the literature, age, gender, BMI, duration of living, daily water drunk, income, sport, and filter use were selected as confounding and or third factors.

Unconditional logistic regression was used to assess the association between fluoride exposure and the risk of OA. To have a better understanding of the quantitative relationship between fluoride exposure and OA risk, we used UF as continuous variable, dichotomous variable (with 2.38 mg/L median concentration as cut-off value), and ordinal variable (1st quarter from 0.35 to 1.61 mg/L, 2nd quarter from 1.61 to 2.38 mg/L, 3rd quarter from 2.38 to 3.30 mg/L and 4th quarter from 3.30 to 7.01 mg/L) in simple logistic regression analysis. Subsequently, we kept UF as an ordinal and continuous variable in multiple logistic regression analysis.

To limit confounding/effect modifiers influence and explore the independent effect of fluoride exposure, we performed stratified analysis by gender, age, and BMI, and UF was used as an ordinal variable. Multiple logistic regression
analysis was done in full sample and stratified group according to gender, age, and BMI. Age was divided into two groups, adult ≤ 60 years old and adult over 60 years. BMI variable was divided into two groups, no-obese and obese, using Chinese criteria of obesity (no-obese BMI < 27 kg/m², and obese BMI ≥ 27 kg/m²). To evaluate the magnitude of fluoride effect in these specific groups, we performed further stratified analysis in non-obese adult women ≤ 60 years (age ≤ 60 years and BMI < 27 kg/m² and female sex). Due to collinearity issue, we did not include age and duration of living in the model at the same time.

**Results**

**Demographic Characteristics**

A total of 372 participants, from which 186 OA cases (OA patients) and 186 controls (healthy participants), were enrolled in this study. The results showed that UF was significantly higher in the cases (2.73 ± 1.18 mg/L) compared to the control groups (2.35 ± 1.24 mg/L) (p < 0.002). Besides, the age in the cases group was significantly higher than that in the control group (63.22 ± 7.11 years versus 58.77 ± 10.23 years), and sex was evenly distributed in the two groups. The population characteristics in cases and controls are summarized and compared in Table 1. Sample descriptive statistics for fluoride exposure and OA subtype rate are shown in Tables 2 and 3, respectively.

**Assessing Association Between Fluoride Exposure and OA Outcome**

In simple logistic regression analysis shown in Table 4, from model 1 (UF as continuous variable), higher UF concentrations were associated with higher odds of getting OA (OR = 1.30, 95% CI: 1.09–1.55, p = 0.003). In other words, a 1 mg/L increase in UF level was associated with 30% higher risk of getting OA diagnosis in this sample. Model 2 (UF as dichotomous variable) showed that high level group (HLG) subjects were associated with 68% higher risk of getting OA as compared to low level group (LLG) subjects (OR = 1.68, 95% CI: 1.11–2.53, p = 0.013). For model 3 (UF as ordinal variable), the risk of getting OA increased with increasing fluoride concentration by category (≤ 1.61, 1.61–2.38, 2.38–3.30, and > 3.30 mg/L). Among the 2nd, 3rd, and 4th quarters, the odds of getting OA for the 3rd and 4th quarters were nearly 2 times and more than 2.5 times the odds as compared to the 1st quarter reference, respectively (OR = 1.87, 95% CI: 1.05–3.38, p = 0.034 and OR = 2.55, 95% CI: 1.42–4.63, p = 0.001).

In the multiple logistic regression analysis (Table 5), after adjusting for duration of living, daily water drunk, income, sport, and filter use covariates, we found that 3rd and 4th quarters were associated with higher risk of getting OA as compared to 1st quarter reference (OR = 1.84, 95% CI: 1.01–3.39, p = 0.048; OR = 2.51, 95% CI: 1.37–4.67, p = 0.003, respectively). However, when the set of factors sex, age, and BMI was introduced, only 4th quarter’s subjects were associated with a significant risk of getting OA (OR = 2.46, 95% CI: 1.34–4.57, p = 0.003). Using UF as continuous variable (Table 6), we found after adjustment for all covariates that a 1 mg/L increase in UF level was associated with 27% higher risk of getting OA (OR = 1.27, 95% CI: 1.06–1.52, p = 0.008).

**Evaluation of Gender, Age, and BMI-Specific Association**

In stratified analysis adjusted for covariates shown in Table 7, sex did not modify the association between fluoride exposure and OA. The 4th quarter’s participants were associated with higher risk of OA in female as well as in male group when compared to 1st quarter’s participants after adjustment (OR = 2.18, 95% CI: 1.01–4.79, p = 0.048; OR = 4.76, 95% CI: 1.59–15.30, p = 0.006, respectively). Before and after adjustment for covariates, body weight modified association between fluoride exposure and OA such that 4th quarter’s participants were associated with higher risk of getting OA when compared to 1st quarter’s participants among non-obese adult women ≤ 60 years (Table 7). We found a very strong association, such that before adjustment, 4th quarter’s participants were 10 times more likely to have OA and after adjustment 12 times more likely to have OA disease as compared to 1st quarter’s participants (OR = 10.22, 95% CI: 2.24–99.29, p = 0.004; OR: 12.55, 95% CI: 2.15–99.65, p = 0.008, respectively).
Discussion

To date, only two ecological studies [19, 23] really attempted to link fluoride exposure to the induction of OA, showing how much data is lacking to discuss this topic. We examined the association between fluoride and OA risk among residents living in Tongyu County (Baicheng city, Jilin province, China), an endemic fluorosis area where water fluoride ranged from 0.94 to 2.30 mg/L, and adjusted
for factors that can influence fluoride exposure/metabolism as well as OA outcome. Instead of water fluoride exposure rate at individual level, we were able to assess exposure at community level and used UF as biomarker due to the long-term exposure with unchanged residence place. UF has been demonstrated as a precise assessment of fluoride ingestion on a population basis [32].

We found in logistic regression analysis that a 1 mg/L increase in UF level was associated with a 27% higher risk of getting OA disease after adjustment. With UF as an ordinal variable, OA risk increased with increasing fluoride concentration by category. The participants in the 4th quarter were associated with a higher risk (OR = 2.55) of getting OA disease as compared to the 1st quarter (group reference). The association remained significant after adjustment (OR = 2.46). These results suggest that fluoride exposure from water source could be a serious independent predictor of OA, particularly as UF concentration increases in an individual, the risk of developing OA increases. Given the scarcity of data on the topic, additional and cohort studies are needed to carefully explore this eventuality.

Articular chondrocytes in the joint are one of the key chondrocytes cell types that may be subject to pathological changes. In most of the fluoride in the body, about 99% is contained in bone in the form of hydroxyapatite crystals [25]. Logically, mineral precipitates containing fluoride could occur in a joint if the concentration of fluoride and other cations such as calcium, magnesium, and aluminum achieved a very high concentration. As reported by Bang et al. in 1985 [39], a case of 74-year-old female who was on
fluoride therapy for osteoporosis for 30 months had developed a layer of calcified cartilage containing 3.9 mg/kg by ash weight in her femoral head. This underlines the possibility that excess fluoride can cause damage to the joints. Likewise, in a study evaluating patient’s groups with a greater number of subjects, Duell and Chesnut [26] found that the use of fluoride at therapeutic doses in rheumatoid patients exacerbated symptoms of rheumatoid arthritis. Another explanation may be the inhibition of osteoblast cell activity. Fluoride stimulates bone cell proliferation by direct inhibition of osteoblastic acid phosphatase activity [40] and by enhancing the mitogenic signals of growth factors [41, 42]. The activity of osteoblast cell produces a huge increase in bone formation at the organ level, producing exostoses, calcification of tendons and ligaments, and osteosclerosis [42].

Table 7 Association between fluoride exposure level and OA in stratified analysis before and after adjustment, Tongyu County, 2019

| Stratification | Unadjusted OR | Adjusted OR |
|----------------|---------------|-------------|
|                | N Category (N) | UF (by quartile group) | p value | Category (N) | UF (by quartile group) | p value |
|                |               | OR (95% CI) |               |               | OR (95% CI) |               |
| Gender         |               |             |               |               |             |               |
| Female (a)     | 230           | 1st Q (63)  | 1 (reference) | 1st Q (63)    | 1 (reference) |               |
|                |               | 2nd Q (64)  | 1.26 (0.62, 2.56) | 2nd Q (64)  | 1.19 (0.56, 2.52) | 0.638 |
|                |               | 3rd Q (45)  | 2.28 (1.05, 5.04) | 3rd Q (45)  | 2.37 (1.03, 5.57) | 0.043* |
|                |               | 4th Q (58)  | 2.15 (1.04, 4.50) | 4th Q (58)  | 2.18 (1.01, 4.79) | 0.048* |
| Male (a)       | 142           | 1st Q (31)  | 1 (reference) | 1st Q (31)   | 1 (reference) |               |
|                |               | 2nd Q (28)  | 3.24 (1.13, 9.77) | 2nd Q (28)  | 5.20 (1.64, 17.93) | 0.006* |
|                |               | 3rd Q (48)  | 1.77 (0.70, 4.68) | 3rd Q (48)  | 2.05 (0.74, 5.94) | 0.169 |
|                |               | 4th Q (35)  | 3.55 (1.31, 10.17) | 4th Q (35)  | 4.76 (1.59, 15.30) | 0.006* |
| BMI            |               |             |               |               |             |               |
| Obese (b)      | 114           | 1st Q (24)  | 1 (reference) | 1st Q (24)   | 1 (reference) |               |
|                |               | 2nd Q (35)  | 1.11 (0.39, 3.19) | 2nd Q (35)  | 1.25 (0.41, 3.88) | 0.688 |
|                |               | 3rd Q (26)  | 1.61 (0.53, 5.02) | 3rd Q (26)  | 2.10 (0.63, 7.25) | 0.228 |
|                |               | 4th Q (29)  | 0.83 (0.27, 2.49) | 4th Q (29)  | 1.06 (0.32, 3.48) | 0.919 |
| Non-obese (b)  | 258           | 1st Q (70)  | 1 (reference) | 1st Q (70)   | 1 (reference) |               |
|                |               | 2nd Q (57)  | 1.98 (0.97, 4.10) | 2nd Q (57)  | 1.86 (0.88, 3.99) | 0.105 |
|                |               | 3rd Q (67)  | 1.97 (0.99, 3.96) | 3rd Q (67)  | 1.76 (0.84, 3.72) | 0.131 |
|                |               | 4th Q (64)  | 4.21 (2.07, 8.84) | 4th Q (64)  | 3.99 (1.86, 8.82) | 0.000* |
| Age            |               |             |               |               |             |               |
| Adult over 60  | 215           | 1st Q (44)  | 1 (reference) | 1st Q (44)   | 1 (reference) |               |
| (c)            |               | 2nd Q (53)  | 1.07 (0.47, 2.41) | 2nd Q (53)  | 1.25 (0.54, 2.91) | 0.601 |
|                |               | 3rd Q (60)  | 0.93 (0.42, 2.03) | 3rd Q (60)  | 1.17 (0.50, 2.70) | 0.711 |
|                |               | 4th Q (58)  | 1.15 (0.52, 2.57) | 4th Q (58)  | 1.29 (0.56, 2.99) | 0.538 |
| Adult ≤60      | 157           | 1st Q (50)  | 1 (reference) | 1st Q (50)   | 1 (reference) |               |
| (c)            |               | 2nd Q (39)  | 2.50 (0.98, 6.61) | 2nd Q (39)  | 3.11 (1.10, 9.18) | 0.034* |
|                |               | 3rd Q (33)  | 3.76 (1.44, 10.26) | 3rd Q (33)  | 4.90 (1.66, 15.39) | 0.005* |
|                |               | 4th Q (35)  | 6.00 (2.34, 16.41) | 4th Q (35)  | 7.69 (2.58, 25.05) | 0.000* |
| Non-obese adult | 72            | 1st Q (26)  | 1 (reference) | 1st Q (26)   | 1 (reference) |               |
| women ≤60 (d)  |               | 2nd Q (19)  | 2.74 (0.58, 15.08) | 2nd Q (19)  | 4.58 (0.84, 29.86) | 0.086 |
|                |               | 3rd Q (13)  | 4.79 (0.96, 28.07) | 3rd Q (13)  | 8.06 (1.22, 67.29) | 0.037* |
|                |               | 4th Q (14)  | 10.22 (2.24, 59.29) | 4th Q (14)  | 12.55 (2.15, 99.65) | 0.008* |

* mean p value less than or equal to 0.05. N sample size of each stratified group.
(a) Adjusted for BMI, age, income, daily water drunk, sport, and filter use
(b) Adjusted for                                  
age, gender, income, daily water drunk, sport, and filter use
(c) Adjusted for BMI, gender, income, duration of living, daily water drunk, sport, and filter use
(d) Adjusted for duration of living, daily water drunk, income, sport, and filter use
Q1: [0.35, 1.61], Q2: [1.61, 2.38], Q3: [2.38, 3.30], and Q4: [3.30, 7.01]
was demonstrated that patients with skeletal fluorosis had a greater severity of knee OA symptoms and osteophyte formation than age- and sex-matched control group patients. In our study, OA proportion increased as UF level increased by category. Everything suggests that people exposed to fluoride have an additional risk of developing OA, even if the entire mechanism is not yet clear. The development of OA relies on an interaction between several factors and so this process may be considered the final product of an interplay between systemic and local factors, genetics, and imbalance in the physiological process [43, 44], which may give the possibility to fluoride to play a certain role knowing that its target tissue is bone and cartilage [25, 39].

Any increase of OA risk in the obese group, female group, and with ageing could be of particular concern because they have been established with an elevated risk [35–37]. We also explored group-specific association and found that a non-obese adult woman ≤ 60 years with UF > 3.30 mg/L is associated with 12.55 times greater odds of getting OA disease as compared to one with UF ≤ 1.61 mg/L. This suggests that being an adult woman ≤ 60 years and non-obese at the same time is a factor that could allow chronic water fluoride exposure to considerably increase OA risk. Given the lack of studies on the topic, further investigations are needed to draw any conclusion, although association has been estimated in more detail in each group.

After dividing age into two groups of adult ≤ 60 years of age and adult over 60 years, we found an increased risk of OA in adult ≤ 60-year group. Before adjustment, 4th quarter’s participants were 6 times more likely to have OA when compared to 1st quarter’s participants. The association remained even stronger and significant after adjustment (OR = 7.7). This surprising association suggests that an adult under 60 years old is at increased risk (seventhfold) of developing OA once exposed to fluoride as compared to an adult over 60 years old. Bone fluoride concentration tends to increase with age due to the continuous accumulation over time [45, 46]. The potential reason for this is the preferential removal of crystallites with little or no fluoride in the elderly [25]. One would have expected an increased risk of OA in adults over 60-year age group as a result. Maybe the wear and tear of joint structure due to ageing is too evolved to be affected by the additional effect of fluoride, perhaps there is an intervention of other unknown factors.

In the non-obese group analysis, the 4th quarter’s participants were 4.21 times more likely to have OA as compared to the 1st quarter’s participants. Association remained significant after adjustment with 3.99 greater odds of getting OA in 4th quarter’s participants. Meanwhile, no significant association was observed in the obese group. This result means that in the fluoride exposure context, only the non-obese group was at increased risk of OA. It seems that obesity was a stage of impairment where the fluoride effect did not have too much influence. However, additional studies are needed for more exploration as data are sparse. Fluoride adverse effect depends on the magnitude and the length of exposure, and how it behaves in the body, whereas the mechanisms underlying its metabolism and biological effects are not clearly understood yet. Any environmental, biochemical, physiological, and pathological condition which interferes with the absorption or excretion of fluoride will influence its destiny in the body and may ultimately increase the risk of musculoskeletal disorders [47].

Limitations

One limitation of our study is the measurement of exposure rate at the individual level. Even if we measure the concentration of UF for every participant, this may not be directly related to the community water. Of course, the source of exposure is from the community water, but there might probably be some unidentified additional sources of exposure contributing to the exposure rate at the individual level as demonstrated by the difference between mean UF (2.54 ± 1.22 mg/L) and mean community water fluoride (1.49 ± 0.32 mg/L) in the study sample. At this point, we were unable to measure the other sources of exposure such as toothpaste, consumed foods and products locally made, and tea consumption. Different levels of exposure should be taken into account in future investigations. In addition, we observed a close relationship between fluoride exposure and OA outcome with some group-specific associations (non-obese and adult ≤ 60-year group). However, the relatively small sample size and the wide CI in stratified analysis associated with some variable could undermine the strength of this study and point out the lack of precision. Since this concerns the stratified analysis, we therefore encourage further explorations in these specific groups with large sample size. Our results should be interpreted with caution. Also, the cross-sectional nature of this study does not allow us to easily state a direction of the association between fluoride exposure and OA outcome. Given this limitation and the scarcity of evidence on the topic, our findings should be viewed along with others and as hypothesis testing. Ultimately, we recommend more prospective studies with a large sample size as possible to deeply explore the influence of fluoride exposure on OA outcome.

The strength of our study is that we used radiographic OA rather than self-report. We also provided data on OA rate at the individual level in endemic fluorosis areas as well as exposure rate at the individual level (UF concentration) with regard to the community level of exposure. Considering an association between fluoride and OA, our study design is better than the previous ones to address this issue. Finally, it is commonly known that age, gender, and body weight are
personal level risk factors for OA [35–37]. We believe that, by performing stratification analysis on these variables, we had overcome the issue of confounding and effect modification, at least to a certain extent.

**Conclusion**

Exposure to a high level of fluoride from water may be a serious independent risk factor for OA disease. Our analyses on the exploration of an association between fluoride and OA risk show that sex distorts the association while age and body weight modify it. Our findings suggest an additional effect on the risk of OA, particularly in a non-obese adult woman ≤ 60 years where OA risk is 12-fold. However, our results should be interpreted with caution and we recommend other large-scale cohort studies. Nonetheless, we would like to raise awareness of the healthcare professionals on the possible existence of fluorotic osteoarthritis, especially in endemic fluorosis areas and/or fluoridation areas.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s12011-021-02937-2.

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**Author contribution** AS—contributed to study design, investigation, UF measurement, statistical analysis, writing (original draft), and interpretation. XM—contributed to investigation, UF measurement, and project management. NZ and YM—contributed to investigation and UF measurement. AL, JW, and HL—contributed to statistical analysis and verification. JP and YG—contributed to conceptualization, resources, funding acquisition, writing (review and editing), and supervision. All authors discussed the results, gave comments, and approved the final manuscript.

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**Data availability** The dataset used and analyzed in this study is available from the authors in reasonable request.

** Declarations**

**Ethics approval** The study was approved by the Ethical Review Board of Harbin Medical University (HMUIRB20120021). Written informed consent was obtained from each participant of the study population. The study was performed according to the Declaration of Helsinki.

**Competing interests** The authors declare no competing interests.

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