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Research article

Analysis of multiple pathways and levels of fluoride intake in fluorosis areas of Southwest China

Junlin Yang [a,b], Chenglong Tu [c,d,*], Quan Jiang [e], Jianying Wang [a], Longbo Li [f], Robert B. Finkelman [g]

[a] *School of Public Health, Guizhou Medical University, Guian New Region, China*
[b] *The Affiliated Hospital of Guizhou Medical University, Guiyang, China*
[c] *Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guian New Region, China*
[d] *Toxicity Testing Center of Guizhou Medical University, Guiyang, China*
[e] *Guiyang University, Guiyang, China*
[f] *Guizhou Institute of Geo-Environment Monitoring, Guiyang, China*
[g] *Department of Geosciences, University of Texas, Dallas Richardson, TX, USA*

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ABSTRACT

In the coal-burning fluorosis areas of China, over 10 million people suffer from dental fluorosis caused by multiple pathways of fluoride intake. However, the link between dental fluorosis prevalence, the geochemical distribution of fluoride, and contributions of different exposure pathways remain unclear. Here, we aimed to quantify the various fluoride exposure pathways and establish the association between dental fluorosis and fluoride intake in Southwest China. Epidemiological data on the peak time of fluorosis prevalence were combined with geochemical analyses of the fluoride content in coal and clay over a large scale, the amounts and ratios of fluoride intake through different exposure pathways were calculated, and the association between the total daily fluoride intake (TDFI) and dental fluorosis severity was analyzed. The prevalence of dental fluorosis was not significantly correlated with the fluoride geo-background of coal and clay on a large scale ($P > 0.05$). The co-combustion of coal and clay contained in hand-made briquettes is the main pathway of fluoride contamination, which occurs through the inhalation of polluted air and consumption of contaminated roasted products. Furthermore, the TDFI per person ranged from 2.78 to 17.32 mg, and it was significantly positively correlated with the prevalence of dental fluorosis ($P < 0.05$). The TDFI from breathing and eating was 1.1–3.2 mg and 1.1–15.1 mg, which accounted for 9%–54% and 40%–90% of the total TDFI, respectively. The combination of living habits and soil geochemical fluoride anomalies resulted in the higher prevalence of fluorosis in rural areas of Southwest China.

1. Introduction

In China, approximately 20 million people have chalky bands or plaques on their teeth which may present other defects or

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* Corresponding author. Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guian new region, China.

E-mail address: chenglongtu@163.com (C. Tu).

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discolouration of the tooth enamel [1]. These changes appear to be symptoms of dental fluorosis, which is usually caused by excessive fluoride intake via drinking water [2]. However, the fluoride levels in water are very low in these areas [3]. Thus, drinking water likely does not represent the main pathway or source of fluoride exposure. Previous studies have found that dental defects are related to the use of coal with high fluoride content. Consequently, developmental defects of the tooth are referred to as coal-burning dental fluorosis [4]. Extensive investigations have revealed that the fluoride levels of coal used in most places are generally lower than the national average [5,6]. Except for a few regions with high fluoride content in coal, this pathway is not the only contributor to the prevalence of dental defects in China [7]. Furthermore, researchers have discovered that locally grown produce only has low levels of fluoride [8]. Thus, the direct ingestion of fresh items is unlikely to cause widespread dental fluorosis. Therefore, the sources and pathways of fluoride exposure in the population have been the focus of many studies.

Scholars have investigated the practices of local people in these places from the 1970s to the beginning of this century and found that a certain amount of clay is blended with coal to form briquettes to facilitate temperature control during cooking and prolong the burning time. They also found that the fluoride concentration in clay is usually over 1000 mg/kg [9–11]. When people burn briquettes, large amounts of fluoride may be discharged into indoor air and concentrated on dry foods [12]. Based on this evidence, the primary sources and exposure pathways of fluoride in humans in this area have been identified [8,13]. Hence, scholars have inferred that the prevalence and severity of dental fluorosis may be positively correlated with the geochemical distribution of fluoride in clay. However, this hypothesis has not been confirmed.

To date, coal-burning dental fluorosis has been reported in 12 Chinese provinces, including Guizhou, Yunnan, Sichuan, Chongqing, Hubei, Shanxi, Hunan, Jiangxi, Shanxi, Guangxi, Henan, and Liaoning, according to the mid-term assessment results of China's Twelfth Five-Year Plan for Endemic Disease Prevention and Control. There are nearly 20 million coal-burning dental fluorosis patients, with more than 60% living in western Guizhou Province (Fig. 1) [14]. Since the turn of the century, the Chinese government has implemented numerous measures to protect the population against fluoride exposure. However, occasional and scattered fluoride exposure pathways in some regions have not been entirely removed, and new cases of dental fluorosis are observed in rural areas [15]. In this study, we aimed to identify the main fluoride exposure pathways and estimate the intake levels of the population, to better understand the tolerance limits of humans to fluorides from different exposure pathways. The objectives of this study were as follows: 1. Determine the distribution pattern of the population with dental fluorosis and the relationship of this pattern to the fluoride geo-background; 2. Estimate the relative contribution of the main fluoride exposure pathways to dental fluorosis; and 3. Examine the relationship between the intake of fluoride and the prevalence of dental fluorosis.

2. Materials and methods

2.1. Dental fluorosis prevalence survey data

According to the Health Statistics Yearbooks of the Ministry of Health of China published over the past 20 years, the number of dental fluorosis patients in Southwest China peaked from 2005 to 2007. More than 60% of dental fluorosis patients are located in

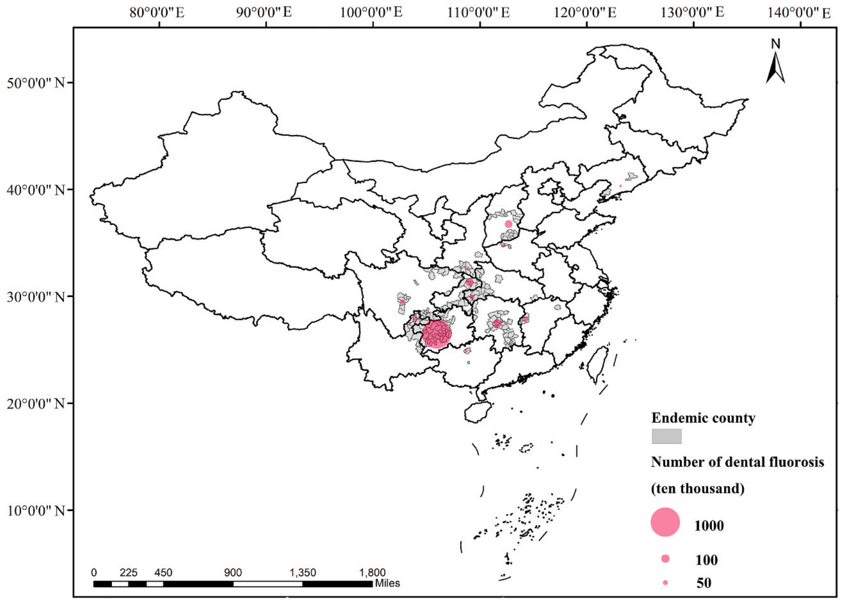


Fig. 1. Distribution map of the coal-burning type of dental fluorosis in China. The grey areas represent endemic counties, and the size of the red circles represents the number of dental fluorosis cases. The data were obtained from statistical reports by Sun and An [14]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

western Guizhou Province. Therefore, epidemiological survey data for 31 counties obtained by the Guizhou CDC in 2007 were extracted and organised as the primary data for this study [16]. In this census, 632,399 primary school pupils in grades 3–6 (8–12 years old) were checked and included in a total of 360 sampled townships. The level of dental fluorosis was classified as questionable, very mild, mild, moderate, or severe based on the severity of enamel mineralisation [17].

Dental fluorosis in students aged 8–12 years was examined by trained medical staff using Dean's method. Dean's index is considered the gold standard of epidemiological research, and the relationship between Dean's index and the prevalence intensity is < 0.4, 0.4–0.6, 0.6–1.0, 1.0–2.0, 2.0–3.0, and >3.0. Dean's index was calculated as Eq. (1):

$$\text{Dean's index} = (\text{questionable}*0.5 + \text{very mild}*1 + \text{mild}*2 + \text{moderate}*3 + \text{severe}*4)/\text{number of detected} \tag{1}$$

2.2. Analysis of epidemic factors

The CDC investigated the influencing factors related to living habits in 134 townships in 21 of 31 epidemic counties (one to five villages were randomly sampled from each township, for a total of 591 villages). The epidemiological survey included 7 categories and 22 subcategories of factors, including living fuel (coal, wood, and clean energy), house structure (straw houses, wooden houses, stone houses, and brick houses), cooking range usage (open stove, chimney of an open stove out of the house, iron stove, and chimney of an iron stove out of the house), the proportion of corn among the staple food (0%–10%, 10%–30%, 30%–50%, 50%–80%, 80%–100%), open drying of corn and chili, unsealed storage of corn and chili, and washing of corn and chili before eating. In 100 townships within 17 of 31 epidemic counties (one to five villages were randomly sampled from each township, for a total of 460 villages), the CDC collected agricultural products (rice, corn, and chili) stored by farmers for more than 3 months to determine the fluoride content.

2.3. Geochemical survey data

Fluoride in coal and clay is widely recognised as the main source of coal-fired fluorosis. Consequently, a geochemical survey of fluoride in coal and clay was conducted between 2013 and 2017, and the chemical analysis of all samples was completed in 2019. A total of 669 coal samples were collected from local mines and residential houses. The survey of fluorine content in clay was combined with the results of the soil fertility census conducted in Guizhou Province. The designed sampling density was nine points/km^2.

The fluoride content in the coal and clay was determined using the high-temperature hydrolyzation ion-selective electrode method. We weighed 0.2 g of powdered samples, passed them through a 100 mesh sieve, placed them in a porcelain boat, and then added 0.1 g of quartz sand to cover the sample surface. A 50 mL colorimetric tube containing 15.0 mL of 0.2 mol/L NaOH solution was placed at the lower end of the condensing tube to receive the condensate. The porcelain boat containing the sample was placed in a quartz combustion tube, through which water vapour and oxygen were passed (290 mL/min). The porcelain boat was gradually pushed from the low-temperature zone (600 °C-700 °C) to the high-temperature zone (1100 °C) in two steps within 5 min, and it was then kept in the high-temperature zone for 10 min. The water vapour flow rate was controlled throughout the process to ensure that the collected condensate was within 41 mL. The sample was neutralised with a 2 mol/L HNO_3 solution until the red colour disappeared and then transferred to a 50 mL volumetric flask. Subsequently, 5 mL of TISAB solution was added, ultra-pure water was added to the scale line, and then the sample was stored for later use.

2.4. Disease mapping

The spatial distribution of diseases usually has one essential feature: nearby regions that have a positive autocorrelation. The Bayesian technique uses prior information, such as global or local risk estimations based on the spatial autocorrelation of variables, to generate a robust point and interval estimates of prevalence, thereby avoiding extreme values in small groups or small regions. In a Bayesian spatial model, the estimated prevalence of each area is affected by its data and data from its neighbours [18].

Let the number of dental fluorosis patients in district i be Y_i, i = 1, 2, …, m.

When the prevalence is not low, assume that Y_i obeys a binomial distribution (Equation (2)):Eq

$$Y_i \sim Bin(n_i \pi_i) \tag{2}$$

where n_i is the number of surveyed populations in i and π_i is the prevalence rate of location i Here, π_i is the unknown parameter of interest. Moreover, for π_i, we have the following (Equation (3)):

$$\text{logit}(\pi_i) = \beta_0 + u_i + \upsilon_i \tag{3}$$

where β_0 is the intercept; u_i and υ_i are the observed and unobserved spatial random effects, respectively; u_i is the spatial structure effect, which reflects spatial dependence; and υ_i is the unstructured spatial effect, which reflects white noise. Assume that u_i and υ_i are independent and have prior distributions. For the spatial unstructured effect υ_i, the a priori values are assumed to be normally distributed as follows (Eq. (4)):

$$\upsilon_i \sim N\left(0, \sigma_\upsilon^2\right) \tag{4}$$

For the spatial structure effect u_i, it is assumed to be subject to conditional auto-regression. In this process, the conditional distribution of each u_i was a normal distribution and the mean value was the weighted average of the adjacent region $u_{j,i\neq j}$, as follows (Eq. (5)):

$$u_i \left| u_{j,i\neq j} \sim N\left(\rho \sum_{j\in\delta_i} u_j \,/\, n_{\delta_i}, \sigma_e^2 \,/\, n_{\delta_i}\right)\right. \tag{5}$$

where ρ is the spatial correlation coefficient, δ_i is the first-order neighbourhood of region i, n_{δ_i} is the number of adjacent regions of region i, and σ_e^2 is the variance of the spatial effect.

WinBUGS software was used to perform the Bayesian modelling and iterative operations. The iteration trajectory, iteration history, and autocorrelation function can all be used to assess iterative convergence. The iteration process converges when the iteration trajectory and history tend to be stable and the autocorrelation function quickly approaches zero.

2.5. Calculation of total daily fluoride intake

The known sources of fluoride mainly include rice, corn, chili, water, and air in coal-burning fluorosis areas. The total daily fluoride intake (TDFI) was calculated as follows (Eqs. (6)–(8)):

$$\text{TDFI} = \text{fluoride content in foods (rice, corn, chili, water)*daily consumption} + \text{daily intake from air} \tag{6}$$

$$\text{Daily intake from air} = \text{fluoride content per-unit volume*amount of respiration*heating time} \tag{7}$$

$$\text{Fluoride content per-unit volume} = ((\text{lump coal dosage*coal fluoride content*release rate of fluoride in lump coal}) + (\text{clay dosage*clay fluoride content} + \text{pulverised coal dosage*coal fluoride content})\text{*release rate of fluoride in briquettes})/\text{house area}/24\text{ h} \tag{8}$$

According to the Exposure Factors Handbook of Chinese Population, the average daily staple food consumption, daily drinking water intake, and respiration amount for children aged 8–12 in the research areas were 0.277 kg/d/p, 1 L/d/p and 13.2 L/d/p, respectively [19]. In addition, previous observations have shown that the staple food of the investigated areas consisted of corn and rice, and the proportion of corn in the staple food varied slightly in different regions [16]. The average consumption of chili was 0.02 kg/d/p [20]. The average fluoride content in drinking water was 0.157 mg/L [21]. The average daily coal consumption per household was 7.13 kg [22]. The ratio of lump coal to briquettes, which are composed of pulverised coal and clay, was approximately 1:1, and the ratio of pulverised coal to clay in the briquettes was approximately 3:1 [16]. The average daily usage of lump coal, pulverised coal, and clay per household was 4.07 kg, 3.06 kg, and 0.765 kg, respectively. The release rate of fluoride in lump coal is approximately 90%, and that in briquettes is approximately 58% [16]. According to our investigation, people remained within heating rooms for 12 h, although coal was burned 24 h a day in winter. The heating room was generally approximately 200 m^3.

2.6. Fitting between TDFI and dental fluorosis prevalence

We compared the linear fitting model, curve fitting model, and polynomial fitting model to determine the optimal fitting model. Smaller AIC and BIC values corresponded to a better fitting degree of the model.

2.7. Statistical analysis

The fluoride content in the coal and clay is represented as mean and range values. Pearson correlation analysis was used to analyse the association between dental fluorosis prevalence and the TDFI and fluoride content in coal and clay using SPSS 23 software. The statistical connections between each epidemic factor and the prevalence of dental fluorosis were assessed using multivariate analysis and a multiple stepwise regression model in SPSS 23 software. Origin 2018 was used to fit the TDFI and dental fluorosis prevalence. The disease map, which included a bitmap of sample sites and a prevalence map of dental fluorosis, was created using ArcMAP 10.4 software. Significance was set at $P < 0.05$.

3. Results

3.1. Distribution pattern of the population with dental fluorosis and its relationship with the geochemical background of fluoride

Numerous studies have shown that chronic endemic fluorosis mainly damages permanent teeth during the calcification stage [9,14]. After the completion of calcification, the status of tooth damage remains relatively stable and irreversible, and the occurrence of dental fluorosis cannot be observed until the eruption of permanent teeth. Therefore, children aged 8–12 are usually examined to estimate the prevalence of dental fluorosis in a particular region [16].

The location map of the sampling sites in 31 epidemic counties and 360 townships were displayed and visualised according to Dean's index (Fig. 2A). The dots represent different sampled townships, and the colour of the dots from light to dark represents Dean's index from low to high (0.005–2.852). According to the Bayesian posterior distribution, among children aged 8–12, the prevalence of dental fluorosis was classified as follows: questionable (0.03%–26.1%), very mild (2.4%–29.2%), mild (0.84%–33.08%), moderate

(0.16%–34.1%), severe (0.01%–13.42%), and total (3.4%–87.5%) (Fig. 2B). The degree of dental fluorosis varies by region. Dental fluorosis cases with mild or less severity were widely dispersed, whereas instances with moderate or severe dental fluorosis were not evenly distributed among regions.

The geochemical background of fluoride in coal and clay in the 31 epidemic counties is shown in Table 1. The fluoride content in coal varied from 29.7 mg/kg to 1585.2 mg/kg, with an average of 186.5 mg/kg. Some coal samples, such as those collected from Guiding, are highly enriched in fluoride. The accumulation of data on fluoride in coal indicates that the coal in Guizhou Province has modest and relatively low levels of fluoride. This result is similar to that of other studies in areas with severe fluorosis, which showed that the fluoride content of coal ranged from 90.2 to 149 mg/kg [5] and had a mean value of 125 mg/kg [6]. The fluoride content in clay ranged from 185 mg/kg to 2809 mg/kg, with an average of 1015.7 mg/kg, which was significantly higher than the Chinese average (478 mg/kg) [23]. This finding is similar to the results of studies conducted in heavily polluted regions [7] or throughout Guizhou Province [24]. The Pearson correlation analysis showed that the fluoride content in coal and the total prevalence of dental fluorosis had values of $r = -0.28$ and $P = 0.133$, respectively, and the fluoride content in clay and the total prevalence of dental fluorosis had values of $r = 0.12$ and $P = 0.51$, respectively. None of the associations were statistically significant (Fig. 3A and B).

3.2. Environmental epidemic factors

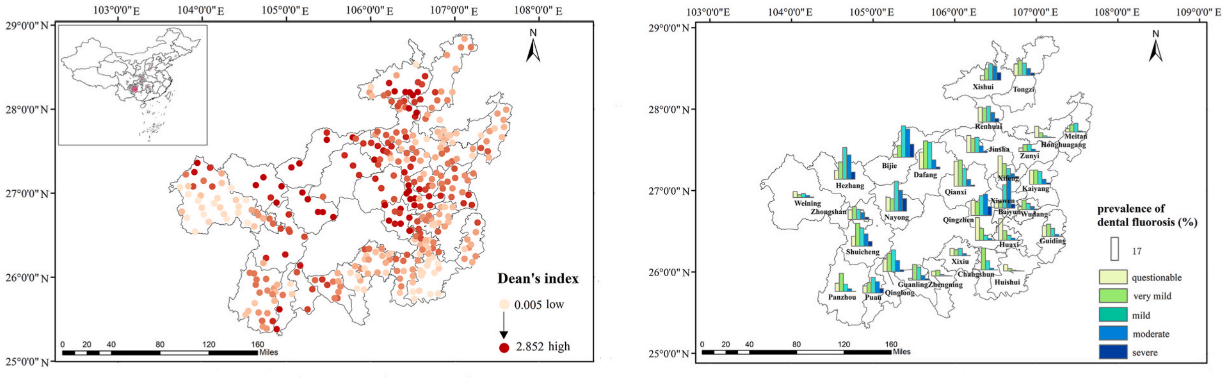
This study organised environmental epidemic factors into seven categories, and the statistical connections between each factor and fluorosis prevalence were assessed using a multivariate analysis (Table 2). Dominant factors were identified using a multiple-stepwise regression model. Coal, straw houses, wooden houses, open stoves, more than 50% corn as a staple food, open drying of corn and chili, and washing of corn all demonstrated positive relationships with the prevalence of dental fluorosis ($P < 0.05$). The prevalence of dental fluorosis was negatively correlated with the proportion of people who used wood or clean energy as living fuel, lived in a stone house, used an iron stove, and consumption of corn as a staple food ($P < 0.05$). The proportion of people living in stone houses, using an iron stove or an open stove, and open-drying of chili were included in the regression model (Table 3) to explain the overall variation in the total prevalence of dental fluorosis.

3.3. Total daily fluoride intake from various exposure pathways

An examination of multiple fluoride exposure pathways in 17 epidemic counties and the computation of fluoride consumption revealed that the TDFI ranged from 2.78 to 17.32 mg/d/p. Fluoride consumption from food ranged from 1.13 to 15.07 mg/d/p, with a mean value of 6.22 mg/d/p. Fluoride intake from chili ranged from 0.7 to 9.5 mg/d/p. The chili fluoride levels ranged from 35.03 to 475.59 mg/kg, with a mean of 245.3 mg/kg. Inhalation of fluoride ranged from 1.1 to 3.2 mg/d/p, with a mean of 1.75 mg/d/p. The fluoride concentrations per unit volume ranged from 0.165 to 0.490 mg/m^3, with a mean of 0.266 mg/m^3. Inhaling fluoride accounted for 9%–54% of the total fluoride exposure, while eating chili accounted for the most significant exposure of approximately 25%–76% (Table 4 and Fig. 4A).

3.4. Correlation analysis between the TDFI and dental fluorosis prevalence

We first performed a Pearson correlation analysis between the TDFI and Dean's index to determine the relationship between the TDFI and dental fluorosis prevalence ($r = 0.24$, $P < 0.05$). We then fitted various models of the TDFI and Dean's index. The fitting model included 460 datasets (460 villages in 17 epidemic counties), and the AIC and BIC values of several fitting models were evaluated, with smaller AIC and BIC values indicating a better fitting model. Polynomial 5 was the best-fitting model, with an R^2 value of 0.129. The model is as Eq. (9):



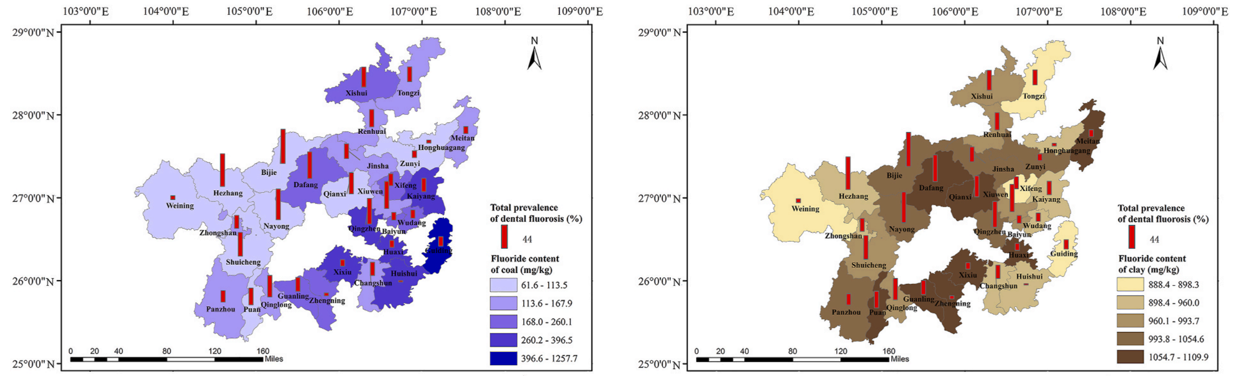
A

B

Fig. 2. Location map of sampling sites (A) and prevalence of dental fluorosis with different exposure degrees (B) in 31 epidemic counties.

Table 1
Geochemical background of fluoride concentration.

County	Coal			Clay		
	Number	Mean (mg/kg)	Range (mg/kg)	Number	Mean (mg/kg)	Range (mg/kg)
Baiyun	10	245.0	73.2–589.9	80	989.3	392.1–1931.8
Bijie	20	62.1	43.7–195.2	1717	1030.0	304.9–2809.8
Changshun	3	138.4	134.9–141.9	373	956.9	282.5–2566.7
Dafang	7	191.7	77.5–545.9	2963	1071.5	313.7–2809.8
Guanling	3	192.0	144.4–239.6	164	1054.7	329.1–2809.0
Guiding	3	1257.7	971.8–1585.2	552	893.7	311.5–2731.9
Hezhang	3	99.7	84.4–125.3	434	948.7	239.6–2736.5
Huaxi	10	312.0	136.9–624.4	98	1064.9	433.6–2580.3
Huishui	3	392.5	107.4–593.0	692	938.4	285.1–2625.7
Jinsha	55	173.9	81.5–288.5	1073	1015.4	282.4–2642.2
Kaiyang	3	396.5	221.4–396.5	1466	932.1	311.6–2608.3
Meitan	3	167.9	101.4–235.8	633	1096.7	327.6–2721.7
Qingzhen	3	299.0	136.5–395.0	703	1013.8	367.2–2566.3
Nayong	343	111.6	78.3–487.2	1726	1035.9	306.6–2781.3
Panzhou	41	129.0	35.9–477.1	2436	1016.4	199.7–2808.0
Puan	3	104.6	97.1–110.1	1024	1109.9	277.6–2680.2
Qianxi	54	113.1	29.6–289.7	1339	1062.5	282.3–2642.4
Qinglong	3	132.1	81.3–182.8	442	993.8	334.7–2781.1
Renhuai	3	142.6	128.8–156.3	340	980.7	310.5–2580.6
Shuicheng	22	102.5	52.3–160.1	1644	976.3	227.6–2781.7
Tongzi	8	144.3	54.0–335.1	819	888.6	285.6–2608.9
Weining	3	96.1	62.1–130.1	907	888.4	185.5–2808.6
Wudang	3	260.2	259.5–260.8	338	930.7	316.3–2625.0
Xifeng	5	191.0	123.4–235.7	129	898.4	310.2–2580.7
Xingren	4	196.0	95.4–351.2	1238	1014.6	227.6–2729.6
Xishui	3	183.6	160.7–207.1	583	987.3	282.3–2566.7
Xiuwen	3	122.5	101.8–143.3	551	988.5	285.1–2625.1
Xixiu	4	344.6	219.7–469.5	910	1073.7	282.2–2642.8
Zhenning	3	264.4	117.3–357.2	738	1104.2	337.3–2706.5
Zhongshan	21	125.6	123.3–127.8	59	951.6	239.1–2672.6
Zunyi	17	84.2	57.1–105.6	382	1024.1	365.8–2608.7



A B

Fig. 3. Relationship between the geochemical background of fluoride in coal (A) and clay (B) and total prevalence of dental fluorosis in 31 epidemic counties. The number 44 in the legend represents the total prevalence rate as indicated by the height of the column.

$$Y = Intercept + B_1 \cdot x\hat{1} + B_2 \cdot x\hat{2} + B_3 \cdot x\hat{3} + B_4 \cdot x\hat{4} + B_5 \cdot x\hat{5} \tag{9}$$

where $Intercept = -2.22848 \pm 0.81251$, $B_1 = 2.82691 \pm 0.63149$, $B_2 = -0.75403 \pm 0.16755$, $B_3 = 0.08707 \pm 0.01969$, $B_4 = -0.00443 \pm 0.00105$, $B_5 = 8.14136\text{E-}5 \pm 2.05962\text{E-}5$.

According to the fitting curve between the TDFI and Dean's index and the polynomial 5 model (Fig. 4), the starting value of Dean's index for the fitting curve was 0.74. The prevalence rates of mild, moderate, severe, and total dental fluorosis were 18.6%, 5.0%, 0.1%, and 42.8%, respectively. The prevalence of mild, moderate, severe, and total dental fluorosis reached 19.5%, 9.7%, 2.6%, and 50.2%, respectively, when the TDFI and Dean's index reached 2.68 mg and 1.0, respectively, suggesting that the region was beginning to display moderate epidemic levels.

Table 2
Pearson correlation analysis of the total prevalence of dental fluorosis and its epidemiological factors.

Variables	Total prevalence of dental fluorosis (%)	
	r	*p*
Living fuel		
Coal (%)	0.086*	0.036
Wood (%)	−0.107**	0.009
Clean energy (%)	−0.122**	0.003
House structure		
Straw house (%)	0.099*	0.016
Wooden house (%)	0.089*	0.031
Stone house (%)	−0.130**	0.002
Brick house (%)	−0.030	0.466
Cooking range usage		
Open stove (%)	0.172**	0.000
Chimney of open stove outside of the house (%)	−0.121**	0.003
Iron stove (%)	−0.156**	0.000
Chimney of iron stove outside of the house (%)	−0.224**	0.000
Proportion of corn in the staple food		
0–10%	−0.131**	0.001
10–30%	0.003	0.950
30–50%	−0.003	0.942
50–80%	0.114**	0.006
80–100%	0.114**	0.006
Open drying of corn and chili		
Open drying of corn (%)	0.228**	0.000
Open drying of chili (%)	0.256**	0.000
Unsealed storage of corn and chili		
Unsealed storage of corn (%)	0.118**	0.004
Unsealed storage of corn (%)	0.139**	0.000
Washing of corn and chili before eating		
Corn washing (%)	0.119**	0.004
Chili washing (%)	−0.003	0.946

Note: *CDC-identified epidemiological factors related to living habits in 21 counties (134 townships and 591 villages), including seven categories and twenty-two subcategories listed in Table 2. A total of 591 sets of data were available for Pearson correlation analysis; $^{**}P < 0.01$, $^{*}P < 0.05$.

Table 3
Multiple-stepwise regression analysis.

Variables	*B*	*SE*	*β*	*t*	*p*
Intercept	58.724	3.414		17.201	0.000
Open drying of chili	0.105	0.023	0.194	4.515	0.000
Open stove	0.101	0.029	0.137	3.516	0.000
Stone house	−0.176	0.032	−0.215	−5.461	0.000
Chimney of iron stove outside of the house	−0.116	0.024	−0.196	−4.753	0.000
R^2	0.154				
F	21.318				
p	0.000				

4. Discussion

4.1. Main exposure pathways of the population to fluoride

In the coal-burning fluorosis areas of China, three primary exposure pathways of the population to fluoride were observed. We used portable fluoride ion detection equipment to inspect more than 500 water sources on site and found that the fluoride in drinking water at more than 30% of the sites was below the instrument's detection limit (<0.02 mg/L) from our past investigations. Li et al. compiled a large amount of data on fluoride in drinking water and calculated an average fluoride content of 0.157 mg/L [21]. Compared with the fluorosis caused by high-fluoride water in northern China or other parts of the world, this exposure pathway is unlikely in the study areas [25–27]. The other two pathways are the inhalation of airborne fluoride through the respiratory tract [5,28] and the consumption of contaminated foods [29,30]. A consensus has not been reached on whether eating or breathing is the more prominent contributor of fluoride to coal-burning fluorosis. In this study, the estimated TDFI ranged from 2.16 mg/d/p to 17.32 mg/d/p. The TDFI from breathing and eating was 1.1–3.2 mg and 1.1–15.1 mg, respectively, which accounted for 9%–54% and 40%–90% of the total exposure, respectively. Concerning the exposure pathways, the amount of fluoride intake through the respiratory tract was relatively small and the difference in TDFI among regions was mainly caused by oral intake.

Table 4
Estimation of fluoride intake by different pathways.

County	Rice			Corn			Chili			Water			Air									TDFI (mg/d/p)
	Fluoride content (mg/kg)	Consumption (kg/d/p)	Daily intake (mg/d/p)	Fluoride content (mg/kg)	consumption (kg/d/p)	Daily intake (mg/d/p)	Fluoride content (mg/kg)	Consumption (kg/d/p)	Daily intake (mg/d/p)	Fluoride content (mg/L)	Water ingestion (L/d/p)	Daily intake (mg/d/p)	Fluoride content of coal (mg/kg)	Fluoride content of clay (mg/kg)	Average usage of lump coal (kg/d/h)	Average usage of pulverised coal (kg/d/h)	Average usage of clay (kg/d/h)	Fluoride per unit volume (mg/m3)	Amount of respiration (L/d/p)	Heating time(h)	Daily intake (mg/d/p)	
Bijie	0.67	0.12	0.08	17.97	0.15	2.78	391.88	0.02	7.84	0.157	1	0.157	62.1	1030.0	4.07	3.06	0.765	0.166	13.2	12	1.093	11.95
Dafang	1.05	0.10	0.10	30.32	0.18	5.45	475.91	0.02	9.52	0.157	1	0.157	191.7	1071.5	4.07	3.06	0.765	0.316	13.2	12	2.087	17.32
Guanling	1.69	0.17	0.29	6.30	0.10	0.65	235.62	0.02	4.71	0.157	1	0.157	192.0	1054.7	4.07	3.06	0.765	0.315	13.2	12	2.079	7.89
Hezhang	1.05	0.09	0.09	15.48	0.19	2.96	229.11	0.02	4.58	0.157	1	0.157	99.7	948.7	4.07	3.06	0.765	0.201	13.2	12	1.324	9.11
Meitan	0.75	0.25	0.19	0.95	0.02	0.02	277.34	0.02	5.55	0.157	1	0.157	167.9	1096.7	4.07	3.06	0.765	0.292	13.2	12	1.925	7.84
Nayong	1.00	0.13	0.13	25.42	0.15	3.69	429.00	0.02	8.58	0.157	1	0.157	111.6	1035.9	4.07	3.06	0.765	0.222	13.2	12	1.466	14.03
Puan	1.58	0.19	0.30	8.52	0.09	0.76	419.87	0.02	8.40	0.157	1	0.157	104.6	1110.0	4.07	3.06	0.765	0.221	13.2	12	1.459	11.07
Qianxi	0.78	0.18	0.14	12.36	0.09	1.14	228.00	0.02	4.56	0.157	1	0.157	113.1	1062.5	4.07	3.06	0.765	0.226	13.2	12	1.494	7.49
Qinglong	1.25	0.13	0.16	3.55	0.15	0.52	192.18	0.02	3.84	0.157	1	0.157	132.1	993.8	4.07	3.06	0.765	0.242	13.2	12	1.594	6.27
Renhuai	0.72	0.25	0.18	1.80	0.02	0.04	148.35	0.02	2.97	0.157	1	0.157	142.6	980.7	4.07	3.06	0.765	0.252	13.2	12	1.664	5.01
Shuicheng	0.57	0.14	0.08	2.33	0.13	0.31	72.87	0.02	1.46	0.157	1	0.157	102.5	976.3	4.07	3.06	0.765	0.206	13.2	12	1.362	3.37
Tongzi	0.73	0.23	0.17	1.96	0.05	0.10	227.48	0.02	4.55	0.157	1	0.157	144.3	888.6	4.07	3.06	0.765	0.246	13.2	12	1.621	6.59
Xishui	0.78	0.24	0.19	1.51	0.03	0.05	173.50	0.02	3.47	0.157	1	0.157	183.6	987.3	4.07	3.06	0.765	0.299	13.2	12	1.975	5.84
Xixiu	1.71	0.25	0.43	6.82	0.02	0.16	345.56	0.02	6.91	0.157	1	0.157	344.6	1073.7	4.07	3.06	0.765	0.490	13.2	12	3.232	10.89
Zhenning	1.81	0.25	0.46	2.87	0.02	0.07	227.18	0.02	4.54	0.157	1	0.157	264.4	1104.2	4.07	3.06	0.765	0.402	13.2	12	2.651	7.88
Zhongshan	1.12	0.20	0.23	2.82	0.07	0.20	35.03	0.02	0.70	0.157	1	0.157	125.6	951.7	4.07	3.06	0.765	0.230	13.2	12	1.520	2.81
Zunyi	0.53	0.22	0.12	0.76	0.06	0.04	60.42	0.02	1.21	0.157	1	0.157	84.2	1024.1	4.07	3.06	0.765	0.190	13.2	12	1.253	2.78

Note: Early epidemiological and geochemical surveys could not be completely matched; therefore, we only estimated the fluoride intake in 17 counties.

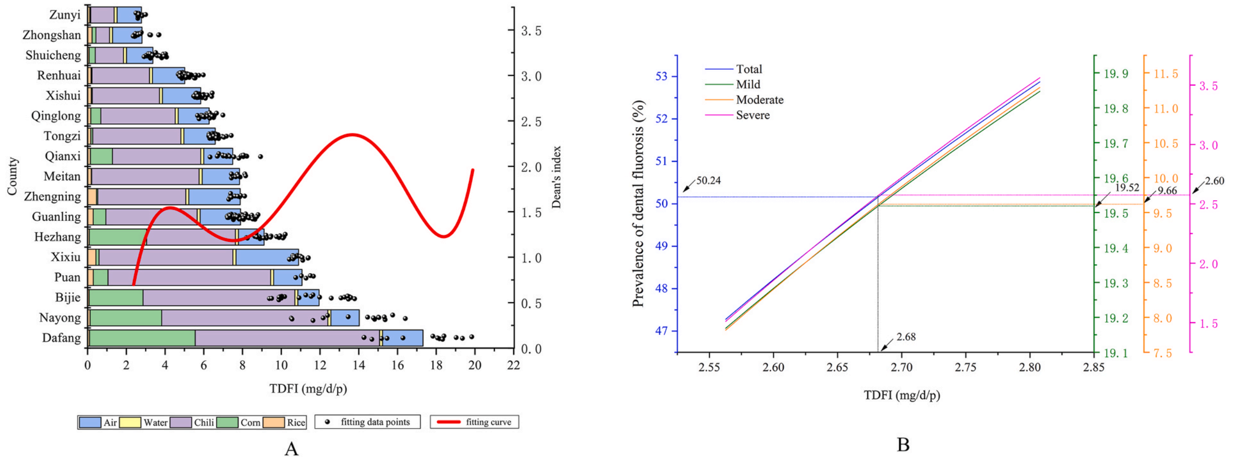


Fig. 4. Bar chart on the left represents fluoride intake by different pathways (eating contaminated rice, corn, and chili, drinking contaminated water, and inhaling polluted air) in 17 epidemic counties. The black dots represent data derived from the fluoride levels in 17 counties (460 villages in 100 towns), and the red line showed the fitting curve between TDFI and Dean's index (A). The prevalence of dental fluorosis (total, mild, moderate, and severe) and TDFI were fitted by the polynomial 5 models, and the fitted data were obtained. A portion of these fitted data was used for plotting to present the prevalence of dental fluorosis when the TDFI and Dean's index were 2.68 mg and 1.0, respectively (B). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

In the investigated areas, fresh produce was placed above an open furnace to dry slowly for long-term preservation. In this process, chili becomes enriched in air-born fluoride, with dried products showing 40–240 times higher value of fluoride relative to fresh products [31]. Moreover, higher fluoride levels corresponded to longer drying times [32,33]. People in the study areas were accustomed to consuming chili peppers to alleviate the effects of the wet and cold climate on their bodies; thus, chili represents an essential part of their diet. As a result of this dietary preference, chili has a high potential to enhance the fluoride produced by coal combustion and accounted for 25%–76% of the TDFI. Eating contaminated chili peppers was the most significant contributor to the TDFI. Our observations also showed that the level of fluoride enrichment in dried chili varied among regions mainly due to the duration of open-fire drying of chili. The main routes of human exposure to fluoride in rural areas of Southwest China were through the diet because of eating roasted foods and through the air because of burning products that contain clay with abnormally high fluoride contents. Although oral ingestion of fluoride-contaminated food was a significant contributor to TDFI, the oral intake of fluoride was not identified as a key trigger for fluorosis. Evidence indicates that fluoride inhaled through the respiratory route is more hazardous than that ingested through the digestive tract. For example, Sun et al. found that although the TDFIs of three villages in Chongqing were 2.92, 6.09, and 11.27 mg/p/d, the prevalence of dental fluorosis (70%) was consistent among the villages [34]. Another case showed although the TDFIs of two sites in northern China were 2.64 mg/p/d and 2.15 mg/p/d, the prevalence of dental fluorosis was not positively related to the TDFI. The fluoride intake by breathing only accounted for 1%–10% of the TDFI in both cases; however, the amount of fluoride intake through respiration surpassed the contaminated air limit by several times [35,36]. This finding implies that the consumption of fluoride through the respiratory system is a more sensitive exposure route than the ingestion of fluoride through other routes. Our findings revealed that the fluoride concentration of indoor air per unit volume in epidemic areas ranged from 0.165 to 0.490 mg/m^3, with a mean value of 0.266 mg/m^3. The average fluoride consumption through the air was 1.75 mg/d/p, with a range of 1.1–3.2 mg/d/p. These findings are consistent with previously reported values [32]. However, we cannot be sure which pathway contributes more to the prevalence of dental fluorosis in the coal-burning fluorosis areas of China because extensive investigations have not been performed on the fluoride dose effects that compare oral and respiratory intake in humans.

4.2. *Correlation of dental fluorosis prevalence with the intake levels and geochemical background of fluoride*

Dental fluorosis is a visible symptom of excessive fluoride ingestion and shows a significant dose-response relationship [21,37]. The content of fluoride in water accounts for almost 40% of the prevalence of dental fluorosis in drinking water [38]. Pamela DenBesten of the US Department of Health and Human Services found that when fluoride levels in drinking water reached 1.2 mg/L, 1.8 mg/L, and 2.6 mg/L, then mild, moderate, and severe dental fluorosis developed, respectively [39]. The prevalence of total dental fluorosis reached 85% when the fluoride content in drinking water reached 6.03 mg/L in Ethiopia [40]. In drinking water fluorosis areas of northern China, observations have shown that the incidence of dental fluorosis in rural children aged 7–15 years could be controlled to within 30% by ingesting fluoride below 2.1 mg/d/p [41]. Based on these reports, the National Health Commission of the People's Republic of China (2010) proposed that the area associated with endemic fluorosis could be considered to meet the control level when the prevalence of dental fluorosis among children aged 8–12 years old (including 16 years old) is less than or equal to 30% [42]. Subsequently, the Chinese Health Industry Standard mandated in 2016 that the TDFI for children aged 8–16 years should be less than 2.4 mg [43].

In the coal-burning fluorosis areas of China, a clear correlation of dental fluorosis prevalence with the intake level of fluoride has not been obtained because of the multiple exposure pathways. In this study, although we could not identify the primary factors underlying the prevalence of dental fluorosis in the population, the prevalence of coal-burning dental fluorosis was positively associated with the intake level of fluoride. When the TDFI was 2.4 mg, the prevalence rate and Dean's index were 42.8% and 0.74, respectively, according to the developed multivariate model (Eq. (9) and Fig. 4B). However, regional control levels of fluorosis will not be reached if we use 2.4 mg as the TDFI limit in coal-burning fluorosis areas.

Furthermore, a stepwise regression analysis showed that four epidemic factors play decisive roles in coal-burning fluorosis areas in China. In field observations, we found that stone houses were relatively closed. Ventilation and smoke exhaust facilities are usually installed during coal burning to alleviate indoor air pollution, thereby reducing the amount of fluoride ingested via the respiratory tract. Wooden houses or straw houses often lack ventilation facilities, and they commonly burn coal in an open stove and dry food on the stove. This will inevitably cause indoor air and food pollution, thereby increasing the intake of fluoride through the respiratory tract and food. Therefore, increasing the proportion of people living in stone houses and using stoves with smoke exhaust facilities may effectively reduce the prevalence of dental fluorosis. Conversely, living in a wooden house without smoke extraction facilities and the increased use of open stoves for drying foods may aggravate the prevalence of dental fluorosis. These four dominant factors were closely related to the individual family financing conditions and living habits and were changeable. According to our field survey, the amount of coal used by people in areas with coal outcrops was significantly higher than that in other locations because people could collect coal themselves. Other areas need to use cash to purchase coal, thus limiting the use of coal in households. Therefore, differences in fluoride intake are induced by differences in people's lifestyles (e.g., coal combustion and house styles) and opportunities to use coal. As a result, the prevalence of dental fluorosis was not significantly correlated with the fluoride geo-background of drinking water sources, coal, or clay on a large scale.

4.3. Limitations

The article did not include the age groups and comparisons among these groups based on fluorosis level, and it also did not perform an interaction analysis between the different fluorosis-causing factors. Given the impact of economic conditions in rural areas of Southwest China, other sources of fluoride in the form of dietary supplements were not considered among the exposure pathways.

5. Conclusion

The main fluoride exposure pathways of the population in coal-burning fluorosis areas of China are breathing contaminated air and eating contaminated food. The prevalence of dental fluorosis was significantly positively correlated with the intake dose of fluoride ($P < 0.05$). The estimated TDFI per person was between 2.78 and 17.32 mg. The TDFI from breathing and eating was 1.1–3.2 mg and 1.1–15.1 mg, thus accounting for 9%–54% and 40%–90% of the total, respectively. Chilis have high potential for enhancing fluoride associated with coal combustion. The drying procedure and consumption of tainted chili peppers represent the primary sources of fluoride exposure in the population. The amount of fluoride intake by children ranged from 25% to 76%.

The key factors that determine coal-burning fluorosis in rural areas of Southwest China are soil geochemical anomalies and the use of coal as energy, and considerable randomness is observed in this unhealthy lifestyle. Therefore, the proportion and dose of fluoride intake through breathing or food consumption varied widely, and the prevalence of dental fluorosis had no significant correlation with the fluoride geo-background of drinking water sources, coal, or clay on a large scale.

According to the current maximum intake limit of fluoride in China (2.4 mg/d/p for aged 8–16 years old), Dean's index and dental fluorosis prevalence reached 0.74 and 42.8%, respectively; thus, allowing values at the maximum limit will not achieve control levels ($\leq 30\%$) in coal-burning fluorosis areas. Consequently, to control the prevalence of dental fluorosis in these areas to values below 30%, the maximum daily intake of fluoride by the human body should be less than 2.4 mg, especially to reduce the amount of intake through the respiratory tract.

Ethics approval

This was an observational study. The Guizhou Medical University Research Ethics Committee approved the study.

Author contribution statement

J Yang; C Tu: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
J Yang; Q Jiang: Performed the experiments.
J Yang, J Wang; L Li; RB Finkelman: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Consent to participate

Informed consent was obtained from all the participants included in the study.

Consent to publish

Additional informed consent was obtained from all participants for whom identifying information was included in this article.

Declaration of competing interest

We declare no competing interests.

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