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A Systematic Review and Meta-Analysis of the Relationship Between the Severity of Dental Fluorosis and Fluoride Biomarkers in Endemic Areas

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Abstract

The intake of high concentrations of fluoride, mainly through drinking water, diet and fluoridated dentifrices, produces fluorosis, which in its early stages is manifested as dental fluorosis (DF). To recognize exposure to fluoride in endemic areas and to evaluate the risk of developing health impairment, the WHO has established several biomarkers that are used to determine systemic fluorine (F^-) exposure. Thus, the aim of this study was to conduct a systematic review and meta-analysis of the relationship between the severity of DF and fluoride biomarkers in endemic areas. The protocol of this study was previously registered as CRD42021244974. A digital search was carried out in PubMed/Medline, SpringerLink, Scopus, Cochrane and Google Scholar by employing the keywords "urine", "nails", "hair", "plasma", "saliva" and "dental fluorosis" for the original studies with content associated with F^- for the biomarkers and DF. The mean difference was established as the effect measure for the meta-analysis. Seven studies fulfilled the eligibility criteria, among which five assessed urine and two employed nails as fluoride biomarkers. A positive significant difference was found between the biomarkers and the severity of DF (0.27, $p < 0.001$) and individually for each biomarker (urine: 0.14, $p = 0.001$; nails: 0.88, $p < 0.05$). The F^- concentration in urine and nails is correlated with the severity of DF, with the most evident differences between healthy individuals and those with mild severity. Both biomarkers are adequate to assess this relationship in endemic areas of fluoride and DF.

Keywords Fluoride · Dental fluorosis · Fluoride biomarkers · Urine · Nails

Introduction

Dental fluorosis (DF), a disease that affects the enamel during the development of the tooth, is one of the earliest manifestations of fluorosis, which is a condition that occurs from long-term exposure to high concentrations of fluoride, mainly through drinking water [1, 2]. It is widely recognized that the intake of adequate levels of these compounds (0.5–1.0 mg/L) prevents the development of dental caries, but when consuming higher levels (1.5–2.0 mg/L), DF develops, and its progression during an intake greater than 4.0 mg/L may cause severe damage to different structures of the body, such as skeletal fluorosis and impairments of the central nervous, cardiovascular, endocrine, respiratory and gastrointestinal systems [3–8]. Besides the drinking water for human consumption, other sources of intake contribute to the total exposure to fluoride and the development of DF, such as the food from diet, fluoridated dentifrices and supplements with fluoride, along with different factors that have

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an influence on the absorption, retention and excretion of these compounds, such as the renal function with variations in the pH of the urine, genetic background, physical activity, altitude, temperature and nutritional status [9–11].

DF is characterized by hypomineralized enamel, in which diverse alterations, such as mottling and pitting, can be detected on the tooth surface, reflecting the severity of the disease [12]. White opacities in specific areas or affecting the entire enamel along horizontal lines of variable thickness are present in mild cases of the disease. Yellow-to-brown stains are visible in moderate cases. Finally, in the most severe cases, the porosity of the enamel increases due to reduced mineralization, which can lead to the loss of the tooth structure under physiological conditions, such as during chewing [8, 13].

Regarding the epidemiological data of the disease, it has been estimated that at least 24 million people are affected by DF, along with the presence of skeletal fluorosis, since studies conducted on the American, African and Asian continents have reported a high prevalence of DF with a recent increase in its severity [13–19]. The increase in the number of recorded cases in recent years has been the result of the use of different supplements that contain fluoride, such as dentifrices, mouth rinses, varnishes and gels, that are employed to prevent dental caries [12, 20].

To assess exposure to high fluoride levels from different sources of intake, in association with the risk of health damage due to toxicity, several biomarkers established by the WHO have been employed to measure the amount of systemic F^- in a subject during a specific time of exposure [21–24]. The main biomarkers employed for this purpose are classified according to their biological characteristics and type of usage, such as bones and teeth, mineralized tissues that retain the highest burden of F^- in order to evaluate long-term exposure. Their main disadvantage is that their collection is invasive. Plasma, urine and saliva are fluids that can be used to assess the acute intake of fluoride, among which urine is considered the most suitable for its easy collection, storage and measuring process, since the F^- level in plasma is affected by different factors such as the age, hematocrit and anatomical site, and its collection is considered invasive. The F^- in saliva is altered by topical applications and food intake; finally, nails and hair are samples that have been used currently to evaluate systemic F^-, due to as keratinized matrices being capable of attaching an amount of F^- that corresponds to subchronic/chronic exposures. Moreover, these samples have several advantages, such as easy collection, storage without degradation or loss of properties, processing and authentic measured F^- levels that make them an adequate alternative for assessing exposure to fluorides [21, 23–27].

In addition to evaluating the fluoride levels within the human body, it has been sought whether these fluoride biomarkers are associated with the clinical manifestations caused by toxicity as a result of the intake of high concentrations of fluoride, specifically with the presence of DF and its different severity degrees [28].

Because of the importance of the use of these biomarkers for monitoring systemic F^- levels in endemic areas of fluoride and the worldwide interest in knowing whether these biomarkers have an association with the presence of DF, the aim of this study was to conduct a systematic review and meta-analysis of the relationship between the severity of dental fluorosis and fluoride biomarkers. The research question addressed for this analysis was the following: what is the relationship between dental fluorosis and fluoride biomarkers in endemic areas?

Methods

Eligibility criteria

Inclusion criteria

1) Studies that employed different fluoride biomarkers for quantifying systemic F^- and evaluated the severity of DF through the most recognized indices in the literature; 2) studies published between January 2000 and March 2021; 3) studies written in English; 4) original articles performed in humans.

Exclusion criteria

1) Studies that did not report adequately the systemic F^- concentration assessed through fluoride biomarkers in relation to the severity of DF; 2) reviews, letters to the editor, systematic reviews or similar; 3) studies with non-associated content in relation to the main subject of the current systematic review and meta-analysis.

Information sources

The literature search was carried out in the main databases PubMed/Medline, SpringerLink, Scopus, Cochrane and Google Scholar. Gray literature was also considered.

Search strategy

The employed keywords, according to the medical subject headings (MeSH), were “urine”, “nails”, “hair”, “plasma”, “blood”, “serum”, “saliva”, “dental fluorosis”, “enamel fluorosis”, with the use of Booleans “AND”, “OR”, “NOT”, through the following search terms: “dental fluorosis” OR “enamel fluorosis” AND “nails”; “dental fluorosis” OR “enamel fluorosis” AND “fingernails” NOT “toenails”;

"dental fluorosis" OR "enamel fluorosis" AND "toenails" NOT "fingernails"; "dental fluorosis" OR "enamel fluorosis" AND "urine"; "dental fluorosis" OR "enamel fluorosis" AND "plasma" OR "serum" OR "blood"; "dental fluorosis" OR "enamel fluorosis" AND "serum"; "dental fluorosis" OR "enamel fluorosis" AND "hair"; "dental fluorosis" OR "enamel fluorosis" AND saliva.

Selection process

The screening of titles and abstracts was carried out by two reviewer authors independently, following the previously described inclusion criteria. The studies considered relevant were retrieved for full-text evaluation. Finally, articles with useful content for the systematic review and meta-analysis were selected after discussion and the agreement of both authors.

Data collection process

Quantitative and qualitative data were extracted in duplicate and independently by two authors through standardized forms to facilitate the analysis of the information. In cases of disagreement, a third reviewer was involved to resolve the discrepancy.

Data items

The abstracted data were: authors of the study, year, place, number of participants, biomarkers used for measuring the systemic F^- concentration, mean concentration of the F-in the biomarkers, prevalence and the severity of DF. As a primary result, the relationship between the mean of the systemic F^- levels of the biomarkers and the severity of DF was established, and the assessment of the mean F^- concentration of each biomarker according to the severity of DF was considered the secondary result.

Risk of bias assessment

Cochrane's Collaboration Tool was employed to evaluate the risk of bias through the following domains: 1) bias arising from the randomization process, 2) bias due to deviations from the intended interventions, 3) bias due to missing outcome data, 4) bias in the measurement of the outcome and 5) bias in the selection of the reported results. Each domain was classified as *low risk*, *some concerns* or *high risk* according to the identified bias. Finally, the overall risk was determined based on the results observed in each domain. The RoB 2.0 tool was employed to produce the figures that indicated the results of the risk of bias in the individual studies. Likewise, this tool was used to analyze the risk of bias across studies.

Effect measures

The continuous outcomes of the mean F^- level in the biomarkers were analyzed according to the weighted mean differences and the standardized mean differences observed in the comparison of the different severity degrees of DF in association with the F^- quantified in each biomarker. The inverse variance statistical method was employed for the analysis.

Synthesis methods

The synthesis of the data was performed with the statistics software RevMan 5.4 and STATA 16.0, with which the meta-analysis, subgroup and sensitivity analysis were carried out. The fixed-effects model was established in this procedure because the F^- levels in the biomarkers were determined through the same measurement scale, with one expected result. A p-value of < 0.05 was considered statistically significant, with 95% confidence interval (CI).

Heterogeneity assessment

The I^2 statistic (0%–40%: not important heterogeneity; 30%–60%: moderate heterogeneity; 50%–90%: substantial heterogeneity; 75%–100%: considerable heterogeneity) was used to assess the statistical heterogeneity across studies. Moderate heterogeneity was considered adequate for developing the meta-analysis. In cases of great heterogeneity ($I^2 \geq 50\%$ or $p < 0.1$), the qualitative characteristics of each study were considered in the analysis.

Sensitivity analysis

The sensitivity analysis was carried out with each included study to verify whether differences in the obtained results occurred by considering the weight when the meta-analysis was conducted.

Meta-bias

The meta-bias was verified when handling the considered data for the meta-analysis in the different established subgroups to accurately interpret the obtained results. The publication bias between studies was verified with Egger's test ($p < 0.05$, indicating publication bias) by corroborating this result visually through a funnel plot.

Certainty assessment

The methodology of the work group GRADE (Grading of Recommendation Assessment, Development and Evaluation) was employed to evaluate the evidence of the included

studies. The quality of the information was defined as *high*, *moderate*, *low* and *very low*.

Results

Study selection

From the digital search, 2629 articles were obtained from the included databases. Among these, seven studies fulfilled the selection criteria and were thus included in the meta-analysis. Figure 1 shows the selection process that was developed for each biomarker during the systematic review of this study.

Risk of bias assessment

Regarding the risk of bias in the individual study assessments, 71% of the studies (5/7) showed low risk, followed by 29% (2/7) where some concerns were observed (Fig. 2). No studies presented a high risk of bias; therefore, it is considered that the risk of bias of the analyzed studies did not represent an important issue for the findings of the current study. Regarding the risk of bias across studies, a low risk predominated in most of the evaluated domains (4/5), excluding the fourth domain, where some concerns were over 50% of the reported bias. A high risk was only found in the second domain in less than 25% of the assessed studies (Fig. 3).

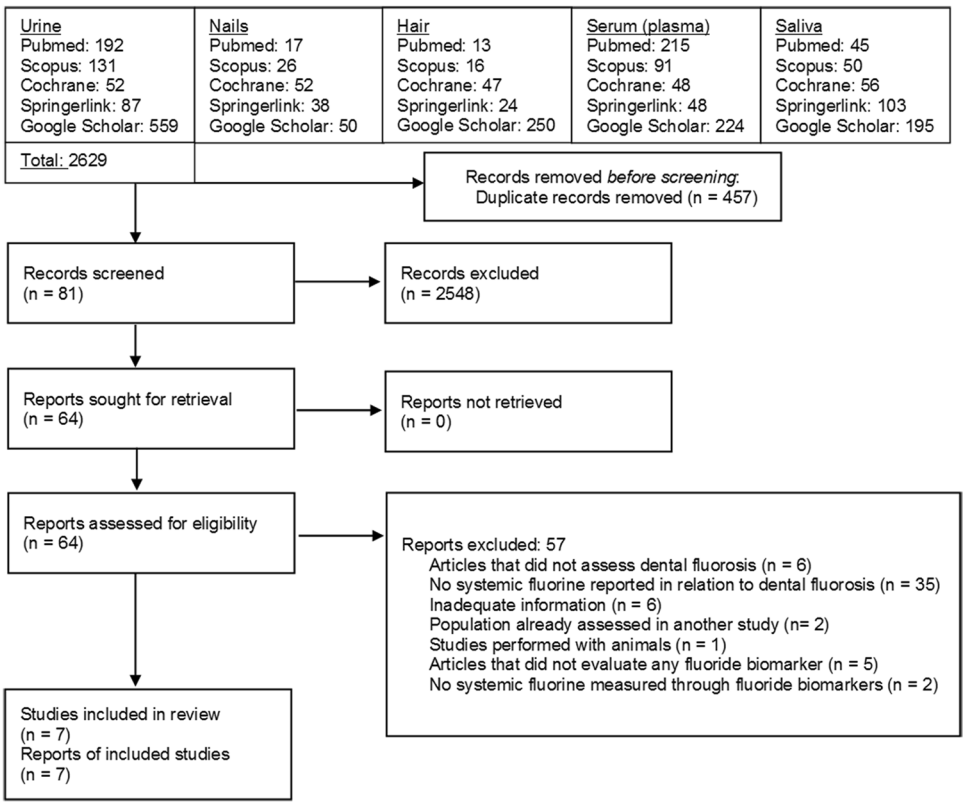

Fig. 1 PRISMA flow diagram for the selection of the included studies for the systematic review and meta-analysis. From a total of 2629 articles, seven fulfilled the eligibility criteria and were included in the current study

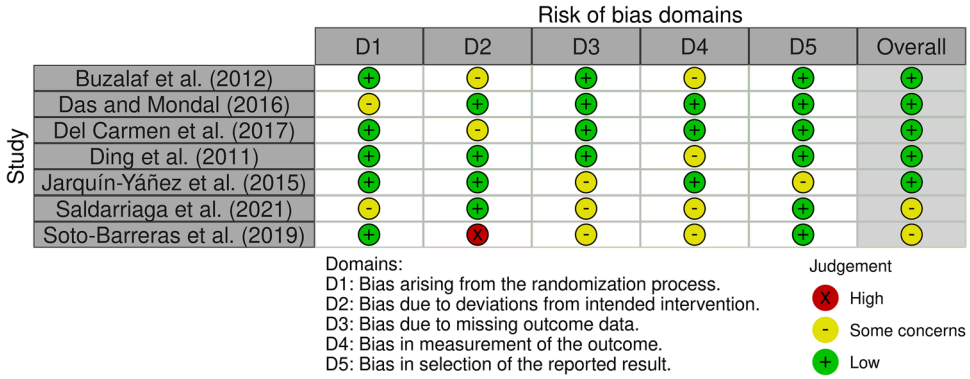

Fig. 2 Risk of bias in individual studies. Overall, a low risk of bias was observed in the analyzed studies (5/7), followed by some concerns (2/7). Only one study presented high risk of bias in the second domain

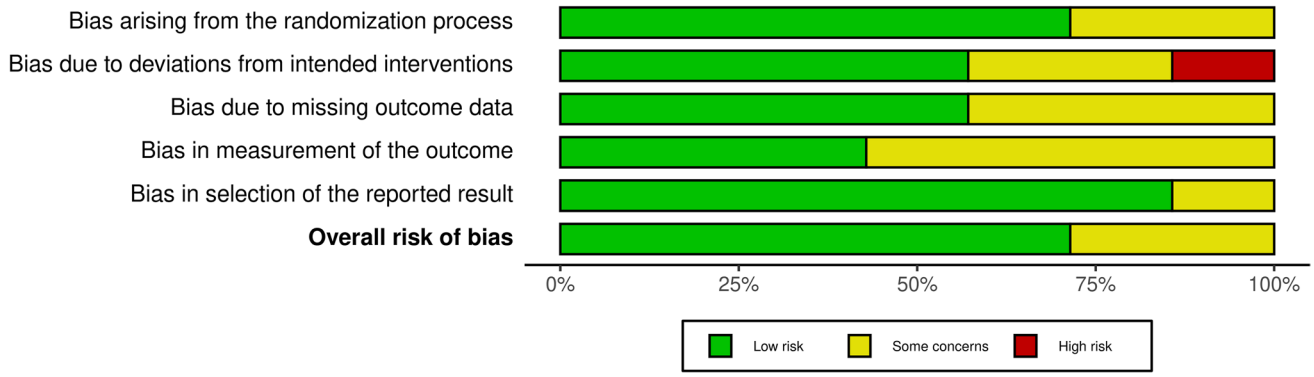

Fig. 3 Risk of bias across studies. A low risk of bias predominated in most of the assessed domains (> 50%), except the fourth domain with some concerns of bias. Only the second domain presented high risk of bias (< 25%)

Study characteristics

Five studies employed urine as biomarker of F^- [29–33], and two used nails [28, 34]. Regarding the rest of the biomarkers, such as saliva, serum (plasma) and hair, no studies fulfilled the required characteristics for their inclusion in the current analysis. Regarding the assessment of the severity of DF, Dean's index (DI) [35] and the Thylstrup–Fejerskov index (TFI) [36] were employed in the selected studies. Two studies assessed DF with DI [29, 31] and five with TFI [28, 30, 32–34]. To quantitatively compare the reported results in association with the mean F^- concentration for the distinct biomarkers and the severity of DF evaluated through both indices, the degrees of DF were adapted into severity groups (SGs), which are shown in Table 1.

Table 2 shows the five studies in which urine was employed as a fluoride biomarker. Three of them were performed in Mexico, one in India and another in China. In each study, a high level of exposure to fluoride through drinking water, according to the WHO, was recorded. For the DF assessment, three studies employed TFI and two DI. Four studies reported significant differences between F^- in urine and the severity of DF, with a proportional increase between both variables. The study conducted by Soto-Barreras et al. [32] did not report significant differences despite a relationship between F^- in urine and the severity of DF [32].

Table 3 includes both studies that employed nails as biomarkers of F^-, where DF was assessed by the TFI. Significant differences were reported between these variables, although the study conducted by Saldarriaga et al. (2021) established an inverse correlation between the biomarker and the severity of DF [34].

Results of syntheses

In the first meta-analysis, the F^- level in both urine and nails was compared; therefore, the standardized mean difference was used as an effect size due to the distinct features and rates of fluoride levels measured in each biomarker. The results indicated significant differences between the F^- quantified in the biomarkers in the different SGs of DF, with a standardized mean difference of 0.27 (95% CI, 0.14–0.40) ($Z=4.11$, $p<0.001$) and moderate heterogeneity ($I^2=51.74\%$) (Fig. 4).

Regarding the meta-analysis performed individually for each biomarker, the mean difference was employed as an effect size, where the results from the urine indicate

Table 1 Severity groups according to the employed indices of dental fluorosis in the included studies of the meta-analysis

Severity group	Studies that employed urine (5)					Studies that employed nails (2)	
	Das and Mondal (2016)	Del Carmen et al. (2017)	Ding et al. (2011)	Jarquín- Yáñez et al. (2015)	Soto-Barreras et al. (2019)	Buzalaf et al. (2012)	Saldarriaga et al. (2021)
[a]0	*Normal	TFI 0	*Normal	-	TFI 0	TFI 0	-
[b]1	Questionable	TFI 1–2	Questionable	-	TFI 1–2	TFI 1–2	TFI 1–2
[c]2	Very mild	TFI 3–4	Very mild	-	TFI 3–4	TFI 3–4	TFI 3–4
[c]3	Mild	TFI 5–6	Mild	TFI 4–5	TFI 5	TFI ≥ 5	TFI 5–6
[d]4	Moderate	TFI 7–9	Moderate	TFI 6–7		-	TFI 7
[d]5	Severe	-	-	TFI 8–9		-	-

TFI: Thylstrup and Fejerskov Index. *Dean's Index: a. Healthy individuals. b. Mild Severity. c. Intermediate Severity. d. High Severity

Table 2 Studies that employed urine as fluoride biomarker

Author	Place	Severity of DF (n)	Mean $F^- \pm SD$ (mg/L)	*p*-value
Das and Mondal (2016)	Eastern Bankura District, India	[a]Normal (4)	2.91 ± 1.76	< 0.01
		Questionable (17)	2.50 ± 2.39	
		Very mild (27)	2.58 ± 1.31	
		Mild (35)	2.95 ± 1.44	
		Moderate (43)	4.82 ± 3.57	
		Severe (23)	3.81 ± 2.51	
Del Carmen et al (2017)	Guanajuato, México	TFI 0 (25)	1.02 ± 1.04	0.003
		TFI 1–2 (54)	1.03 ± 0.93	
		TFI 3–4 (66)	1.04 ± 0.87	
		TFI 5–6 (124)	1.39 ± 1.21	
		TFI 7–9 (38)	2.02 ± 1.88	
Ding et al (2011)	Hulunbuir, China	[a]Normal (136)	0.80 ± 0.55	< 0.05
		Questionable (54)	1.13 ± 0.73	
		Very mild (74)	1.11 ± 0.74	
		Mild (39)	1.31 ± 0.78	
		Moderate (28)	1.46 ± 0.79	
Jarquín-Yáñez et al (2015)	San Luis Potosí, México	TFI 4–5 (33)	2.66 ± 0.89	< 0.01
		TFI 6–7 (50)	3.11 ± 1.06	
		TFI 8–9 (28)	3.75 ± 1.10	
Soto-Barreras et al (2019)	Chihuahua, México	TFI 0 (32)	0.48 ± 0.23	0.088
		TFI 1–2 (45)	0.51 ± 0.38	
		TFI 3–4 (60)	0.62 ± 0.32	
		TFI > 5 (24)	0.67 ± 0.41	

F^-: Fluorine. DF: Dental fluorosis. SD: Standard deviation. TFI: Thylstrup–Fejerskov index. a: Dean's index

Table 3 Studies that employed nails as fluoride biomarkers

Author	Place	Severity of DF (n)	Mean $F^- \pm SD$ (μg/g)	*p*-value
Buzalaf et al (2012)	Brazil, Paraíba and Bauru	TFI 0 (19)	2.24 ± 1.09	< 0.001
		TFI 1–2 (22)	3.35 ± 1.40	
		TFI 3–4 (8)	3.66 ± 2.11	
		TFI 5 (7)	7.58 ± 2.72	
Saldarriaga et al (2021)	El Cedro, Colombia	TFI 1–2 (8)	3.07 ± 1.76	0.015
		TFI 3–4 (17)	2.96 ± 2.70	
		TFI 5–6 (11)	1.42 ± 1.77	
		TFI 7 (1)	1.48 ± 0	

F^-: Fluorine. DF: Dental fluorosis. SD: Standard deviation. TFI: Thylstrup–Fejerskov Index

significant differences that favor a larger amount of F^- with an increase in the severity of DF, with a mean difference of 0.14 (95% CI 0.05–0.22) (Z = 3.19, $p = 0.001$) and moderate heterogeneity ($I^2 = 41.45\%$) (Fig. 5).

In the meta-analysis of the studies that employed nails as fluoride biomarkers, statistically significant results were observed, with the greatest mean F^- difference in the entire analysis, with a value of 0.88 (95% CI 0.22–1.55) (Z = 2.35, $p = 0.02$) in relation to the higher severity of DF, with substantial heterogeneity ($I^2 = 85.94\%$), being the highest registered throughout the current study (Fig. 6).

The funnel plots for the visual evaluation of the publication bias of each meta-analysis showed symmetry in association with the articles that underwent this assessment; thus, it is considered that no bias was present in the analysis of the results (Fig. 7). This was confirmed by Egger's test, in which the results were not statistically significant (urine and nails: $p = 0.203$; urine: $p = 0.092$; nails: $p = 0.742$).

The sensitivity analysis performed for the meta-analysis of both biomarkers and solely in urine did not indicate any modifications of the overall effect by omitting each included study. Changes were only observed for the size effect within the distinct subgroup analysis, which did not modify the final result. On the other hand, modifications of the overall effect are shown in the last meta-analysis focused on nails

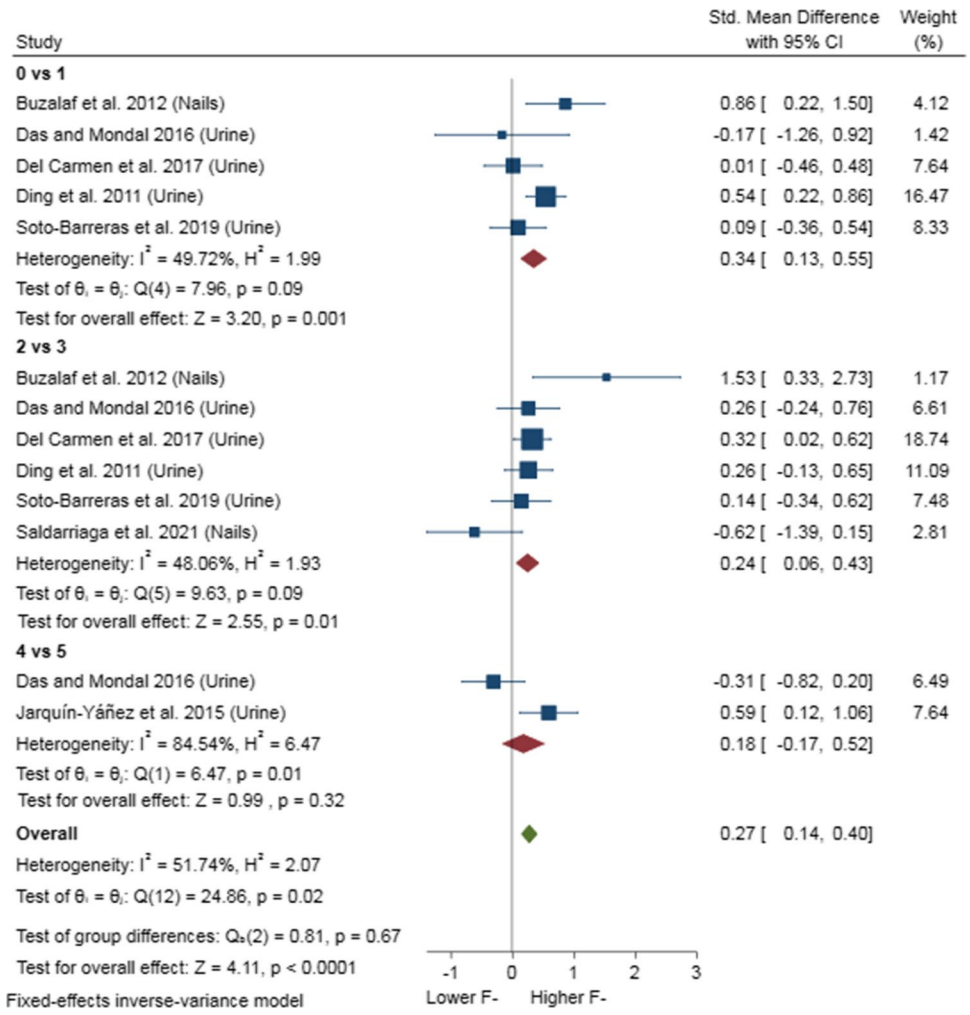

Fig. 4 Forest plot of the meta-analysis performed of the fluorine (F^-) concentration in urine and nails in relation to dental fluorosis. A significant standardized mean difference was observed between the F^- content in the biomarkers and the distinct severity degrees of dental fluorosis ($p < 0.0001$)

by omitting the study by Buzalaf et al. (2012) because it is the only article included in the first subgroup, and only two studies were analyzed in this assessment [28].

The quality of the assessed information of the included studies was considered *high* according to GRADE, which means that the confidence of the estimate of effect is very unlikely to be altered by further research.

Discussion

Relationship between fluoride biomarkers and the severity of dental fluorosis

The current meta-analysis demonstrates that there is a positive correlation between the F^- quantified in the assessed biomarkers, urine and nails and the increase in the severity of DF (Fig. 4). In the first analyzed subgroup, differences were more evident with the increase in F^- in the biomarkers and the DF of SGs 0 and 1 ($p = 0.001$), where the comparison of the individuals considered healthy, according to DI and TFI, and those who presented DF with mild severity of the disease, was performed. Therefore, both biomarkers are adequate to distinguish between individuals who do not have the disease and those with mild disease according to the F^- concentration in both biomarkers. This difference was also evident, although with less distinction, in the following subgroup, where those with an intermediate severity of DF were included (SGs 2 vs. 3) ($p = 0.01$). However, the F^- levels in urine and nails were not significantly distinct when comparing the SGs with the highest severity of DF (SGs 4 vs. 5) ($p = 0.32$). Thus, it may be established that the greatest differences in the systemic F^- levels assessed through these biomarkers are more evident between cases without DF and those with mild severity of DF, and although this concentration increases gradually in association with a higher severity, the differences are not as considerable for the most severe degrees of DF. However, with both biomarkers, it is possible to distinguish the cases in which DF develops with greater severity due to fluoride exposure and intake, in contrast to those individuals who present with no or minimal damage.

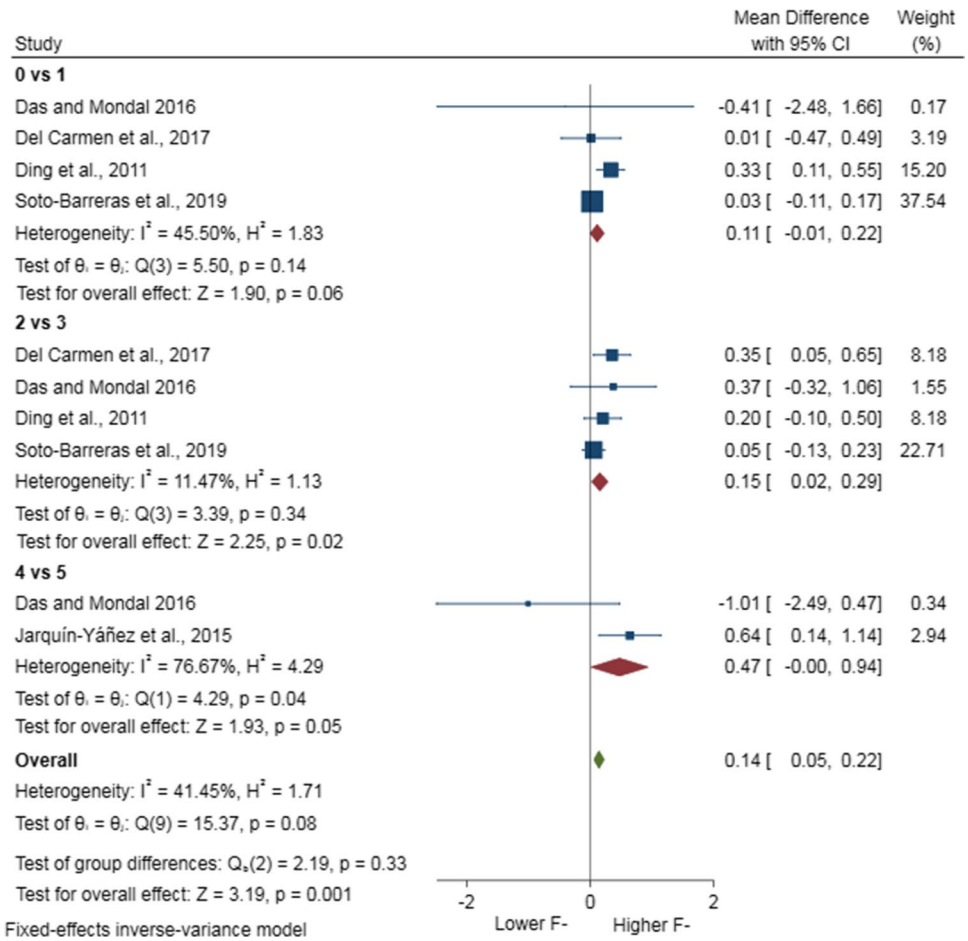

Fig. 5 Forest plot of the meta-analysis performed of the fluorine (F^-) concentration in urine in relation to the severity of dental fluorosis. A positive significant mean difference was determined between the F^- content in urine and the degree of severity of dental fluorosis ($p = 0.001$)

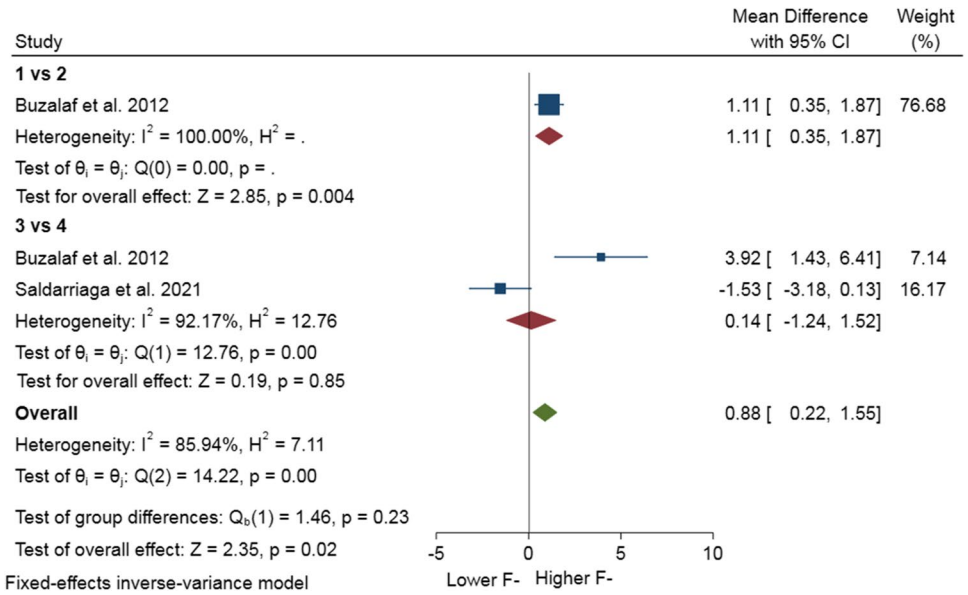

Fig. 6 Forest plot of the meta-analysis performed on nails. A positive significant mean difference was determined between the fluorine (F^-) content in nails and the degree of severity of dental fluorosis ($p = 0.02$)

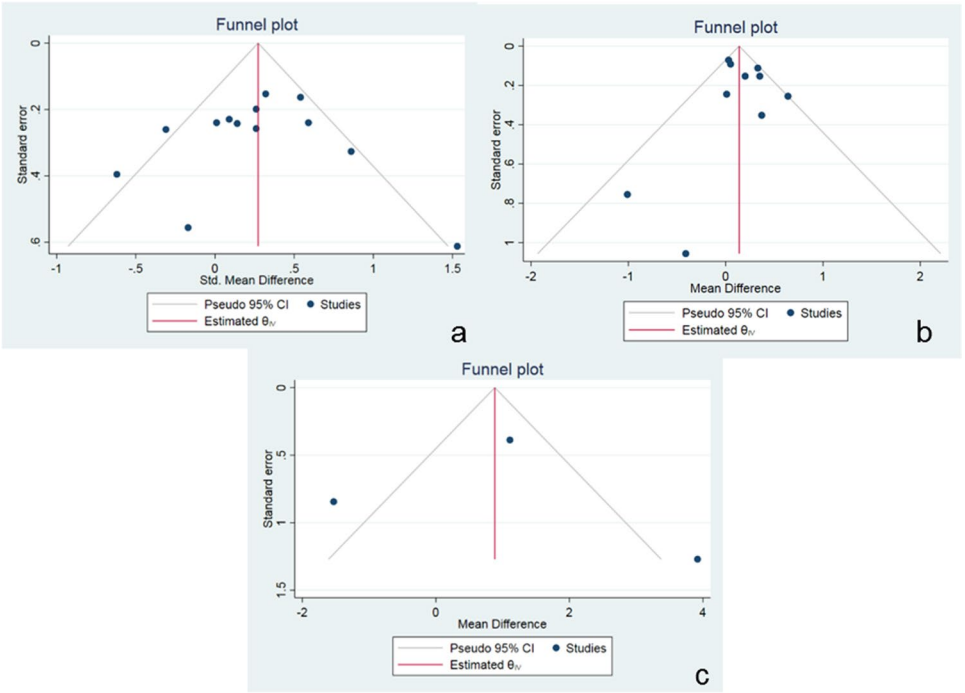

Fig. 7 Funnel plot of the publication bias assessment. **a** Urine and nails assessment. **b** Urine assessment. **c** Nails assessment. No publication bias was detected with the visual evaluation, where symmetry in the dot distribution was identified

Relationship between urine as a fluoride biomarker and dental fluorosis

In a meta-analysis performed exclusively with studies that employed urine as fluoride biomarker, a greater increase of F^- in the biomarker was observed in association with a greater severity of DF, although the differences of the values in each subgroup were not as evident as in the first meta-analysis, where both urine and nails were included (Fig. 5). Regarding the comparison of SGs 0 and 1, no significant differences in the mean F^- were found according to the registered data from each included study ($p > 0.05$). Nonetheless, this value was positive in relation to the healthy group (SG 0) and the group with mild severity (SG 1), with a mean difference of 0.11. This difference increased when comparing SGs 2 and 3, where positive significant results were shown in intermediate severity ($p = 0.02$). Finally, in the subgroup with a greater severity of DF (SG 4 vs. 5), a positive significant difference was observed ($p = 0.05$). Thus, it could be determined that this biomarker had higher sensitivity to measure systemic F^- in relation to the intermediate and severe degrees of DF, and it had less sensitivity when identifying differences between healthy individuals and those with mild disease. It is important to highlight that, as a result of this systematic review, it is clear that urine has become the most commonly used biomarker to study the relationship between systemic F^- levels and DF; hence, conclusions about the use of this biomarker for this purpose are more accurate.

Relationship between nails as biomarkers of fluoride and dental fluorosis

Finally, the meta-analysis performed with the studies that used nails as fluoride biomarkers in relation to DF showed that differences between systemic F^- levels and the severity of the disease were positive and significant ($p < 0.05$), with some variations within each analyzed subgroup (Fig. 6). Unlike urine, nails present a more evident mean F^- difference in SGs 0 and 1, although only one study supports this result. In the next subgroup (SGs 2 vs. 3), the results showed no differences in the F^- concentration between the biomarker and the severity of DF ($p > 0.05$). Thus, as represented in the meta-analysis performed together with urine and nails, it may be determined that there is a greater sensitivity of this biomarker when comparing healthy individuals with those who develop the disease with mild severity, in contrast to the intermediate subgroup. In this meta-analysis, the comparison between SGs 0 vs. 1 and 4 vs. 5 of the study conducted by Saldarriaga et al. (2021) could not be included, since a TFI 0 group was not reported and only one study subject was diagnosed with the highest severity of DF identified in the research (TF 7) [34]. However, it is necessary to perform additional studies that employ nails as biomarkers of fluoride exposure that assess the severity of DF in relation to systemic F^- levels, since only two studies were retrieved to develop this analysis, where Buzalaf et al. (2012) reported a positive significant correlation between the biomarker and DF [28]; otherwise, Saldarriaga et al. (2021) found decreased F^- levels

in nails at the most severe levels of DF [34]. Additionally, in the meta-analysis performed for this biomarker, the greatest mean F^- difference in relation to the degrees of DF was registered (0.88), which might be explained by nails retaining the highest amount of this element as a result of long-term exposure to fluoride.

The analysis throughout this study indicates that both urine and nails may be employed to evaluate the relationship between the systemic F^- concentration after fluoride exposure in endemic areas and the clinical damage demonstrated with DF, although due to their biological features, both should be used in different circumstances for this purpose.

Urine is considered the most adequate biomarker to evaluate short-term exposure to fluoride, where a 24-h sample turns out to be suitable to determine daily F^- excretion, although it is only considered useful for measuring this type of exposure at a community level, not for individual measurements [37].

On the other hand, nails, as keratinized matrices with the ability to retain F^- from fluoride intake and the plasma concentration during their growth period, can be employed for determining subchronic/chronic exposure to fluoride [21].

It is noteworthy that the geographic differences of each assessed region of the included studies have a particular influence on the exposure and intake of fluoride. Overall, natural phenomena mainly contribute to the high concentration of fluoride in groundwater deposits in comparison with anthropogenic activity, where the presence of volcanic rocks and hydrothermal deposits favors the increase in F^--bearing minerals (fluorite, fluorapatite, hydroxyapatite and cryolite). These concentrations are regulated by environmental conditions, such as high temperatures in water, pH, solubility of minerals, time, among others [38].

In almost all the regions of the Asian countries, fluoride levels in water above 1.5 mg/L have been reported, with variations that depend on weather, composition of rocks, precipitation and topography [39]. Particularly in the northern China, concentrations of fluoride in water between 5 and 10 mg/L have been registered as a consequence of the geographic characteristics of the zone [40]. The northern and central Mexico are considered as arid/semiarid areas, a condition that enhances the elevated concentration of fluoride in groundwater deposits as a result of high rates of evaporation and chemical weathering. Other factors, such as high levels of pH, saline underground deposits and sediments with abundant volcanic glass, contribute to the levels of fluoride in water [41]. The greatest severity of fluorosis has been reported in the northeast area of Brazil, which is considered as a semiarid region with high levels of fluoride in groundwater [42]. Finally, the composition of the soil, rocks and active sediments has been studied in endemic areas of DF in Colombia, without establishing an evident association with the amount of fluoride found in drinking water for human consumption. Hence, other factors, such as fertilizers used in agricultural activity, the consumption of table salt and the use of fluoridated dentifrices, must be considered when assessing the exposure to these compounds, along with the presence of DF [43].

The limitations of this study are focused on the lack of identified articles for developing the current meta-analysis, since few conducted studies report the systemic F^- levels quantified through the fluoride biomarkers in relation to DF and its different degrees of severity, despite the great interest in evaluating the exposure to fluoride through well-known biomarkers. Thus, it is necessary to conduct further research in this area to provide more supportive information for what is reported in the current meta-analysis, in which, besides employing urine and nails as fluoride biomarkers along with the examination of DF, more biomarkers, such as saliva, hair and plasma, could be included to verify their usefulness for this assessment.

Conclusion

The systemic F^- levels quantified through the fluoride biomarkers evaluated in the current study, both urine and nails, are positively correlated with the severity of DF, with differences that are more evident among individuals who do not present with the disease and those who develop it with mild severity.

These findings are significant to evaluate the exposure to fluoride at different levels through urine and nails, along with a clinical examination for DF, which makes it plausible to anticipate higher systemic F^- levels as a result of exposure to these compounds in individuals who present with different degrees of DF in comparison with those considered healthy. Hence, it would be possible to prevent systemic health impairment as a result of the exposure and intake of fluoride at concentrations considered harmful by recognizing DF as an earlier manifestation of systemic fluorosis and by verifying the systemic F^- of an individual affected by this disease.

Both urine and nails, due to their distinct characteristics and type of use, may be employed to verify the exposure to fluoride in endemic areas in relation to the detected severity of DF, since the recorded F^- levels in each biomarker are the result of short-term (for urine) and long-term (for nails) exposure.

Other information

Registration and protocol

The protocol of this analysis was registered in the database PROSPERO, with registration number CRD42021244974. This study was performed according to the PRISMA guidelines [44].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12011-022-03227-1.

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Authors' contributions J.L.-C., N.M.-F. and M.V.-O., performed the digital search, the selection, analysis, and extraction of the information. R.B.-M. and R.G.-G. drafted the manuscript. All the authors contributed in the risk of bias assessment strategy. R.G.-G., M.A.I.-E. and E.G. made the tables and figures. J.L.-C. and N.M.-F. performed the meta-analysis. All the authors approved the final version of the manuscript.

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Data availability The data that were produced during the development of the current study are included throughout this paper.

Declarations

Ethics approval This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42021244974.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare that they have no conflict of interest.

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