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REVIEW ARTICLE

Dental fluorosis prevalence in Saudi Arabia

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KEYWORDS

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Abstract *Aim:* In order to improve the understanding of dental fluorosis prevalence in Saudi Arabia and have a good idea of the quality of the studies that have been conducted, a systematic review was conducted to evaluate the prevalence of dental fluorosis among people who live in Saudi Arabia.

Methods: Online databases EMBASE and MEDLINE and the Cochrane Library were searched, without any restriction regarding age. In addition, there were no study design filters applied to the search engine. Study selection and data extraction were conducted in duplicate. Studies were included if they were conducted in Saudi Arabia on any population (adults and children) and collected dental fluorosis data. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies. A narrative synthesis was conducted.

Results: Seven cross-sectional studies were identified. Areas of weakness in study design/conduct were low response rates, and identification and handling of confounding factors. Statistical pooling of data was not appropriate due to substantial heterogeneity, due in part to variation in sample size, variation of water fluoridation concentration, index used, targeted population and age group. Seven studies present dental fluorosis at any level. The proportion of dental fluorosis prevalence at any level ranged from 0.00 to 0.91. Six studies explored the prevalence of dental fluorosis of aesthetic-only level of concern. The proportion of dental fluorosis in this category ranged from 0.07 to 0.76.

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Conclusion: The proportion of dental fluorosis at any level ranged from 0.00 to 0.91 and fluorosis at aesthetics level ranged from 0.07 to 0.76. However, current data does not provide a complete assessment of dental fluorosis across Saudi Arabia. Existing studies are limited in terms of the population covered. The included studies had methodological flaws.

Contents

1. Introduction

Fluoride is used to prevent dental caries, especially in areas where they have high-risk factors for the development of dental caries (such as huge sugar intake). Although the main known source of the fluoride is water fluoridation, fluoride is also present in fish, tea, formula milk, salt and fluoride supplements (toothpaste, fluoride varnish application and mouthwash) (Mascarenhas, 2000). However, excess intake of fluoride will lead to dental fluorosis, which is a state that occurs when a person consumes an excessive amount of fluoride during tooth formation. This will influence the ameloblast cells, which help in the development of enamel; leading into appears effective at the enamel surface of the tooth. The appearance of dental fluorosis at the tooth surface ranges from a white spot to brown discoloration (Fejerskov et al., 1990). To measure this range, there are two indices which are commonly used to category the severity and describe the dental fluorosis level: Dean's Index (Dean et al., 1942) and Thylstrup and Fejerskov Fluorosis Index (TFI) (Thylstrup and Fejerskov, 1978). Both indices classify the dental fluorosis into six levels (normal, questionable, very mild, mild, moderate and severe); however, Dean's Index has five points to score (from 0 to 5) while the TFI has 10 points, as it counts all the tooth surfaces, "buccal, lingual and occlusal surfaces". Furthermore, there are others indices such as Developmental Defects of Enamel Index (DDE) and Tooth Surface Index of Fluorosis (TSIF) (Rozier, 1994). This appearance of fluorosis on the dental surface, especially in its more severe forms when it becomes darker in colour, is considered to be an aesthetic issue. However, the impact of dental fluorosis goes further than simply aesthetics, as there are some arguments that fluorosis can be a risk factor for dental caries. (Fejerskov et al., 1990) stated that dental fluorosis prevalence is linked to the prevalence of dental caries; they argued that dental fluorosis undermines the enamel surface of the tooth, making it weak. This has been supported by a review conducted by (Shilpa, 2017), who came to the same result. (Shilpa, 2017) stated that taking excess amounts of fluoride would cause the enamel to "mottle", which would lead to dental caries as well as dental fluorosis (Shilpa, 2017). This argument was support by a study conducted in Brazil, when the authors came to the conclusion that suffering from dental fluorosis can weaken a tooth and make it more likely to have dental caries. They indicated that a tooth that is diagnosed

with dental fluorosis at level number 3 on the TFI is weaker than a sound tooth (Marín et al., 2016).

It has been suggested that dental fluorosis is more likely in areas of Saudi Arabia where water fluoridation is present, and therefore the number of dental caries is likely to be reduced (Aldosari et al., 2010). However, another study found the opposite; (Akpata et al., 1997) found that there is no reduction of dental caries in areas with high prevalence of dental fluorosis.

There have been several studies conducted in Saudi Arabia aimed at measuring the prevalence of dental fluorosis as a result of the wide variations in water fluoride concentrations, which have been found to range from 0.10 to 5.40 ppm (Alabdulaaly et al., 2013). Some of these studies have targeted certain provinces in Saudi Arabia, while others have covered the whole country. They reported various results regarding the prevalence of dental fluorosis. To gain a fuller understanding of dental fluorosis across Saudi Arabia, a systematic review was proposed and aimed at evaluating studies that measured the prevalence of dental fluorosis, assessing their methodological quality and the location of the study.

2. Methods

2.1. Search strategy

The search strategy was designed to be as comprehensive as possible by following the standards of the PRISMA statement. Three databases used to identify articles MEDLINE via OVID, EMBASE via OVID and Cochrane Library. Hand searching of the Saudi Dental Journal was also undertaken. A mix of free text terms and MeSH terms was utilised for the key concepts, comprising dental fluorosis, fluoride, and Saudi Arabia. On this search, no study design filters applied.

The identified papers from the search strategies were collected and checked for duplication in Endnote X9. A visual double check was conducted to identify any duplication that could have been missed by Endnote. The titles and abstracts of all the remaining articles were read in order to check for relevance according to the inclusion criteria.

2.2. Inclusion criteria

The included studies must have used a valid measurement to evaluate dental fluorosis in any area within Saudi Arabia. There were no restrictions regarding participants' age. Only primary studies published in either English or Arabic languages were included.

2.3. Exclusion criteria

Studies were excluded from the review if they aimed to measure other oral conditions with no consideration of dental fluorosis or they were not conducted in Saudi Arabia.

2.4. Study selection

Three reviewers (F.A., L.O.M., and A.M.G.) independently reviewed all papers. Full copies of all potentially relevant articles were retrieved and reviewed until a final agreement was reached regarding inclusion.

2.5. Data extraction

Relevant data from included papers were extracted and transferred to a pre-specified data table (Table 1). The data extracted were the key characteristics of the study including: Study author, place of the study, sample size, age group, participants gender, measurement tool, dental fluorosis prevalence, water fluoridation level according to the study and water fluoridation level from a third-party study, (Alabdulaaly et al., 2013).

2.6. Assessment of risk of bias

The validity of the studies was assessed by evaluating the quality of the methodology using a modified version of the Newcastle-Ottawa Scale (Wells et al., 2012). The NOS items included sample methods, sample size, outcomes validity, outcomes reliability, confounders identified and dealing with confounding factors.

2.7. Dental fluorosis measurement and synthesis analysis

To interpret the finding from included studies, dental fluorosis data were plotted according to geographical location separating data of fluorosis into either at any level or at aesthetic level of concern only. Participants of each study were considered to have dental fluorosis if they scored more than zero in DDE, TSIF, TFI indices and 'questionable' level or greater in Dean's Index. Participants who scored dental fluorosis of either 3 or more in the TFI, 2 or more in the TSIF and mild or higher in Dean's Index were categorised as suffering from aesthetic matter due to dental fluorosis.

3. Results

3.1. Search results

A total of 25 articles were found through electronic searches and one extra study was identified in the Saudi Dental Journal. These were imported into Endnote X9. There were no duplications, so the title and abstract of all 26 studies were screened.

After screenings of titles and abstract, four studies were excluded, as they not conducted in Saudi Arabia, 15 were excluded, as they did not provide any information on dental fluorosis prevalence. One more study were excluded, as the authors population of interest was Pakistani children (Khan et al., 2015).

The final number of the studies included in the review was 7 (Fig. 1). The characteristics of the included studies are presented in Table 1.

3.2. Risk of bias

None of the included studies were of high quality. All of them failed to identify confounding factors; as a result, no strategy was found to deal with confounding factors. Additionally, four studies did not justify their sample size (Al-Banyan et al., 2001; Almas et al., 1999; Bhayat and Ahmad, 2014; Khan, 2001). However, all the studies had a clear method for their sampling strategy and all of them used a valid measurement to measure

Table 1 Study characteristics.

Study	Study place	Sample size	Age group	Gender	Measurement tool to measure the prevalence of dental fluorosis	Dental fluorosis prevalence	Water fluoridation level according to the study	Water fluoridation level from another source (Alabdulaaly et al, 2013)
Akpata et al (1997)	Hail	2355	12–15 years old	Male and Female	TFI	1–2: 347 3–4: 736 5–6: 639 7–9: 413	0.5 to 2.8 ppm	0.30 to 4.00 ppm
Bhayat and ahmad (2014)	Medina	360	12 years old	Male	Dean's Index	Questionable: 0 Very mild: 0 Mild: 0 Moderate: 0 Severe: 0	N/A	0.65 to 2.00 ppm
Almas et al (1999)	Qassem	800	12 to 65 years old	Male	Dean's Index	Questionable: 42 Very mild: 99 Mild: 99 Moderate:48 Severe: 51	2–3 ppm	0.10 to 5.40 ppm
Khan et al. (2001)	Riyadh	297	30 to 41 years old	Male	Dean's Index	Questionable: 45 Very mild:96 Mild: 64 Moderate:19 Severe: 0	N/A	0.12 to 4.90 ppm
Al-Banyan et al. (2001)	Riyadh	272	5 to 15 years old	Male and Female	Dean's Index	Questionable: 0 Very mild: 0 Mild: 38 Moderate: 0 Severe: 0	N/A	0.12 to 4.90 ppm
AlDosaeri et al. (2010)	Saudi	7688	6 to 18 years old	Male and Female	TFI	1–2: 1198 3–4: 261 5–6: 15 7–9: 278	>0.14 to 2.5 ppm	0.10 to 5.40 ppm
Al-Shammery et al. (1997)	Saudi	7,377	6 to 74 years old	Male and Female	Dean's Index	Questionable: 484 Very mild:506 Mild: 412 Moderate:276 Severe: 137	0.5 to 2.8 ppm	0.10 to 5.40 ppm

the prevalence of dental fluorosis (Table 2). Two measurements were used to measure the prevalence of dental fluorosis: TFI and Dean's Index. In general, only two studies were considered to be moderate quality (Akpata et al., 1997; Al-Shammery et al., 1997), while the rest were considered to be low quality.

3.3. Study settings

Two studies were national surveys covering the whole country (Al-Shammery et al., 1997; Aldosari et al., 2010). Five studies conducted across four provinces. Two studies conducted in Riyadh (Al-Banyan et al., 2001; Khan, 2001) and a single study conducted in each of Hail (Akpata et al., 1997); Madinah (Bhayat and Ahmad, 2014) and Qassim (Almas et al., 1999).

3.3.1. Target population

3.3.1.1. National surveys. Two national surveys recruited different age groups (Al-Shammery et al., 1997; Aldosari et al., 2010).

(Al-Shammery et al., 1997) conducted their survey with a sample size of 7,377 participants from 10 provinces of Saudi Arabia; using Dean's Index to measure the dental fluorosis prevalence. They found out that 24.6% (1,815) of their sample was suffering from dental fluorosis. Among participants who have dental fluorosis, 484 (27%) suffered of dental fluorosis at questionable fluorosis level, 506 (28%) at very mild fluorosis level, 412 (23%) at mild fluorosis level, 276 (10%) at moderate fluorosis level and 137 (9%) at severe fluorosis level.

(Aldosari et al., 2010), conducted their survey with a sample size of 12,200 participants from 11 provinces of Saudi Arabia. In their study, they used the TFI to measure the dental fluoro-

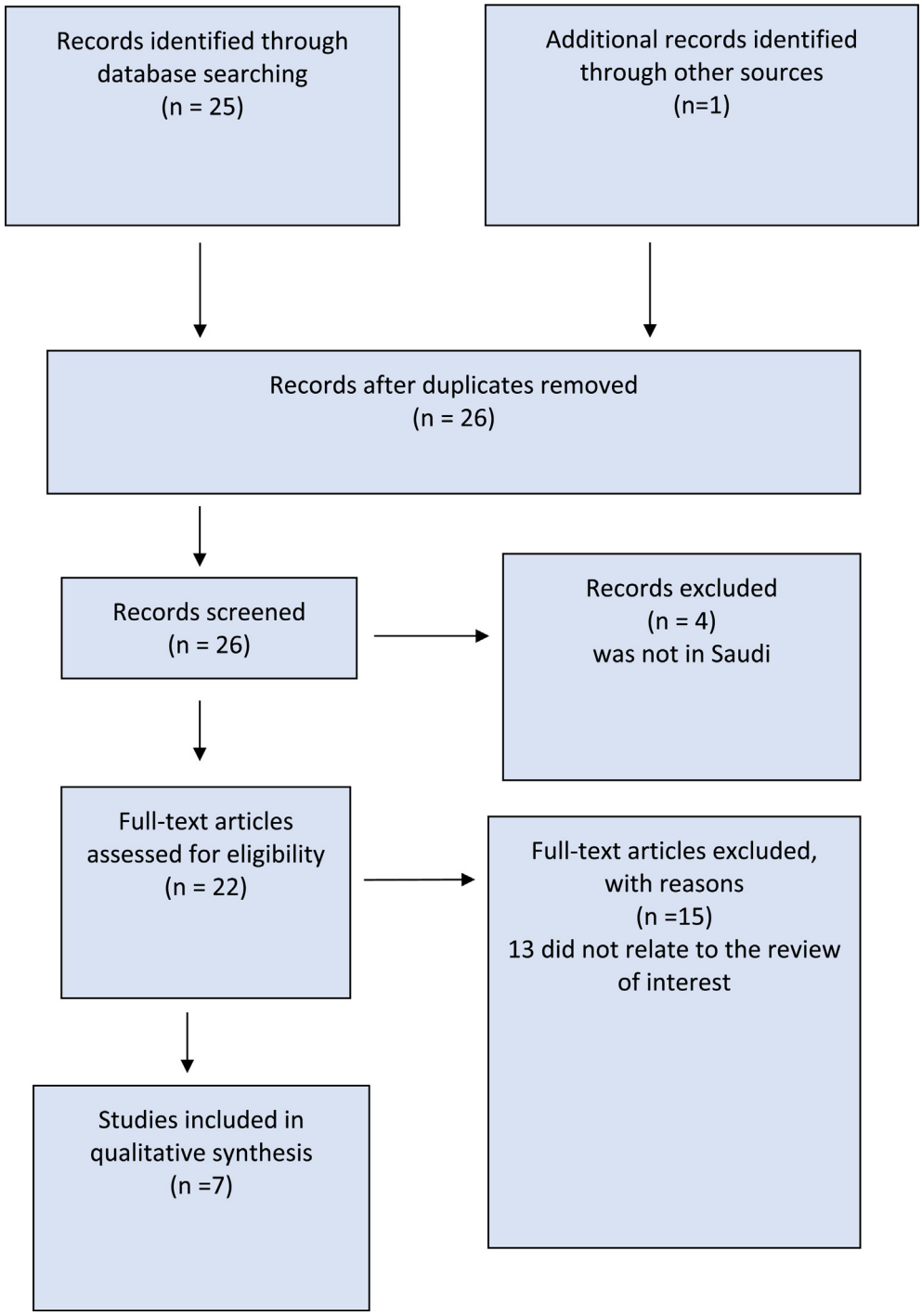

Fig. 1 PRISMA Flow Chart.

sis prevalence. They found out that (17.8%) of their sample suffer from dental fluorosis. Among participants who have dental fluorosis (9.2%) at mild fluorosis level, (1.4%) at moderate fluorosis level and (7.2%) at severe fluorosis level. They indicated that (40%) of the dental fluorosis is affecting the maxillary front teeth, raising the aesthetic issue. They mentioned that dmft ranged from 2.68 to 7.07 and DMFT ranged from 1.81 to 4.70. They stated that dental fluorosis was more severe in areas of high-water fluoridation; they also argued that dental caries is reduced when dental fluorosis is more severe. They pointed out that, during their research, they noticed that when the water fluoridation ranged from 1.01 to 1.5 ppm the dental caries was reduced on both primary and permanent teeth. They indicated that the reduction among the primary teeth was 50% and among the permanent teeth 33%; however, they indicated that dental fluorosis had increased to 33%, where 10% of participants were suffering from moderate fluorosis. They also indicated that, when water

Table 2 The studies against NOS: "Y = Yes; N = No; ?= Not clear: "Each of those items were marked either Yes, No or Not clear. Each item that received a Yes was scored "1"; items were scored zero if they received a No and "0.5" if they were unclear. The total account of the scores for every study will help the reviewers to categorise the studies into three types to clarify their quality; the scores ranged from 0 to 6. Studies scoring 5 and above will be considered high quality, studies ranging from 4 to 5 will be considered moderate studies, and studies scoring lower than 4 will be considered low quality".

Study	Sampling methods	Sample size	Valid outcome measurement	Reliable outcome measurement	Confounders identified	Confounders appropriately handled
Akpata et al (1997)	Y	Y	Y	Y	No	No
Al-Shammery et al. (1997)	Y	Y	Y	Y	No	No
Albanyan et al. (2001)	Y	No	Y	No	No	No
Khan (2001)	Y	No	Y	?	No	No
Almas et al (1999)	?	No	Y	Y	No	No
Aldoseri et al. (2010)	Y	Y	Y	?	No	No
Byhat and Ahmed (2014)	Y	No	Y	Y	No	No

fluoridation ranged between 0.60 and 1.00 ppm, the dental caries reduced by 13% and dental fluorosis prevalence was only 13% among primary teeth and from 7 to 8% among permanent teeth. They argued that the safest and most advantageous amount of water fluoridation in Saudi Arabia should be between 0.60 and 1.00 ppm (Aldosari et al., 2010).

3.3.1.2. Hail. (Akpata et al., 1997) recruited children aged 12 to 15 years who lived in rural areas of the Hail region. They examined 2,355 children using the TFI. They found that 90% of their participants suffered from dental fluorosis. Among participants who had dental fluorosis, 31.25% had very mild fluorosis, 14.7% had mild fluorosis, 27.13% had moderate fluorosis, and 17.5% had severe fluorosis. Additionally, the authors reported that the DMFT ranged from 2.73 to 3.16, and water fluoridation ranged from 0.5 to 2.8 ppm. They stated that the maxillary anterior teeth are the teeth most likely to suffer from dental fluorosis, which is a considerable aesthetic issue.

3.3.1.3. Riyadh. Two studies were conducted in two different age groups with almost the same sample size. Both used the same tool (Dean's index) to measure the prevalence of dental fluorosis.

(Al-Banyan et al., 2001) recruited their sample of children aged (5 to 12 years) visited the dental clinic at the National Guard Hospital. They found out that 14% (38) of their sample (272) suffered from mild dental fluorosis. Furthermore, they measured the dental caries prevalence of those children and found that 99% of them had dental caries.

(Khan, 2001), recruited their sample of adults aged 30 years old and above. They found out that 75% (223) of their sample (292) suffering from dental fluorosis. Among participants who have dental fluorosis (15%) at questionable fluorosis level, (21.5%) at mild fluorosis level, (32.3%) at mild fluorosis level and (8.5%) at moderate fluorosis level.

3.3.1.4. Qassim. (Almas et al., 1999) recruited their sample of different age groups, starting from age 12 years to 65 years old. They used the TFI to examine 800 participants in their study. They found that 339 (42%) participants suffered from dental fluorosis. Among the participants who had dental fluorosis, 42 (12%) had questionable fluorosis, 99 (29%) had very mild fluorosis, 99 (29%) had mild fluorosis, 48 (14%) had moderate fluorosis and 51 (15%) had severe fluorosis. They stated that majority of the participants with dental fluorosis were aged from 35 to 45 years old.

3.3.1.5. Madinah. (Bhayat and Ahmad, 2014) recruited a sample of male primary school children aged 12 years. None of the participants had dental fluorosis at any level; however, dental caries had a DMFT of 1.53 (SD 1.88).

3.4. Dental fluorosis data

Fluorosis data were divided into two groups: fluorosis at any level and fluorosis at the aesthetic level. In both cases, there was substantial heterogeneity in the effect estimates (I^2 = 100%). Due to the substantial heterogeneity, it was not appropriate to statistically pool the data.

3.4.1. Dental fluorosis at any level

Among all participants in all included studies, 6,303 had dental fluorosis (Table 3). The prevalence of dental fluorosis at any level is presented in Fig. 2 and ranged from 0.00 to 0.91.

3.4.2. Dental fluorosis at the aesthetic level

Among all the included participants in the included studies, 3,486 had dental fluorosis at the aesthetic level (Table 3). The prevalence of dental fluorosis at the aesthetic level is presented in Fig. 3 and ranged from 0.07 to 0.76.

4. Discussion

This review aimed to assess studies that measured the prevalence of dental fluorosis across Saudi Arabia. The proportion of dental fluorosis at any level ranged from 0.00 to 0.91 and fluorosis at the aesthetic level ranged from 0.07 to 0.76. There was significant heterogeneity between studies (I^2 = 100). This heterogeneity between studies came as a result of weak methodology, the main areas of weakness being:

Table 3 Dental Fluorosis Prevalence at any level and at aesthetic concern level.

Study	Water fluoridation level according to the study (ppm)	Fluorosis at any level	Fluorosis of aesthetic concern
Akpata et al (1997)	0.5 to 2.8	2135/2355 (90.7%)	1788/2355 (75.9%)
Al-Shammery et al. (1997)	0.5 to 2.8	1815/7377 (18.4%)	825/7377 (11.18%)
Almas et al. (1999)	2.0 to 3.0	339/800 (42.4%)	198/800 (24.75%)
Khan (2001)	N/A	224/297 (75.42%)	83/297 (27.95%)
Al-Banyan et al (2001)	N/A	38/224 (16.96%)	38/224 (16.96%)
AlDoasri et al (2010)	>0.14 to 2.5	1752/7688 (22.79%)	554/7688 (7.01%)
Bhayat and Ahmad (2014)	N/A	0/360 (0.00%)	0/360 (0.00%)

- Lack of justification for sample size (4/7 studies).
- Lack of information regarding confounding factors (7/7 studies).
- Lack of adjustment for confounding factors (7/7 studies).

We could not categorise participants by age into children and adults because only a few studies had been conducted. However, we noticed that there is a difference in dental fluorosis experiences based on age. In Riyadh, (Al-Banyan et al., 2000) reported a low prevalence of dental fluorosis among children aged 5 to 12 years, at only 14%, while (Khan, 2001) stated that dental fluorosis prevalence was 75% of their sample, which was aged from 31 to 45 years old. In Qassim, dental fluorosis prevalence found to be higher in the age group from 35 to 45 years old (Almas et al., 1999). They indicated that almost half of the people who get dental fluorosis are aged between 30 and 45 years old. (Warren et al., 2001) stated that primary teeth are less likely to have dental fluorosis as they developed during pregnancy while permanent teeth are more likely to be affected due to the person consuming excessive amounts of fluoride.

The time period that people exposure fluoride is associated with dental fluorosis. (Evans and Darvell, 1995) stated that the critical time period of exposure to fluoride that will result in fluorosis in males is between the ages of 15 to 24 months, while in females between 21 and 30 months. (Bhagavatula et al., 2016) argued that this period be extend up to 8 years old, as some of the teeth are formed later on and this poses aesthetic issues. Furthermore, (Mascarenhas, 2000), stated fluoride is core to the development of dental fluorosis, however, the duration of fluoride exposure during the amelogenesis will explain the occurrence of dental fluorosis among children. However, none of the included studies considered this point.

When measuring fluorosis levels and comparing these to levels of fluoride in the water (perhaps to explore clinically meaningful correlations between the two) one of the confounding factors is population mobility – if there is a highly mobile population, there is less certainty about the conclusions one can draw from the data. It is an issue, which affects the validity

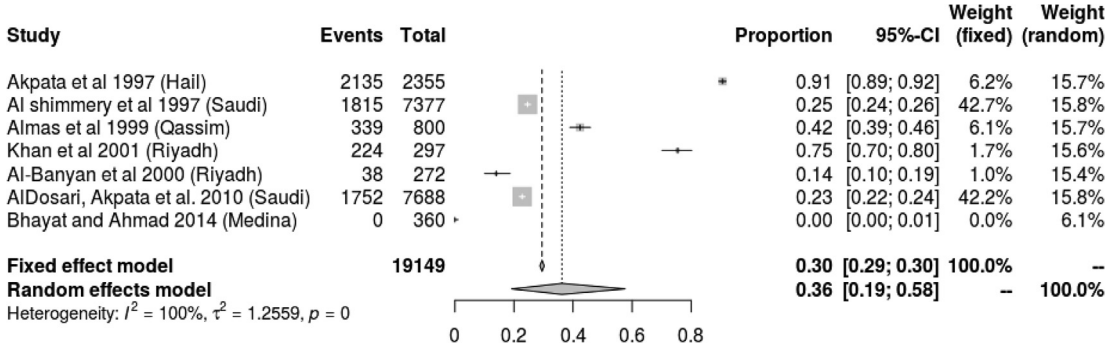

Fig. 2 Data for dental fluorosis at any level.

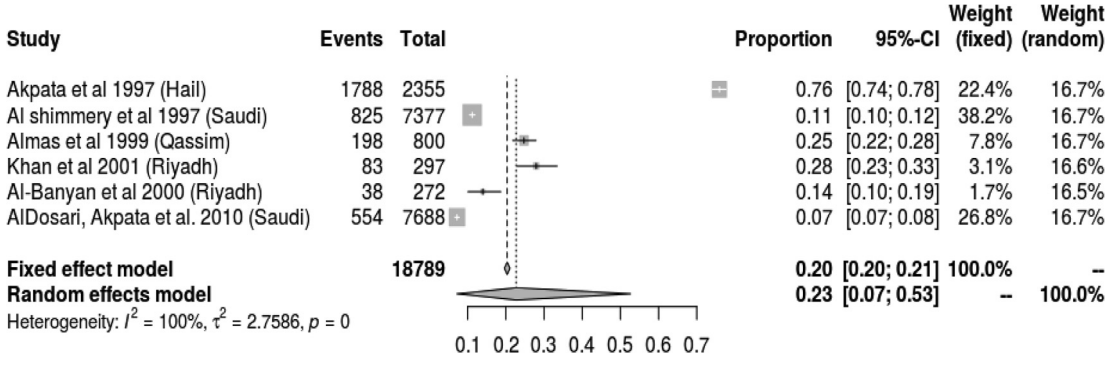

Fig. 3 Data for dental fluorosis at aesthetics level.

of the data and therefore something to consider when interpreting the association between water fluoridation levels and fluorosis.

We found that more than half (55.3%) of participants with dental fluorosis were considered to have dental fluorosis at the aesthetic level. However, there was no discussion across the included studies about the effect of dental fluorosis, except for two studies that raised the aesthetic issue (Akpata et al., 1997; Aldosari et al., 2010). Both studies stated that the majority of teeth with dental fluorosis are the anterior teeth, which has an effect on the participants' social life. A study conducted in Mexico indicated that children with level 4 or more fluorosis on the TFI have some difficulty in their social life (García-Pérez et al., 2017). This matter was also found in children in China when (Li et al., 2014) stated that dental fluorosis had a negative effect on children with regard to their social life. Thus, we think that it will be appropriate to conduct a future study to see how dental fluorosis affects Saudi people.

Almost all the included studies argued that the main reason for dental fluorosis is water fluoridation. However, none of the studies considered the socio-economic status (SES) of participants, as some of the participants could consume bottled water rather than well water. (Iheozor-Ejiofor et al., 2015) stated that the safe amount of water fluoridation to prevent dental caries and avoid dental fluorosis depend on the target population's socioeconomic status (SES), oral health practice and the use of other sources of fluoridation (such as fluoride toothpaste). As result, the safe amount of water fluoridation should take in consideration the other sources of fluoride in order to strike a balance between prevention of dental caries and avoidance of dental fluorosis.

Similarly, all the included studies failed to gain information about water used in cooking. A study conducted by (McGrady et al., 2012) aimed to measure the dental fluorosis prevalence in Thailand, taking into consideration the water used in cooking and counting it as a risk factor of dental fluorosis. In the same way there was no consideration of any other source of fluoride such as fluoride applications. (Wong et al., 2011) argued that children who have exposure to high levels of water fluoridation should not use toothpaste with over 1,000 ppm fluoride as this can cause mild fluorosis. Accordingly, it will be good idea to conduct a survey to determine the percentage of Saudis who use fluoride toothpaste and how often. In general, the majority of the included studies were considered as low-quality studies as they all did not consider the confounding factors.

According to the Saudi Ministry of Health, there is a programme that includes application of fluoride that targets primary schools. However, this kind of programme (intervention) should consider the particular areas in which children might be over-exposed to fluoride through drinking water and be re-evaluated for its effectiveness. Therefore, new strategies of applying this intervention are required.

It is vital that examiners undergo training in order to standardise their methodology and use of fluorosis scales prior to soliciting their opinions on the main sample of teeth to limit inter- and intra-examiner variability. This will help to eliminate the effect of variables, such as moisture and examiner experience, to provide a more objective result and more reliable data on the severity of dental fluorosis. There is also the possibility of including modern techniques for measuring discoloration, such as a digital imaging system, which can use either traditional digital cameras, quantitative light fluorescence, or polarized white light. These modern methods will be ideal for providing objective data with minimal room for human variance by enabling blinding and reducing the risk of poor inter-examiner reliability (Pretty I.A. et al., 2012). It is recommended to have a national level study on the prevalence of dental fluorosis with all those suggestions, which come a long with (Alshammary et al., 2020).

5. Conclusion

The proportion of dental fluorosis at any level ranged from 0.00 to 0.91 and fluorosis at the aesthetic level ranged from 0.07 to 0.76. However, none of the studies conducted until now provide a clear picture of its prevalence; therefore, another study should be conducted, which could be a national survey with the latest information for each province. The study should also consider other sources of fluoride and not be limited to water fluoridation, when assessing the risk factors of dental fluorosis. Furthermore, there should be different studies targeting different age groups and measuring dental fluorosis in primary teeth and permanent teeth.

Funding

No funding was received for this research.

7. Objective

Improve the understanding of dental fluorosis prevalence in Saudi Arabia and have a good idea of the quality of the studies that have been conducted, a systematic review was conducted to evaluate the prevalence of dental fluorosis among people who live in Saudi Arabia.

8. Essence of our approach

A systematic review search conducted by using the online databases EMBASE and MEDLIN and the Cochrane Library were searched, without any restriction regarding age. In addition, there were no study design filters applied to the search engine. Study selection and data extraction were conducted in duplicate. Studies were included if they were conducted in Saudi Arabia on any population (adults and children) and collected dental fluorosis data. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies. A narrative synthesis was conducted.

CRediT authorship contribution statement

Falah R Alshammari: the main author **Marwan Aljohani:** analysising. **Lubomir Botev:** analysising. **Lucy O'malle:** re-check and hepled in research. **Anne.Marie Glenny:** re-check and hepled in research.

Declaration of Competing Interest

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

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