RESEARCH

Prevalence of Mandibular Second Premolar Agenesis in Individuals and Associated Factors: A Meta-Analysis

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ABSTRACT

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Background: The purposes of this study were to determine the prevalence and patterns of mandibular second premolar agenesis in individuals by meta-analysis methodology.

Methods: Two investigators conducted a literature search independently by inclusion criteria to reveal articles on mandibular second premolar agenesis. PubMed, Google Scholar, Ovid Medline, Web of Science Core Collection databases were scanned and a total of 3,988 studies were initially extracted from all databases, then 12 articles were selected which met inclusion and exclusion criteria for the meta-analysis.

Results: The estimated overall prevalence of mandibular second premolar in individuals was 3.26 %. No statistically significant difference was found in the prevalence of mandibular second premolar agenesis by gender [95 % CI: 1.18 (0.96, 1.45); p>0.05]. Males were found to have a significantly higher prevalence of unilateral mandibular second premolar agenesis than females (combined OR 0.69; 95 % CI: 0.38-1.25; p<0.05). However, females had a significantly higher prevalence of bilateral mandibular second premolar agenesis than males (combined OR 1.57; 95 % CI: 0.91-2.72; p<0.05). No difference was found in the prevalence of mandibular second premolar agenesis between the right and left mandibular region [95 % CI: 1.04 (0.91-1.20); p>0.05].

Conclusion: This study supports some previous findings regarding mandibular second premolar agenesis and presents new observations on gender differences, inter-maxillary patterns of mandibular second premolar agenesis in the mandible—including unilateral and/or bilateral occurrence and jaw site.

KEYWORDS

Mandibular Second Premolar, Agenesis, Hypodontia, Prevalence, Congenitally Absent Teeth

ÖZ

Bireylerde Mandibular İkinci Premolar Eksikliğinin Prevalansı ve İlişkili Faktörler: Meta-Analiz Çalışması

Amaç: Bu çalışmada, bireylerde görülen mandibular ikinci premolar agenezisi prevalansının ve ilişkili faktörlerin meta-analiz yöntemi ile değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Dahil edilme kriterlerinden bağımsız olarak, mandibular ikinci premolar agenezisi ile ilgili çalışmalar iki farklı araştırmacı tarafından tarandı. PubMed, Google Scholar, Ovid Medline, Web of Science Core Collection veritabanları kullanılarak yapılan başlangıç taraması sonucunda 3.988 çalışma belirlendi. Bu çalışmalardan değerlendirilmek üzere, meta-analiz yönteminin uygulanabilmesi için gerekli kriterleri sağlayan toplam 12 çalışma seçildi.

Bulgular: Bireylerdeki mandibular ikinci premolar agenezisi prevalansının % 3.26 oranında olduğu görüldü; ancak prevalans oranları cinsiyete göre değerlendirildiğinde kadınlar ve erkekler arasında istatistiksel açıdan anlamlı bir farklılık saptanmadı [% 95 CI: 1.18 (0.96, 1.45); p>0.05]. Erkeklerin kadınlara kıyasla anlamlı derecede daha yüksek oranda unilateral mandibular ikinci premolar agenezisi prevalansına sahip olduğu görüldü (ortak OD 0.69; % 95 CI: 0.38-1.25; p<0.05). Bununla birlikte, mandibular ikinci premoların bilateral agenezisinin kadınlarda erkeklere göre anlamlı derecede daha yüksek oranda olduğu görüldü (ortak OD 1.57; % 95 CI: 0.91-2.72; p<0.05). Mandibular ikinci premolar agenezisi, sağ veya sol mandibular bölgede görülme sıklığına göre değerlendirildiğinde ise istatistiksel olarak anlamlı bir farklılık bulunmadı [% 95 CI: 1.04 (0.91-1.20); p>0.05].

Sonuç: Bu çalışma, mandibular ikinci premolar agenezini kapsayan önceki çalışmalardaki bulguların bir kısmını desteklemekle beraber aynı zamanda mandibular ikinci premolar prevalansının cinsiyete göre, tek ve/veya iki taraflı olmasına göre ve sağ/sol tarafta olmasına göre değerlendirildiği yeni bulgular sunmaktadır.

ANAHTAR KELİMELER

Mandibular Ikinci Premolar, Agenezis, Hipodonti, Prevalans, Konjenital Eksik Diş

The term of dental agenesis also known as hypodontia defines the developmental absence of one or more teeth in the primary or permanent dentition, and it is one of the most common dental developmental anomalies.[1,2] Tooth agenesis causes serious complications, such as malposition, malocclusion, dysfunction of masticatory elements of the oral cavity, degradation in alveolar bone height, speech alteration, and aesthetic results.[3] Affected children mostly have a tooth development delay, and atypical tooth morphology and positioning, with a decreased mesio-distal crown diameter.[4] Since pediatric dentists are generally the first to detect this anomaly, they are obliged to have a knowledge regarding the etiological factors and management of this condition.

The congenital absence of teeth derives from defects during the initiation and proliferation stages, which are

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the initial stages of tooth formation.[1] Etiology of this anomaly was associated with the local, systemic, evolutive and genetic factors.[5] However, previous studies have shown genetic factors may play an active role in dental agenesis.[6–9] Gene mapping studies revealed an association between the "a familial autosomal dominant point mutation in the MSX-1 (Muscle Segment Homeobox-1) gene" and the dental agenesis in the premolar-molar region.7 Furthermore, it has been stated that the PAX-9 (Paired Box-9) gene is expressed during the tooth development process and the mutation of this gene causes the absence of permanent molars and second premolars.[8] Cobourne[9] reported that polymorphic variants in the AXIN-2 (Axis Inhibition Protein-2) gene, which is the regulator of the Wnt-Signal Pathway, may be associated with hypodontia and oligodontia, is responsible for non-syndromic tooth deficiencies.

Many previous studies have consisted of a vast amount of information on the different types of hypodontia and, prevalence and distribution in populations with the different ethnic groups. In the study by Rakhshan[10], which was conducted to report the most frequently missing permanent teeth excluding the third molars, and included 81 studies, it was concluded that the mandibular second premolars (MnP_2) had the greatest share of missing among all missing teeth reported in the epidemiological studies. However, there are some exceptions that the most frequently missing teeth in different retrospective studies were the maxillar and mandibular lateral incisors.[11,12]

The data presented in the vast majority of literature focusing on the prevalence of dental agenesis have been concluded based on the total number of missing teeth.[4,13–16] The number of studies in which the prevalence rates of the relevant missing tooth were evaluated by the number of individuals with hypodontia in the sample population, is very limited. The purpose of this study is to increase the insight into the prevalence of individuals with MnP_2 agenesis by the method of meta-analysis, and provide more reliable predictions for the prevalence of MnP_2 agenesis by presenting information about determinants such as gender and jaw site.

MATERIALS AND METHODS

1.Selection of studies and search criteria

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) criteria were used in the preparation stage of the meta-analysis.[17]

PubMed, Google Scholar, Ovid Medline, Web of Science Core Collection databases were scanned on November 20, 2020 using MnP_2 agenesis prevalence with the keywords (mandibular premolar OR second premolar OR premolar absence prevalence AND =(prevalence OR premolar deficiency OR second =(prevalence OR premolar deficiency OR second premolar agenesis), mandibular second premolar absence incidence=(mandibular premolar OR second premolar OR premolar absence incidence AND =(incidence OR premolar deficiency OR second premolar deficiency) to identify proper studies.

The studies obtained from the scanned databases were selected by two researchers independently by checking first the titles and abstracts, then the full-text articles. No limits were placed in a year of publication. In case of inconsistency in the selection or uncertain situations, it was decided by a consensus of the two researchers to include the relevant article into the study or not. The article selection process was summarized in the PRISMA flow chart in Figure 1.

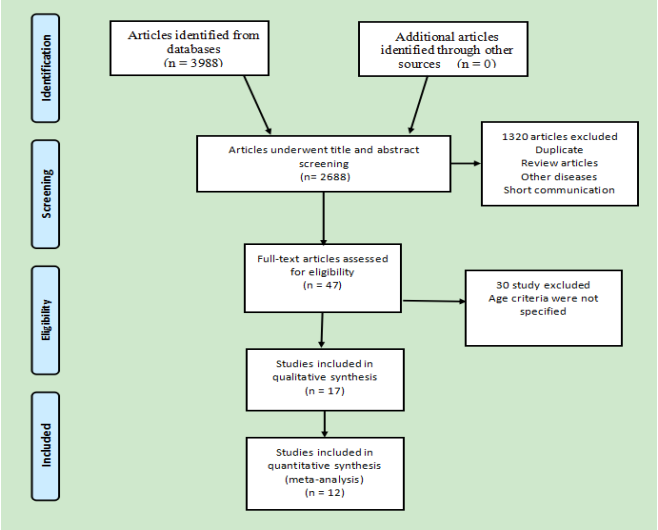

Figure 1

PRISMA flow chart

2.Eligibility criteria for inclusion and exclusion

The inclusion criteria were:

- presence of a proper data in an English abstract/summary/manuscript;
- diagnosis of tooth agenesis with the radiographic examination;
- age of subjects between 8y to 15y;
- reporting the frequency of MnP_2 agenesis as the number of individuals with at least one deficient MnP_2.

The exclusion criteria were:

- informing the frequency of MnP_2 agenesis as only the number of affected teeth;
- reporting of MnP_2 agenesis frequency without information regarding sample size, but only in a level of percentage;
- researches limited to specified patient groups with developmental disorders or craniofacial syndromes without the control group to compare;
- reporting of MnP_2 agenesis frequency combinates with frequencies of agenesis in other teeth;
- a study using the previous study's subjects;
- presence of another effect size estimate depending on the same subjects within the same study;
- studies that did not examine the prior extraction of any MnP_2 of the subjects.

3.Data extraction and obtaining numerical data

For all included studies, extracted data were documented to a specially designed form. The data extraction form consisted the information of the studies: first author, year of publication, the number of participants, age, gender distribution, design of the study, study populations' characteristics, the method of measurement (clinical and/or radiographical), and the number of individuals with MnP_2 agenesis overall or by gender or by the location of missing teeth in the jaw.

In order to determine which standard population is based on in calculating the values standardized in each article evaluated, or to obtain standardization according to the same population, studies conducted with individuals between the ages of 8-15 were evaluated, and the prevalence and numerical data of these studies were used. The numerical data required for analysis were gathered from text, tables or figures; mostly calculations were needed.

4.Consideration of bias

All studies to be analyzed were evaluated by the researchers, taking into account the population representation power, measurement standards and missing data. Small-scale ($n<100$) studies with weak sampling potential and that do not completely represent the sample and studies containing non-probabilistic samples were excluded from this meta-analysis. After the studies with high bias risk were eliminated, statistical analyzes were performed. During the evaluation of the results, more focus was placed on studies with low bias risk.

5.Statistical analysis

The consistency between the observers was evaluated with Cohen kappa statistics for the article selection and bias scores, which were made independently from each other.[18]

Analyses were performed by combining the remaining studies after the bias score evaluation and excluding the articles that did not meet the criteria. The meta-analysis of the data (pooled estimates) was calculated using the fixed effect model and the random effects model, but the results of the random effects model were used for interpretation.

The heterogeneity between studies was assessed by Cochran Q and I^2 statistics. A p value of <0.10 in the Cochran Q statistic with a conservative approach was interpreted as a significant heterogeneity. If the I^2 value was above 75 %, it was evaluated that the heterogeneity was high. A funnel plot was plotted to show the small study effect, publication bias, and other possible causes of heterogeneity. The sensitivity analysis was evaluated by the change in the result, one study at a time.

REVMAN 5.4.1 (Cochrane Training, https://www.cochrane.org/) was used for analysis. Except for Cochran Q statistics, other p values of <0.05 were considered significant.

RESULTS

1.Study selection

As a result of scanning the databases, 3988 studies were reached. Different database examination showed that 1320 studies were found to be the same. With a further examination of the remaining 2688 studies, 2621 of them were unrelated to the subject or not had calculative data and they were excluded. After the exclusion of 30 studies with the unspecified age criteria, the bias score was evaluated and five more studies were excluded because of their high risk of bias. The agreement between the observers was found to be excellent in the selection of the articles and the scoring of the selected articles in terms of bias [Cohen kappa values of 0.95 (95 % confidence interval [CI] 0.9-1) for article selection, 0.97 (95 % CI 0.9-1) for bias scoring].

2.Prevalence of MnP_2 agenesis by gender

With the examination of the studies, which were evaluating the prevalence of MnP_2 agenesis by gender, it was found a total of 11 studies (16417 females, 15629 males) that met the inclusion criteria (Figure 2).[13,19-28]

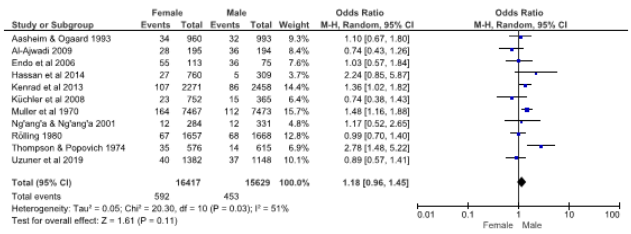

Figure 2

Forest plot of the MnP_2 agenesis prevalence by gender: The vertical line at 1 represents unity in the odds ratio. Black-filled diamond's width and position indicate the 95 % confidence interval (95 % CI) and mean of the average odds ratio. Error bars represent 95 % CIs and black-filled squares denote each study, scaled by its effect on the average proportion.

Analysis of the data showed there was no statistically significant difference in the prevalence of MnP_2 agenesis between females and males ($p > 0.05$).

3.The gender distribution of unilateral and bilateral MnP_2 agenesis

It was determined there were five studies (6257 females, 5833 males) evaluating the relationship between the prevalence of MnP_2 agenesis and gender, in the terms of unilaterally and bilaterally. Examination of the obtained data from included studies showed the unilateral agenesis was more common in males, and the difference between the genders was statistically significant ($p<0.05$). The results of the evaluated studies were presented in Figure 3.

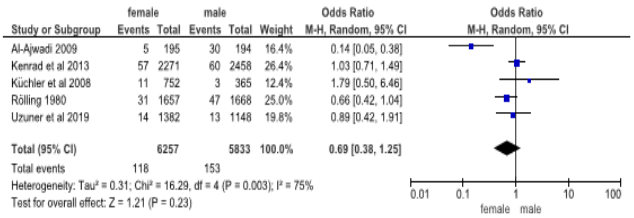

Figure 3

Forest plot of the the gender distribution of unilateral MnP_2 agenesis: The vertical line at 1 represents unity in the odds ratio. Black-filled diamond's width and position indicate the 95 % confidence interval (95 % CI) and mean of the average odds ratio. Error bars represent 95 % CIs and black-filled squares denote each study, scaled by its effect on the average proportion.

Another analysis of these five studies revealed bilateral agenesis was more common in females and there was a significant difference ($p<0.05$) in the prevalence of bilateral agenesis between females and males. The obtained results of the studies were presented in Figure 4.

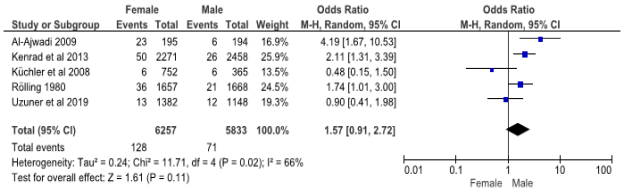

Figure 4

Forest plot of the gender distribution of bilateral MnP_2 agenesis: The vertical line at 1 represents unity in the odds ratio. Black-filled diamond's width and position indicate the 95 % confidence interval (95 % CI) and mean of the average odds ratio. Error bars represent 95 % CIs and black-filled squares denote each study, scaled by its effect on the average proportion.

4.MnP_2 agenesis by location in the jaw site

As a result of the evaluation of the included studies' data, it was determined that six of these studies examined MnP_2 agenesis according to the location in the mandible (Figure 5). There was no significant difference between the prevalence of right and left MnP_2 agenesis ($p>0.05$).

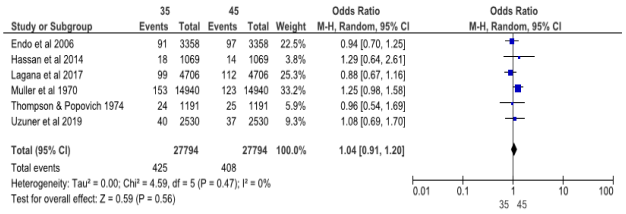

Figure 5

Forest plot of MnP_2 agenesis by location in the jaw site: The vertical line at 1 represents unity in the odds ratio. Black-filled diamond's width and position indicate the 95 % confidence interval (95 % CI) and mean of the average odds ratio. Error bars represent 95 % CIs and black-filled squares denote each study, scaled by its effect on the average proportion.

DISCUSSION

Since tooth agenesis is the most common developmental dental anomaly, it is essential to be managed properly on a clinical basis.[29] The careful multidisciplinary management, with input from a pediatric dentist, a radiologist, an orthodontist, an oral surgeon and, mostly, a geneticist are the requirement of the effective clinical treatment.[20] Hypodontia also can be accompanied by another dental anomalies and systemic syndromes and, therefore, patients with hypodontia need to be examined for other abnormalities.[29]

For many years, tooth agenesis has been the focus of numerous studies, from retrospective studies to clinical evaluations of large populations.[1,4,5,11-16,19,29,31,32] Mapping the occurrence of agenesis, dental development and other common dental anomalies was the main purpose of these studies. In studies proving that genes are the main etiologic factor of tooth deficiency, it was observed that infra-occlusion of deciduous molars and an ectopic

eruption of first molars were frequently related to agenesis of the second premolar. Based on the presence of MnP_2 agenesis, early detection of associated anomalies could permit the early intervention of the possible complications. Thus, it has been emphasized that in MnP_2 agenesis, the necessity of determining treatment options depending on various factors and planning the management of the space in a multidisciplinary manner, especially when considering the prevalence frequency.[33]

This study was an attempt to examine a comprehensive database of published articles for estimating the average of MnP_2 agenesis prevalence, afterwards to assess the level of heterogeneity among study results and to determine whether specific predictors could clarify for this. Therefore, it is the objective of the present meta-analysis to assess the literature which were met the inclusion criteria on the areas of prevalence MnP_2 agenesis and to detail its association with gender and jaw site. To our knowledge, the present study is the first meta-analysis regarding the prevalence of MnP_2 agenesis, though similar studies have been carried out on the evaluation of all permanent tooth agenesis.[2,10,34,35]

Subgroup analyses of this study were conducted to assess the influence of gender, region of agenesis (unilateral or bilateral) and effected jaw site on the prevalence of MnP_2 agenesis. The total rate of MnP_2 agenesis in individuals was found to 3.26 %. The difference in the prevalence of MnP_2 agenesis between males and females was not significant ([95 % CI: 1.18 (0.96, 1.45)]; Figure 2). The existence of gender differences in agenesis rate has been a continuous source of controversy, and it was reported that higher rates for females with tooth agenesis.[3,36,37] Although most of the previous studies were found gender differences in the prevalence of agenesis, it was concluded these differences were not statistically nor clinically significant.[19,38,39] Nevertheless, very few studies were conducted on the relationship between gender and missing tooth types.[31,40]

Although it was reported the frequency of MnP_2 agenesis was higher in females than males in some previous studies, a significant difference was not found between genders.[25,26] Similarly, the present study revealed there was no significant difference between genders. This result is perhaps expected when considering the I^2 index of heterogeneity (51 %), especially after the exclusion of studies which we cannot calculate the number of patients with MnP_2 agenesis from the data. However, it is essential to determine whether variation amongst study outcomes is the result of biological diversity or bias. In this study, none of the two artifactual moderators tested ("study publication year" and “ethnic origin of the population the study focused on”) was shown to have a significant effect on the frequency difference of MnP_2 agenesis between genders. Thus, the heterogeneity seen in MnP_2 agenesis rate can be based on the environmental or genetic variation among populations instead of the gender differences.

Age of the target population is another important factor as it directly influences the results. If the subjects are too young, hypocalcification of tooth buds could cause a false-positive diagnosis of agenesis during the radiographic examination.[4] If the subjects are too old, the medical history of these individuals may be incorrect and complex. Decay and dental trauma can also increase the uncertainty of diagnosis by causing the absence of teeth.[29] Considering the tooth development, the age of the subjects was set as 8 to 15 years old.

In this study, 2.24 % of all patients had unilateral MnP_2 agenesis. It was found that a significantly higher rate ($p<0.05$) of unilateral MnP_2 agenesis in males than females ([95 % CI: 0.69 (0.38, 1.25)]; Figure 3). In contrast to Küchler et al. study, the relative risk of males was found 0.7 times higher than females.[25] As considered by the I^2 index of heterogeneity (75 %), the gender distribution of unilateral MnP_2 agenesis contains much among-study variance. Also, the evaluation of the affected jaw site was showed, no significant difference between the prevalence of right and left MnP_2 agenesis. ([95 % CI:1.04 (0.91-1.20)]; $p>0.05$; Figure 5).

In previous studies which excluded the 3rd molar teeth, one of the most common teeth with bilateral agenesis were MnP_2. Uzuner et al. stated that MnP_2 agenesis was the second most common bilateral hypodontia after maxillary lateral incisors.[13] In the study of Küchler et al, the most common teeth with bilateral agenesis were MnP_2.[25] In this study, it was observed that 1.6 % of MnP_2 agenesis cases were bilateral and the rate of bilateral MnP_2 agenesis was found significantly higher ($p<0.05$) in females than males (female relative risk 1.6 time higher, ([95 % CI:1.57 (0.91, 2.72)]; Figure 4). Comparison of the two outcomes of this study revealed that MnP_2 agenesis was seen more bilaterally than unilateral in females.

Though there is still no definitive answer to the mechanism of asymmetry in the head region, progress has been made in detailed mapping of the early development of right-left asymmetry. Bilateral agenesis coordination mechanism in the dental/jaw development is unknown (kenrad).[33] Although, studies have revealed that gender is an affecting factor in dental/jaw development, it has been suggested that dental formation is under influence of peripheral nerves originating from the trigeminal ganglion.[27,41] Kjær and Nolting[42] suggested dysplastic and compensatory craniofacial development may also be

coordinate from peripheral nerves, based on their study on immunohistochemical PGP 9.5 (protein gene product) positivity in osteoblasts. It is clear that symmetrical coordination in the dentition must be seen in relation with the early stage of body axis development, including the right-left sided development.[43]

Rune and Sarnäs[44] demonstrated a trend towards delayed formation in teeth contralateral to the missing tooth and, Uslenghi et al.[32] confirmed these outcomes by reporting an average delay of 1.5 years in patients with one or more tooth agenesis. Kenrad et al. showed that in patients with bilateral agenesis of the MnP_2, the delay in dental maturity was significant only in females and a delay in tooth formation in the molar region only with female patients.[27] This study shows marked, and previously described limitedly, gender differences in MnP_2 agenesis patterns. But there is no doubt that the symmetrical and asymmetrical differences in dental development between genders reflect the genetic effect on different tissue structures which play a role in dental development.[27] This aspect requires for further attention.

Despite the use of meticulous search methods approved by the PRISMA guidelines and include span various databases, there is a possibility that some grey literature was not included in the study sample.[45,46] This is a particular concern for the present meta-analysis, considering there were limited studies that could be examined, due to the inability of calculating the prevalence of individuals with MnP_2 agenesis.

"Random" samples of dental patients are not entirely free from selection bias. Some degree of selection bias is inevitable in such studies, due to ethical concerns about unnecessary radiography and the fact that patients seeking dental exams include in the sample size of studies.

The main reason for exclusion was that many studies did not present the available data on the number of individuals with MnP_2 agenesis. Most studies had calculated prevalence over the total number of missing teeth. The raw data of the study by Sisman et al.[47], presented in table form was inconsistent. The reason for excluding this study was that when numerical data were recalculated to correct the error, the requested information could not be obtained. Muller et al.[19] investigated the influence of ethnic origin on the prevalence of congenitally missing teeth, and the data of both sample groups of that study with different ethnicity were combined and included in this meta-analysis.

In future studies, data should be extracted from larger meta-samples and evaluated with more sophisticated statistical approaches. In addition, other dental anomalies associated with mandibular second premolar agenesis and the prevalence of these anomalies should be investigated.

The conclusions of this study can be summarized as follows:

- No statistically significant difference was found in the prevalence of MnP_2 agenesis by gender.
- Males were found to have a significantly higher prevalence of unilateral MnP_2 agenesis than females (combined OR 0.69; 95 % CI: 0.38-1.25). However, females had a significantly higher prevalence of bilateral MnP_2 agenesis than males (combined OR 1.57; 95 % CI:0.91-2.72).
- The rate of unilateral MnP_2 agenesis was slightly higher than bilateral MnP_2 agenesis.
- No difference was found in the prevalence of MnP_2 agenesis between the right and left mandibular region

The outcomes of this study are valuable as they have current information on the prevalence of MnP_2 agenesis to plan and improve healthcare delivery. This knowledge is expected to contribute not only to pedodontist and orthodontist but also to all clinicians, involved in the management for the treatment protocol of MnP_2 agenesis cases.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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