

Congenitally missing second permanent molars in non-syndromic patients (Review)

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Abstract. Hypodontia (tooth agenesis) is regarded as the most common congenital dental anomaly. The present review discusses the epidemiological characteristics of congenitally missing second permanent molars (CMSPMs) within a systematic review of the literature. The review was based on Pubmed library associated with the search of various scientific databases or academic resources, improved by hand search of reference lists. The terms 'hypodontia' or 'anodontia' in combination with 'prevalence' or 'epidemiology' were searched in the data sources for studies published between January 2001 and December 2020. Abstracts of non-English papers were also analyzed. The inclusion criteria were as follows: i) Study provided precise data about CMSPMs, even if no second permanent molar was reportedly missing; ii) the number of CMSPMs distributed by jaw was provided and iii) studies on subjects >3 years were used. The exclusion criteria were as follows: i) Studies on patients with history of trauma of the maxilla or the mandible, any type of syndrome affecting bone metabolism, metabolic disorders, previous extraction or tooth loss due to dental caries, cleft lip and palate; ii) studies performed on cohorts of patients with hypodontia and iii) studies reporting data including third molars, except for those that presented sufficient data to perform correct calculations. A total of 79 studies were selected, accumulating a population of 281,968 people, with an average sample size of 3,524.60±11,255.25. The prevalence of CMSPMs (IpHSPM) was 2.79±3.16% among all missing teeth (1.03±1.59% for upper CMSPMs and

1.76±2.32% for lower CMSPMs; P=0.011). There were no significant differences (P=0.250) in IpHSPM between men (1.59±1.52%) and women (2.13±1.67%). However, significant differences were recorded between continents. Furthermore, lower CMSPMs were found more frequently in orthodontic samples (P=0.033). The prevalence of CMSPMs is low compared with the overall prevalence of CM teeth. Despite the rarity of these anomalies, early detection is important to enable practitioners to plan and start treatment at the best time for optimal results.

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1. Introduction

Oral health plays a major role in public health. Congenitally missing (CM) teeth, one of the most frequent dental anomalies (1-3), negatively affects both aesthetics and function, and may require a combination of expensive orthodontic, prosthodontic and surgical treatments (4-6). Hypodontia of permanent teeth is associated with several complications, such as malocclusion with mastication problems, periodontal trauma, reduced growth of the alveolar bone, difficult pronunciation and unfavorable aesthetics (7-9). Hypodontia is determined by disturbances of the early stages of tooth development (10). Local pathology or trauma, endocrine disorders or developmental anomalies are also considered etiological factors (11). A polygenic mode of inheritance is the most supported etiological theory, involving epistatic genes and environmental factors influencing phenotypic expression (10,12). Dental agenesis may be caused by mutations in several genes, including MSX, PAX9, TGFA and AXIN2 (13-17). Recently, the WNT10A gene was reported as a major candidate gene for non-syndromic hypodontia (18). Genes involved in tooth agenesis are associated with

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colorectal cancer (19,20) and ovarian cancer (21); however, the exact mechanisms remain unclear (22). Understanding the molecular mechanism may help identify an efficient protocol for the early detection of cancer in patients with hypodontia.

In 2004, Mattheeuws *et al* (23) suggested that hypodontia was diagnosed more often during the 20th century. Larmour *et al* (24) reported a maximum hypodontia prevalence of 11.3% with racial differences regarding the most affected tooth. Notably, almost all studies reported higher incidence of hypodontia in women (23-25). Khalaf *et al* (25) reported that the worldwide overall prevalence of hypodontia in permanent teeth was 6.4%, with statistically significant differences between continents. Prevalence of hypodontia in Africa was the highest (13.4%), followed by Europe (7%), Asia (6.3%) and Australia (6.3%), while North America (5%) and Latin America and Caribbean (4.4%) exhibited the lowest values (25).

Hypodontia in permanent dentition can be an isolated anomaly (26) or associated with various genetic syndromes affecting the head and neck region (27). In non-syndromic patients, the absence of second permanent molars (SPM) is rare, similar to that of canines and first molars, and mostly occurs in mandibular arch (25). According to the American Association of Pediatric Dentistry, the calcification of SPM begins at 30-36 months, with the completion of enamel mineralization at 7-8 years (28). Thus, radiological studies regarding the congenital absence of SPM should be performed after 3 years (28).

Review data regarding the CMSPMs among all missing teeth is scarce. The present review discusses the epidemiological characteristics of CMSPMs within a systematic review of the literature.

2. Data selection

For the present review, the search was based on Pubmed library associated with the search of various scientific databases (SpringerLink, <https://link.springer.com/>; Nature, <https://www.nature.com/>; Wiley Online, <https://onlinelibrary.wiley.com/>; and ScienceDirect, <https://www.sciencedirect.com/>) or academic resources (ResearchGate, Academia and SemanticScholar). Hand search of existing reference lists and Google search consistently improved the depth of the present review. The terms 'hypodontia' or 'anodontia' and 'prevalence' or 'epidemiology' were searched in the data sources for studies since 2001. Abstracts of non-English papers were also analyzed. The literature review was performed in February 2021. PRISMA guidelines (29) were followed when performing this review.

The inclusion criteria were as follows: i) Precise data about CMSPMs was mandatory for inclusion even if no SPM was missing; ii) the number of missing SPMs distributed by location was required; iii) sex distribution of missing SPM was registered if available; iv) only radiological studies on cohorts of patients >3 years were used and v) only studies published since 2001 were eligible. The exclusion criteria were as follows: i) All studies had to exclude patients with a history of trauma of the maxilla or the mandible, any type of syndrome affecting bone metabolism, metabolic disorders,

previous extraction or tooth loss due to dental caries, cleft lip and palate; ii) studies on cohorts of patients with hypodontia were excluded and iii) studies only based on clinical evaluation were excluded.

The data collected data included authors, year of publication, area/city of study, country and continent of study, characteristics of the study population, number of participants, mean age or age limits, sex distribution, prevalence of overall hypodontia, number of CMSPMs and prevalence of CMSPMs by jaw and by sex (when it was available).

A total of 79 studies were selected. All data presented within selected articles were checked for calculating errors, and double digits were used throughout the review. When data were available, the prevalence of CMSPM was calculated for men and women, respectively. CMSPMs values were calculated as percentages of all CM teeth. Given that CMSPMs are rare, corresponding authors were contacted if published data suggested the existence of non-mentioned missing molar teeth. Statistical analyses were performed using ANOVA, independent samples t-test, and correlation analyses were performed using SPSS 19.0 software (IBM Corp.). $P < 0.05$ was considered to indicate a statistically significant difference. The review was submitted for registration at PROSPERO (no. 281147).

3. Studies reporting data on CMSPMs

Studies reporting no CMSPMs ($n=30$) (2,30-58) were performed on cohorts that ranged from 250-6,015 patients (mean value, $1,723.55 \pm 1,421.56$), presenting a prevalence of hypodontia (IpH) of 6.94% (Table I).

Studies with CMSPMs ($n=49$) (3,33,48,59-104) were performed on cohorts that ranged from 139-100,577 patients, with a mean sample size of $4,627.70 \pm 14,133.27$. The mean value of prevalence of IpH was $8.52 \pm 10.13\%$ for 228,916 evaluated patients. Among all CM teeth, the prevalence of CMSPMs (IpHSPM) was $4.47 \pm 2.91\%$. A total of 25/50 studies provided data regarding sex distribution of CMSPMs, while IpH was calculated for 47 studies (two studies reported a hypodontia prevalence including third molars) (Table II).

4. Epidemiological characteristics of CMSPMs

Studies reporting no CMSPMs. For this category of studies, the highest mean value of IpH was found in Asia (7.74%), followed by Europe (5.88%), South America (4.79%) and Africa (4.68%). Most of the studies were based on Asian populations ($n=19$), six were performed in Europe, three in Africa and one in South America. Studies on orthodontic patients were most frequent ($n=12$; 40%), followed by studies on pediatric dentistry patients ($n=4$), sampled studies ($n=4$), general practice patients ($n=3$), orthodontic and pediatric dentistry patients ($n=3$), radiological patients ($n=2$) and non-orthodontic patients/medical students ($n=1$). Regarding the type of study group, radiological patients had the highest prevalence of IpH (16.45%), followed by sampled studies (7.51%), orthodontic patients (6.62%), pediatric patients (6.58%), orthodontic and pediatric dentistry patients (6.31%), non-orthodontic patients (5.50%), general practice patients

Table I. Studies reporting no CMSPMs.

First author/s, year	Location	Study population	No. patients	Age range/mean age, years	IpH	(Refs.)
Ng'ang'a and Ng'ang'a, 2001	Nairobi/Kenya	OP	615	8.00-15.00	6.30	(30)
Albashaireh and Khader, 2006	Irbid/Jordan	NOP	1,005	14.00-46.00	5.50	(31)
Altug-Atac and Erdem, 2007	Ankara/Turkey	OP	3,043	8.50-14.75	2.62	(2)
Küchler <i>et al</i> , 2008	Rio de Janeiro/Brazil	PP	1,167	6.00-12.00/8.90	4.79	(32)
Harris and Clark, 2008 ^a	Memphis/United States	OP	600	12.00-18.00	36.29	(33)
Aslam <i>et al</i> , 2010	Rawalpindi/Pakistan	OP	1,185	12.00-37.00/ 18.11	4.30	(34)
Ajami <i>et al</i> , 2010	Mashhad/Iran	SQ	600	9.00-14.00/10.63	9.00	(35)
Bud <i>et al</i> , 2011	Târgu-Mures/Romania	OP	804	11.00-21.00	6.84	(36)
Amini <i>et al</i> , 2012	Teheran/Iran	OP	3,374	10.00-20.00/ 13.90	5.21	(4)
Sheikhi <i>et al</i> , 2012	Multiple regions/Iran	SQ	2,422	7.00-35.00/9.30	10.90	(37)
Cantekin <i>et al</i> , 2012	Erzurum/Turkey	OP/PP	1,291	8.00-14.00	6.19	(38)
Al-Jabaa and Aldrees, 2013	Riyadh/Saudi Arabia	OP	602	Permanent dentition	19.10	(39)
Mani <i>et al</i> , 2014	Kuala Lumpur/Malaysia	RP	834	12.00-16.00	27.21	(40)
Affasn and Serrou, 2014	Khartoum/Sudan	MS	2,401	Permanent dentition	2.66	(41)
Hassan <i>et al</i> , 2014	Khartoum/Sudan	OP	1,069	>8.00	5.10	(42)
Kramerova <i>et al</i> , 2014	Olomouc/Czech Rep	PP	434	8.00-19.00	9.45	(43)
Shokri <i>et al</i> , 2014	Hamadan/Iran	RP	1,649	7.00-35.00/21.79	5.70	(44)
Majeed <i>et al</i> , 2014	Karachi/Pakistan	OP	250	12.00-37.00/ 18.11	2.85	(45)
Al Jawad <i>et al</i> , 2015	Doha/Qatar	OP/PP	1,269	8.00-20.00/11.60	6.22	(46)
Zhang <i>et al</i> , 2015	Hebei/China	GP	6,015	10.00-26.00	5.89	(47)
Hashim and Al-Said, 2016	Doha/Qatar	OP	1,000	10.00-26.00/ 16.40	7.80	(48)
Gokkaya and Kargul, 2016	Istanbul/Turkey	PP	1,658	7.00-12.00	6.15	(49)
Sajjad <i>et al</i> , 2016	Al-Jouf/Saudi Arabia	OP	1,267	9.00-30.00/16.77	6.10	(50)
Al-Abdallah <i>et al</i> , 2015	Amman/Jordan	OP/PP	3,315	8.60-25.40/17.40	6.54	(51)
Ameen <i>et al</i> , 2017	Erbil/Iraq	OP	600	10.00-34.00	6.66	(52)
Sola <i>et al</i> , 2018	Madrid/Spain	RS	2,500	8.00-11.00	3.48	(53)
Reshitaj <i>et al</i> , 2019	Kosovo (8 regions)	RS	3,306	15.00-21.00	6.66	(54)
Georgescu <i>et al</i> , 2019	Bucharest/Romania	GP	755	<18.00/10.20	2.91	(55)
Musaed <i>et al</i> , 2019	Multiple regions/Yemen	GP	5,100	9.00-25.00/15.00	3.23	(56)
Farcaşiu <i>et al</i> , 2020	Bucharest/Romania	PP	453	8.75	5.96	(57)

^aThird molars included. RP, radiological patients; OP, orthodontic patients; SQ, sampling quota; PP, paediatric dentistry patients; NOP, non-orthodontic patients; SC, school children; GP, general practice; MS, medical students; IpH, prevalence of hypodontia.

(4.01%) and medical students (2.66%). No significant correlations were observed between the prevalence of hypodontia

and type of study (P=0.097), sample size (P=0.245) or continent (P=0.061).

Table II. Prevalence of agenesis of SPMs in non-syndromic patients: Distribution by arch and sex in studies reporting at least one CMSPM.

First author/s, year	Location	Study population	No. patients	IpH	Age range/mean age, years	Upper IpHSPMs (%) M/F (n)	Lower IpHSPMs (%) M/F (n)	(Refs.)
Fekonja,	Maribor/Slovenia	OP	212	11.32	12.70	0.00	2.08 0/1	(58)
Endo <i>et al</i> , 2006	Niigata/Japan	OP	3,358	8.51	5.00- 15.00	3.01 8/13	4.31 13/17	(59)
Sisman <i>et al</i> , 2007	Kayseri& Kirrikale/Turkey	OP	2,413	7.54	9.00-36.00	1.32 1/4	1.32 3/2	(60)
Maatouk <i>et al</i> , 2008	Sayada/Tunisia	PP	262	13.30	12.00- 18.00/14.10	1.61	1.61	(61)
Goya <i>et al</i> , 2008	Matsudo/Japan	OP	2,072	9.74	3.00- 17.00/9.40	4.35 6/19	1.91 2/9	(3)
Abu Sakra and Alqaqaa, 2008	Amman/Jordan	OP+PP	1,524	4.40	8.00-20.00	1.01	1.01	(62)
Chung <i>et al</i> , 2008	Seoul/Korea	OP	1,622	11.20	>10.00	0.60	1.20	(8)
Harris and Clark 2008a	Memphis/USA	OP	1,100	36.29	12.00-18.00	1.81 2/1	2.42 4/0	(33)
Rølling and Poulsen, 2009	Aarhus/Denmark	SC	8,138	7.38	9.00-12.00	1.21 2/11	2.05 9/13	(63)
Aktan <i>et al</i> , 2010	6 regions/Turkey	GP	100,577	3.12	5.00-37.00	0.85 12/15	1.01 13/19	(9)
Pekker <i>et al</i> , 2009	Ankara/Turkey	RP	139	73.38	10.00-71.00	5.07 6/7	3.51 5/4	(64)
Gomes <i>et al</i> , 2010	Brasilia/Brazil	OP	1,049	6.29	10.00- 15.70/13.16	0.92 0/1	3.70 1/3	(65)
Topkara and Sari, 2011	Selcuk/Turkey	OP	2,761	6.77	9.00- 46.00/14.10	3.20 4/8	1.60 3/3	(66)
Vahid-Dasterji <i>et al</i> , 2010	Teheran/Iran	OP	1,751	9.13	9.00- 27.00/12.50	1.36	2.72	(67)
Tallón -Walton <i>et al</i> , 2010	Girona/Spain	GP	1,518	7.25	6.00-83.00	4.71	4.71	(68)
Carvalho <i>et al</i> , 2011	Porto/Portugal	OP	139	6.47	8.00-17.00	0.00	6.25 0/1	(69)
Kim, 2011	Seoul/Korea	OP	3,055	11.30	9.00-30.00	3.00	0.76	(70)
Kazanci <i>et al</i> , 2011	Erzurum/Turkey	OP	3,165	4.29	9.00- 25.00/14.17	0.00	1.30	(71)
Masamichi <i>et al</i> , 2011	Kanto/Japan	PP	2,125	11.80	7.00-20.00	4.26	2.22	(72)
Coelho <i>et al</i> , 2012	Porto/Portugal	PP	1,438	7.99	6.00- 15.00/8.82	1.87	1.12	(73)
Medina, 2012	Carcas/Venezuela	OP	607	4.11	5.00-11.00	0.00	8.00	(74)
de Freitas <i>et al</i> , 2012a	Sao Paulo/Brazil	OP	512	9.18	6.00-20.00	8.47	3.38	(75)
Uzuner <i>et al</i> , 2013	Ankara/Turkey	OP	2,530	4.98	7.00-16.00	0.39 1/0	1.17 2/1	(76)
González- Allo <i>et al</i> , 2012	Portugal	GP	2,888	6.05	7.00- 21.00/14.06	2.34 7/0	6.04 8/10	(77)

Table II. Continued.

First author/s, year	Location	Study population	No. patients	IpH	Age range/mean age, years	Upper IpHSPMs (%) M/F (n)	Lower IpHSPMs (%) M/F (n)	(Refs.)
Hyunsoon <i>et al</i> , 2013	Cheonbuk/Korea	PP	3,302	5.39	7.00-15.00	3.23 13/5	2.87 13/3	(78)
Kerekes-Máthé <i>et al</i> , 2013	Târgu-Mureş Romania	GP	947	7.39	9.00- 34.00/16.51	0.00	0.73	(79)
Al-Amiri <i>et al</i> , 2013	New York/USA	OP	496	9.47	16.30	1.96	1.96	(80)
Hedayati and Dashlibrun, 2013	Shiraz/Iran	OP	494	7.66	10.00-18.00	1.07 1/0	4.30 2/2	(81)
Bozga <i>et al</i> , 2014	Bucharest/Romania	OP	518	6.75	6.00-41.00	0.00	6.38	(82)
Herrera- Atoche <i>et al</i> , 2014	Yucatan/Mexico	OP	670	5.82	9.00-20.00	0.00	10.60	(83)
Pop Acev and Gjorgova, 2014	FYROM regions/FYROM	OP	8,160	7.52	8.00- 18.00/11.29	1.03 2/11	2.95 9/28	(84)
Zhang <i>et al</i> , 2015	Beijing/China	OP	2,781	7.48	10.00-26.00	2.38 9/2	1.51 5/2	(47)
Abu-Hussein <i>et al</i> , 2015	Almothalath/Israel	GP	2,200	2.59	12.00- 39.50/16.20	0.59	1.19	(85)
Dang <i>et al</i> , 2017	New South Wales/Australia	SC	1,050	5.14	6.00- 18.00/10.20	0.00	8.69	(86)
Hagiwara <i>et al</i> , 2016	Tokyo/Japan	SC	9,584	3.88	16.00-18.00	0.64 2/2	0.00	(87)
Badrov <i>et al</i> , 2017	Split reg./Croatia	OP	4,430	7.78	6.00- 15.00/10.60	1.33 3/6	5.05 13/21	(88)
Gracco <i>et al</i> , 2017	Padua region/Italy	OP	4,006	8.96	9.00-16.00	1.42 5/5	2.99 11/10	(89)
Laganà <i>et al</i> , 2017	Rome/Italy	NOP	4,706	7.11	8.00- 12.00/9.60	1.91 6/6	2.95 12/11	(90)
Souza- Silva <i>et al</i> , 2018	Sergipe/Brazil	OP	2,239	3.03	8.00-30.00	1.75	2.63	(91)
Ifesanya <i>et al</i> , 2018	Ibadan/Nigeria	OP	216	10.18	10.00- 46.00/14.00	5.55	1.81	(92)
Altan <i>et al</i> , 2019	Antakya/Turkey	PP	9,831	2.80	8.00-14.00	0.00	0.96 0/6	(93)
	Gaziosmanpasa/Turkey	PP	11,372	1.63		0.00	1.01 2/2	
Fauzi <i>et al</i> , 2019	Pahang Darul Makmur/Malaysia	GP	3,481	1.00	12.00- 60.00/23.53	1.33 0/1	0.00	(94)
Allhadad <i>et al</i> , 2019	Kerbala/Iraq	GP	1,150	30.60 ^a	9.00- 44.00/21.20	0.69 4/0	0.00	(95)
Kielan- Grabowska <i>et al</i> , 2019	Wroclaw/Poland	OP	674	11.57	6.00-15.00	2.94	7.64	(96)
Wiener and Waters, 2019	West Virginia/ USA	PP	500	12.00	6.00-12.00	1.48	3.70	(97)

Table II. Continued.

First author/s, year	Location	Study population	No. patients	IpH	Age range/mean age, years	Upper IpHSPMs (%) M/F (n)	Lower IpHSPMs (%) M/F (n)	(Refs.)
Wiener and Waters, 2019	West Virginia/ USA	PP	500	12.00	6.00-12.00	1.48	3.70	(97)
Chan <i>et al</i> , 2019	Singapore	OP	2,508	11.10	14.00-25.00	1.68	1.12	(98)
De Stefani <i>et al</i> , 2019	Padua/Italy	OP	600	9.00	9.00	1.00 -48.00	3.00	(99)
Gupta and Rauniyar, 2020	Kathmandu/Nepal	OP	601	7.48	10.00 -35.00/16.42	0.00	2.77	(100)
Çakir and Yildirim, 2020	Selcuk/Turkey	PP	9,950	1.51	5.00-14.00	0.30 0/1	0.60 0/2	(101)

^aThird molars included. RP, radiological patients; OP, orthodontic patients; PP, paediatric dentistry patients; NOP, non-orthodontic patients; SC, school children; GP, general practice; IpH, prevalence of hypodontia; SPMs, second permanent molars.

Table III. Hypodontia and CMSPMs in selected studies (%).

Variable	Worldwide	North America	Asia	Africa	Europe	Australia	South America
IpH	7.91±8.54	10.73±1.78	8.50±11.15	7.50±4.22	7.39±2.10	5.14	4.80±1.31
IpHSPMs	2.79±3.16	2.50±2.40	1.85±2.36	2.11±3.24	3.67±3.39	8.69	6.57±4.42
Upper CMSPMs	1.03±1.59	0.98±0.89	0.93±1.39	1.43±2.40	0.98±1.28	0.00	1.85±3.31
Lower CMSPMs	1.76±2.32	1.57±1.63	0.91±1.20	0.64±0.93	2.68±2.53	8.69	4.71±3.86
Males CMSPMs	1.59±1.52	0.97	1.64±1.55	-	1.65±1.76	-	0.92
Females CMSPMs	2.21±1.65	0.15	1.77±1.52	-	3.30±1.48	-	3.70

IpH, prevalence of hypodontia; CMSPMs, congenitally missing second permanent molars; -, not available.

Studies with CMSPMs. Hypodontia was most prevalent in Africa (11.74%), followed by North America (10.73%), Asia (9.11%), Europe (8.03%), Australia (5.14%) and South America (4.81%). Most of the studies were based on Asian populations (n=24), 14 were performed in Europe, five in South America, three in North America, two in Africa and one in Australia. Most studies were performed on orthodontic samples (n=29; 58%), followed by pediatric dentistry patients (n=9; 16%), general practice patients (n=7; 14%), school children (n=3; 6%), radiological patients (n=2; 4%) and non-orthodontic patients (n=1; 2%). IpH was highest in radiological studies (38.89%), followed by orthodontic samples (7.96%), non-orthodontic patients (7.11%), pediatric dentistry patients (7.05%), school children (5.46%) and general practice patients (4.56%). Hypodontia values were significantly associated with the type of study group (P<0.001). Statistical analysis demonstrated that radiological patients presented a significantly higher prevalence of hypodontia (P<0.001) compared with orthodontic patients, who had more missing teeth than general practice samples (P=0.004).

No statistically significant differences were observed between studies reporting or not missing SPMs regarding the prevalence of hypodontia (8.52 vs. 6.94%; P=0.369) or mean

number of subjects within the respective categories of studies (1,686.10 vs. 4,627.70; P=0.151), although studies reporting CMSPMs had greater values for IpH.

All selected studies cumulated a population of 281,968 people, with an average sample size of 3,524.60±11,255.25. The highest prevalence of hypodontia was found in North America, followed by Asia, Africa, Europe, Australia and South America. CMSPMs had an overall prevalence of 2.79±3.16% among all missing teeth (1.03±1.59% for upper SPMs and 1.76±2.32% for lower SPMs; P=0.011). Only 25 studies reported sex values. There were no significant differences (P=0.250) between men (1.59±1.52%) and women (2.13±1.67%). European studies presented significantly higher differences for mean values of lower vs. upper CMSPMs (P=0.009). Lower SPM was missing more frequently in Europe compared with Asia (P<0.001) and Africa (P=0.010), and in South America compared with Asia (P<0.001). Furthermore, European women had more CMSPMs compared with Northern American women (P=0.016) (Table III).

The prevalence of IpH was highest for radiological patients, with a significant ANOVA test (P=0.001) vs. all other types of cohorts, which were statistically similar. However,

Table IV. Hypodontia and CMSPMs by study type (%).

Variable	RP	OP	SQ	PP	OP + PP	NOP	SC
IpH	27.65±32.21	7.58±3.10	7.51±3.19	6.89±4.05	6.31±0.19	6.30±1.13	5.46±1.77
IpHSPM	2.65±4.06	3.51±3.27	0.00	2.23±2.48	0.00	2.43±3.43	4.19±4.10

RP, radiological patients; OP, orthodontic patients; SQ, sampling quota; PP, paediatric dentistry patients; NOP, non-orthodontic patients; SC, school children; IpH, prevalence of hypodontia; IpHSPM, prevalence of congenitally missing second permanent molar.

Table V. Comparison of hypodontia and CMSPMs between orthodontic samples and all other type of cohorts (%).

Type of cohort	IpH	Upper CMSPM	Lower CMSPM	Males CMSPM	Females CMPSM	IpHSPM
Orthodontic	7.58±3.10	1.20±1.78	2.31±2.54	0.54±0.97	0.94±1.65	3.51±3.27
Other	8.40±11.88	0.89±1.39	1.21±1.95	0.46±1.28	0.44±0.97	2.10±2.93

IpH, prevalence of hypodontia; CMSPMs, congenitally missing second permanent molars.

there were no significant differences regarding the prevalence of CMSPMs depending on the population type (ANOVA; $P=0.311$) (Table IV). Orthodontic cohorts had a lower IpH prevalence than the mean value for other cohorts. CMSPMs were more frequently observed in orthodontic samples, the difference being significant for lower CMSPMs ($P=0.033$) and overall ($P=0.045$) (Table V).

European orthodontic samples had significantly higher prevalence values for lower CMSPM ($P=0.029$) and for IpH ($P=0.035$) compared with other samples, in agreement with Rakhshan (102). European samples' prevalence values in orthodontic cohorts for lower CMSPMs were significantly higher than Asian ($P=0.009$) and African ($P=0.009$) values. Overall missing CMSPMs ($P=0.017$) were significantly higher in Europe compared with Asia. IpH in orthodontic cohorts was significantly higher in Europe compared with South America ($P=0.006$). Northern Americans (Caucasians) in cohorts other than the orthodontic ones had significantly lower CMSPMs compared with Asians ($P=0.006$) (Table VI).

Most European studies exhibited more missing lower SPMs with the exception of two studies from Iberian countries. Tallón-Walton *et al* (68) reported a similar involvement of upper and lower SPMs, while Coelho *et al* (73) reported more missing upper SPMs. Analysis demonstrated that European women had more CMSPMs than men, except for two studies, González-Allo *et al* (77) and Gracco *et al* (89). For European studies, only the mean values from Italy exhibited more missing SPMs in men. All studies reported a higher prevalence of lower CMSPMs, except for Spain (Table VII).

A total of two studies from Italy (68,90), performed in the same year (2017) in Rome (non-orthodontic patients) and the Padua region (orthodontic patients) reported similar values for CMSPMs. Sexes were affected similarly regarding upper CMSPM, while there were more lower CMSPMs in men. A total of two Romanian studies reporting CMSPMs were performed

in different regions of the country. Both studies reported lower CMSPMs, with different prevalence, 6.83% (79) and 0.73% (82).

The situation varied for Asian studies. Data from Iran, Israel and Nepal, and mean values for Turkey sustained a higher prevalence for lower CMSPMs, whilst reports from Iraq, Japan, Korea and Malaysia supported higher prevalence of upper CMSPMs. A certain pattern was set by Korea and Japan, with more upper CMSPMs compared with Asia and Turkey (Table VIII).

There were seven studies from various areas of Turkey, two of which reported more CMSPM in the maxilla compared with the mandible (64,66), although they were based in different regions (Ankara-central Turkey vs. Selcuk, Eastern Mediterranean Coast). The other five studies reported a higher proportion of CMSPMs in the lower arch. A large cohort study performed by Altan *et al* (93) in two distant regions of Turkey confirmed regional differences regarding sex and maxillary/mandibular distribution of CMSPMs.

Studies from Korea and China reported similar values (3.88 and 3.89%, respectively), while research from Japan exhibited the highest continental prevalence of CMSPMs (5.17%). Notably, studies from Korea and China reported more missing SPMs in men, while studies from Japan reported more women with missing SPMs. South American studies found a 2.5 times higher absence of lower SPMs compared with upper SPMs. Only one of the five studies had sex-related results, with women 4 times more affected by CMSPMs than men. There are few reviews regarding IpH in recent years. Mattheeuws *et al* (23) reviewed data published since 1936 on Caucasian patients, and confirmed that hypodontia has been diagnosed more often in recent studies. Only studies with >1,000 examined children were selected. The prevalence of hypodontia ranged between 0.1-10.1% and was slightly higher for girls.

A significant increase was noted in 1956, which may be due to improvements in imaging and increasing dental awareness or, according to Brook (103), due to a yet

Table VI. Comparison of IpH and IpHSPM between orthodontic samples and all other types of cohorts by continent (%).

Continent	Sample, n	CMSPMs	Upper CMSMP	Lower CMSPM	Males CMSPM	Females CMSPM	IpH
Europe	Orthodontic, 9	4.87±2.99	0.85±0.99	4.02±2.44	0.61±1.01	1.95±2.21	8.46±1.91
	Other, 11	2.69±3.50	1.09±1.51	1.60±2.12	0.55±1.51	0.50±1.15	6.51±1.89
Asia	Orthodontic, 21	2.30±2.33	1.06±1.36	1.23±1.35	0.70±1.14	0.81±1.49	7.70±3.63
	Other, 23	1.44±2.36	0.81±1.43	0.62±1.00	0.50±1.30	0.49±1.96	8.87±15.09
Africa	Orthodontic, 3	2.45±4.24	1.85±3.20	0.60±1.04	-	-	7.19±2.65
	Other, 1	3.22	1.61	1.61	-	-	13.30
North America	Orthodontic, 3	1.60±2.01	0.81±1.02	0.86±0.99	0.32±0.56	0.10±0.86	3.15±5.46
	Other, 1	12.00	1.48	3.70	-	-	12.00
South America	Orthodontic, 5	7.89±3.39	2.22±3.56	5.66±3.46	0.18±0.41	0.74±1.65	3.85±2.51
	Other, 1	0.00	-	-	-	-	4.79
Australia	Orthodontic, 0	-	-	-	-	-	-
	Other, 1	8.69	0.00	8.69	-	-	5.14

IpH, prevalence of hypodontia; CMSPMs, congenitally missing second permanent molars; -, not available.

Table VII. CMSPMs data in European studies (%).

Country	IpHSPMs	Upper CMSPMs	Lower CMSPMs	Males CMSPMs	Females CMSPMs
Croatia	6.24	1.33	4.91	2.38	4.01
Denmark	3.26	1.21	2.05	1.02	2.24
Italy	4.42	1.43	2.98	2.27	2.13
N. Macedonia	3.97	1.03	2.94	0.87	3.10
Poland	10.58	2.94	7.64	-	-
Portugal	5.87	1.40	4.47	2.51	4.80
Romania	3.55	0.00	3.55	-	-
Slovenia	2.08	0.00	2.08	0.00	2.08
Spain	9.42	4.71	4.71	-	-

IpHSPMs, prevalence of congenitally missing second permanent molars; CMSPMs, congenitally missing second permanent molars; -, not available.

unidentified environmental factor influencing the phenotype. Larmour *et al* (24) reported a prevalence of hypodontia between 2.6-11.3%. The authors reported race-dependending variations regarding the most common missing tooth with Caucasians more frequently missing the mandibular second premolars and maxillary lateral incisors, while Asians were more frequently missing the mandibular incisors, and a prevalence ratio of 3/2 in favor of women (24). However, neither of these reviews made any reference to CMSPMs.

In a meta-analysis regarding the prevalence of agenesis of permanent teeth in Caucasian populations, Polder *et al* (104) reported a higher prevalence of hypodontia for both sexes in Europe (men, 4.6% and women, 6.3%) and Australia (men, 5.5% and women, 7.6%) compared with Caucasians in North American (men, 3.2% and women, 4.6%). For a total of 112,334 people, the authors found 11,422 missing teeth, of which 208 were SPMs (67 upper CMSPMs, 0.58% and 141 lower CMSPMs, 1.23%) (104).

Bondemark and Tsiopa reported a prevalence of 0.8% CMSPMs in a sample of 1543 Swedish children aged 10-16 years. A total of 23 CMSPMs (15 lower and 8 upper SPMs) were missing in 12 children, with a lower/upper ratio of 1.87 (105). Khalaf *et al* (25) performed a systematic review and meta-analysis on studies published between 2002-2012. Similarly, the authors analyzed the abstracts of non-English papers. The prevalence of hypodontia varied significantly by continent, unlike data reported by Rakhshan and Rakhshan (106), and was the highest in Africa, followed by Europe. Women were found to have a higher prevalence than men. A total of 39/93 studies were taken from two previous systematic reviews (23,104). Khalaf *et al* (25) reported a prevalence of 1.8% for lower CMSPMs while upper CMSPMs represented 1.5% of the total number of missing teeth.

The current study has the highest mean value of sample size and the greatest value of IpH, confirming the trend of

Table VIII. Prevalence of CMSPMs in Asia (%).

Country	IpHSPMs	Upper CMSPMs	Lower CMSPMs	Males CMSPMs	Females CMSPMs
Japan	5.17	3.05	2.12	1.57	3.16
Korea	3.88	2.27	1.61	4.67	1.43
China	3.89	2.38	1.51	3.03	0.86
Malaysia	1.33	1.33	0.00	0.00	1.33
Singapore	2.80	1.68	1.12	-	-
Jordan	2.02	1.01	1.01	-	-
Iraq	1.49	1.49	0.00	1.49	0.00
Iran	4.73	1.22	3.51	3.22	2.15
Israel	1.78	0.59	1.19	-	-
Nepal	2.77	0.00	2.77	-	-
Turkey	2.62	1.22	1.38	1.14	1.63

Not all studies reported sex data. IpHSPMs, prevalence of congenitally missing second permanent molars; CMSPMs, congenitally missing second permanent molars; -, not available.

Table IX. Current research data comparison with previous reviews.

Author, year	Mean sample size	Number of studies taken into account	IpH	IpHSPM	Lower/Upper CMSPMs ratio	(Refs.)
Polder <i>et al</i> , 2004	3404.00	33	4.83	1.82	2.00	(104)
Khalaf <i>et al</i> , 2014	1291.00	93	6.40	3.30	1.20	(25)
Current study, 2021	3524.60	79	7.91	2.79	1.70	-

CMSPMs, congenitally missing second permanent molars; IpH, prevalence of hypodontia; IpHSPM, prevalence of congenitally missing SPMs.

increasing prevalence set by the two previous reviews. Both previous reviews exhibited more missing lower SPMs, which are in accordance with the results presented here (Table IX).

5. Conclusions

The prevalence of CMSPMs is low compared with the overall prevalence of CM teeth. Significant differences in the prevalence of CMSPMs have been reported between continents, as well as between various geographical regions, in most cases with higher values for the mandible. Despite its rarity, early detection is important to enable practitioners to plan and start treatment at the best time for optimal results. Further studies on the association with other pathologies may allow early screening for diseases with later onset, such as colorectal or ovarian cancer, which can help improve patient outcomes. Future studies on CM teeth are required to ease comparisons and reduce risks for errors.

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Competing interests

The authors declare that they have no competing interests.

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