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Systematic review

Meta-analysis and systematic review of the number of non-syndromic congenitally missing permanent teeth per affected individual and its influencing factors

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Summary

Background and purpose: Dental aplasia (or hypodontia) is a frequent and challenging anomaly and thus of interest to many dental fields. Although the number of missing teeth (NMT) in each person is a major clinical determinant of treatment need, there is no meta-analysis on this subject. Therefore, we aimed to investigate the relevant literature, including epidemiological studies and research on dental/orthodontic patients.

Methods: Among 50 reports, the effects of ethnicities, regions, sample sizes/types, subjects' minimum ages, journals' scientific credit, publication year, and gender composition of samples on the number of missing permanent teeth (except the third molars) per person were statistically analysed (α = 0.05, 0.025, 0.01).

Limitations: The inclusion of small studies and second-hand information might reduce the reliability. Nevertheless, these strategies increased the meta-sample size and favoured the generalisability. Moreover, data weighting was carried out to account for the effect of study sizes/precisions.

Results: The NMT per affected person was 1.675 [95% confidence interval (CI) = 1.621–1.728], 1.987 (95% CI = 1.949–2.024), and 1.893 (95% CI = 1.864–1.923), in randomly selected subjects, dental/orthodontic patients, and both groups combined, respectively. The effects of ethnicities ($P > 0.9$), continents ($P > 0.3$), and time (adjusting for the population type, $P = 0.7$) were not significant. Dental/orthodontic patients exhibited a significantly greater NMT compared to randomly selected subjects ($P < 0.012$). Larger samples ($P = 0.000$) and enrolling younger individuals ($P = 0.000$) might inflate the observed NMT per person.

Conclusions: Time, ethnic backgrounds, and continents seem unlikely influencing factors. Subjects younger than 13 years should be excluded. Larger samples should be investigated by more observers.

Introduction

Congenitally missing teeth (CMT), dental aplasia, or hypodontia are terms referred to the absence of tooth buds due to genetic and/or space problems, infection, trauma, and drugs (1–10). Because of being very frequent (1–6), having serious aesthetic and functional sequelae (2–4,7–9,11–19), and needing challenging multidisciplinary treatments (9,11), CMT is of remarkable anthropological and clinical concern (18,20–22), and its early diagnosis is crucial to prevent or reduce the complications (8,12,19).

The CMT prevalence has been reviewed extensively (18,21–26). It might differ between continents and ethnicities, but it is unlikely changing over time (18,21,23,24). It might be biased by the minimum age of patients studied, as well as sampling methods (random versus sampling dental patients), gender imbalances in researched populations, and sample sizes (25).

Despite the importance of CMT prevalence, there are more clinically relevant aspects that are not assessed at length. One of these features is the number of teeth missing in each individual affected by CMT. This factor determines the severity of dental aplasia, being defined as mild (three or fewer teeth missing), moderate (between four and six), and severe (more than six) (10). However, even mild cases are serious, as mild and moderate cases in any quadrant are considered as the highest need for orthodontic treatment (27). In addition, the absence of anterior teeth or aplasia of more than two teeth in the same quadrant may be indications for orthodontic treatment need (8,18,19). Therefore, it would be of interest to know the average number of missing teeth (NMT) per person, and the factors potentially influencing it or those possibly biasing the observed rates. Hence, we aimed to summarise the relevant literature and extensively analyse, for the first time, the numerous factors potentially affecting the NMT per affected person at any age or in any gender.

As the PRISMA statement's PECOS items, there were no interventions assessed. The exposures were ethnical groups, geographical regions, and time. There was no comparator group in this review, as all the reviewed studies were only observational. The outcome variable was the NMT per each person affected by CMT. Included study designs were any available studies (either epidemiological research or studies on dental patients); the available literature was limited to observational studies only.

Materials and methods

During September 2012 till July 2013, two examiners independently searched for the relevant keywords and their variations: 'CMT', 'hypodontia', 'anodontia', 'oligodontia', 'dental aplasia', 'dental agenesis', and 'prevalence' using three Internet search engines (Pubmed, ISI Web of Science [WoS], and Google Scholar). The reference lists and summarisations of the full articles were as well searched for relevant studies, with no time span limits (18,20,21,25). The inclusion criteria were:

1. The presence of English abstracts or key article parts (tables, etc.) that allowed data collection, or the possibility of careful translation of useful information using online translators.
2. The number of non-syndromic missing permanent teeth (excluding the third molars) per individual was reported or calculable.
3. Some local or old studies were not accessible directly, but were adequately summarised in newer articles. In that case, the second-hand information would still be collected if the inclusion criteria were fulfilled.
4. Diagnosis of 'dental agenesis' needed to be based on radiographic examination.
5. There was no limitation on the study designs (e.g., epidemiological studies or research on dental patients). All the available designs were observational. Article authors would be contacted via email, asking for full texts and/or points not addressed in their articles (18,20,21,25).

Method error

The data were abstracted by two observers. Each article was reviewed at least twice by each author. There was perfect consistency between the two datasets.

Statistical analyses and the variables sought

The level of significance was set at 0.05 for the statistical analyses, unless specified below.

Descriptive statistics

The NMT per person and its 95% confidence interval (CI) were calculated for different types of populations.

Publication bias and meta-sample homogeneity

Heterogeneity and publication bias were assessed for epidemiological and non-epidemiological samples as well as the total meta-sample, using a Q-test and an Egger regression.

The role of the affecting factors

Effects of ethnicities and continents on the NMT per person

The D'Agostino-Pearson omnibus test passed the normality test. The numbers of missing teeth per patient in different ethnicities and continents were compared using an analysis of variance (ANOVA) (for the means) and a Kruskal–Wallis test (for the medians).

Studies' raw data were recovered, assuming that every included patient did not have any extractions and thus had to have an expected number of teeth = 28. They were also compared using a chi-square test at a 0.01 level of significance.

Associations with the publication year

The correlations between the year of publication and the NMT per person were evaluated using a Spearman correlation coefficient, a weighted least squares regression, and a multiple weighted least squares regression adjusting for the role of population types.

Potentially biasing effect of sample types

The sample types were categorised as epidemiological samples (e.g. schoolchildren, army recruits, etc.), orthodontic patients, and non-orthodontic dental patients including paediatric dental patients. Samples composed of both orthodontic and non-orthodontic dental patients were excluded from the analyses pertaining to this particular factor. The weighted numbers of missing teeth per patient in different sample types (epidemiological and dental + orthodontic patients) were compared using a Welch *t*-test at a 0.025 level of significance modified using the Bonferroni method. They were all compared together using an ANOVA and a Tukey test.

Again, the raw data were compared using a chi-square test at a 0.01 level of significance.

Potentially biasing effect of sample sizes, enrolling disproportionate numbers of males and females, minimum ages of patients included, and scientific credit of journals

A Spearman correlation coefficient and a weighted least squares regression were used to assess the potential correlation between the sample size and the NMT per person.

The same analyses were used for evaluating the effect of sample imbalances in terms of gender, as well as the effect of the minimum age, and the scientific credit of the publishing journal. Journal credits were assumed 0 (the article was not found on Pubmed or WoS), 1 (found on one of them), or 2 (found on both).

The cutoff minimum age after which, the biasing effect might disappear

Studies with minimum ages of included patients below and above a certain cutoff age were compared in terms of the NMT, using a Welch *t*-test. This analysis was repeated for different cutoff ages (5–14 years old).

Results

Fifty reports from 45 studies having information or data pertaining to the NMT per person were obtained (Figures 1 and 2) (3–10,12–17,19,27–56). A study on patients referred to a centre specialised in dental anomalies was excluded from the analyses because of the very high rate of missing teeth due to sampling the most serious cases (Ireland, 8.51 teeth missing per person) (10). Another study was summarised in Figure 1 but was excluded from the analyses, since its sample size was not available (Czechoslovakia, 2.29 teeth per patient), disallowing statistical weighting (57).

Recovering the aggregate raw data showed that the overall NMT per affected person was 1.893 (95% CI = 1.864–1.923). These were 1.675 (95% CI = 1.621–1.728) and 1.987 (95% CI = 1.949–2.024) in epidemiological samples and dental/orthodontic patients, respectively (Figure 2).

The meta-sample was heterogenous

The Q test showed a significant heterogeneity in the meta-sample (Q = 670.7, I-square = 93.4, P = 0.000), the epidemiological studies (Q = 54.8, I-square = 72.6, P = 0.000), and reports on dental patients (Q = 519.2.7, I-square = 94.6, P = 0.000).

Publication bias

The Egger regression did not detect a significant publication bias in epidemiological samples (intercept = −1.74, P = 0.158). Nevertheless, there were publication biases in studies of dental and orthodontic patients (intercept = −4.63, P = 0.018), or in all the samples together (intercept = −4.25, P = 0.002, Figure 3).

There were no significant ethnical variations

The ANOVA and Kruskal–Wallis tests failed to detect significant differences respectively between the weighted mean and median numbers of teeth per person among three ethnicities: Negroids (a study on Africans and a report on African-Americans), Caucasians, and Mongoloids (both P values = 0.950).

The chi-square test confirmed the above result on the aggregated raw data showing 1.871, 1.900, and 1.889 missing teeth per each affected Negroid, Mongoloid, and Caucasian, respectively (P = 0.929, Table 1).

There were no significant geographical differences

The ANOVA (P = 0.329) and Kruskal–Wallis tests (P = 0.496) did not detect a significant difference among the compared continents (Figures 1 and 2).

There was no significant association between the year of publication and the NMT, adjusting for the population type

No significant correlations were found between the NMT per person and the year of publication (n = 48, Spearman ρ = 0.035, P = 0.817). However, the weighted least squares regression analysis showed a significant increase in recent years (β = 0.326, P = 0.024).

A multiple weighted least squares regression was used to control for the effect of sample types ‘dental patients’ and ‘orthodontic patients’ enumerated the recent studies in the literature. This analysis showed that when controlling for the effect of sample types [n = 45, β = −0.339 (greater NMT in dental/orthodontic patients), P = 0.110], the variable ‘publication year’ had no detectable effects (β = 0.074, P = 0.723).

The NMT differed among sample types

The ANOVA showed a significant difference (P = 0.0004) among the weighted means of the numbers of missing teeth per person in three types of samples: epidemiological (1.699 ± 0.180), dental patients (2.093 ± 0.494), and orthodontic patients (2.010 ± 0.322). The Tukey test showed a significant difference between randomly collected samples and dental patients (P = 0.0003) and between randomly collected samples and orthodontic patients

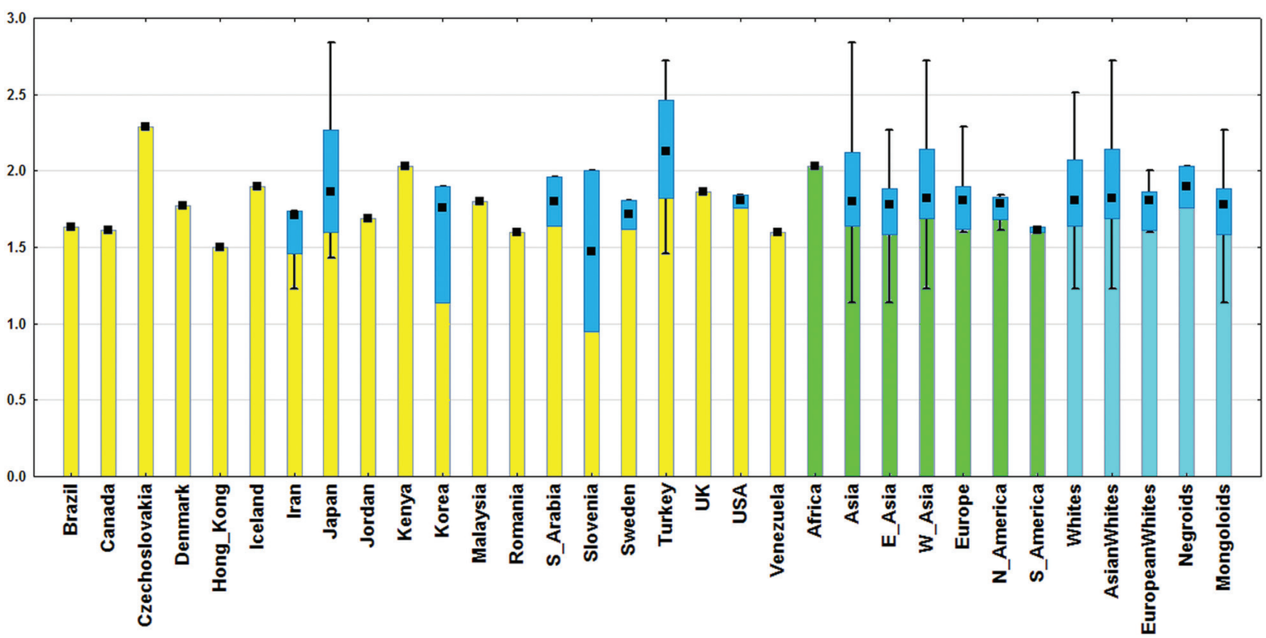

Figure 1. Box plots demonstrating the median, minimum, Q1, Q3, and maximum of the numbers of missing teeth per subject in each country, ethnicity, and continent.

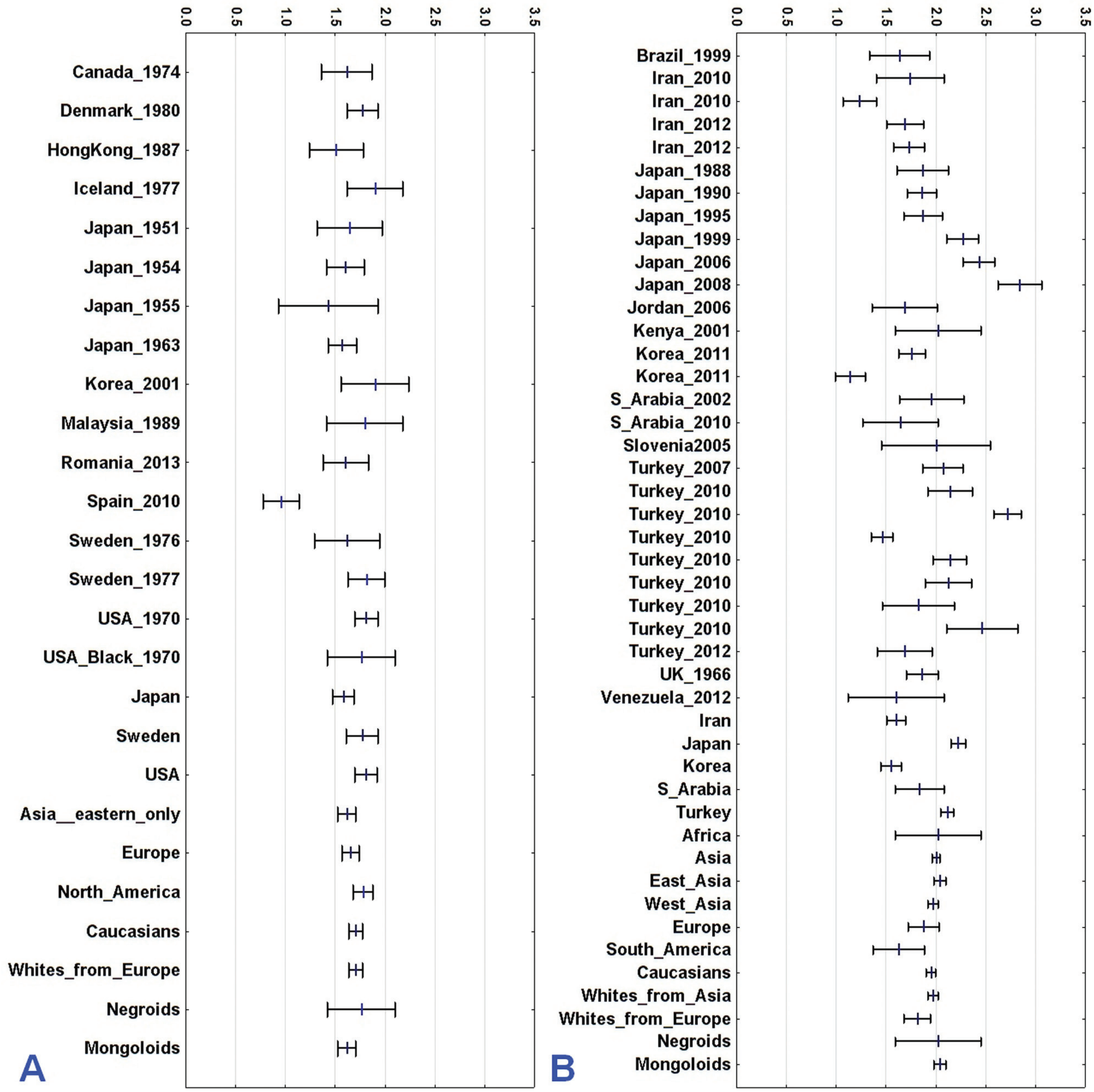

Figure 2. Forest plots showing the mean NMT per person (and 95% confidence interval) as the effect size measures, in randomly selected subjects (A) and dental or orthodontic patients (B) according to countries, times, ethnicities, and continents.

(P = 0.0118), but not between dental and orthodontic patients (P = 0.639).

The Welch t-test (α = 0.025) was used to compare the weighted mean NMT per person in dental/orthodontic patients (2.076 ± 0.442) and in epidemiological samples (1.699 ± 0.180). The difference was significant (P = 0.0000).

The difference between the weighted mean NMT in orthodontic and dental patients was not significant, with non-orthodontic dental patients having a slightly greater weighted NMT (2.093 ± 0.493) compared to orthodontic patients (2.010 ± 0.322) (P = 0.380).

The chi-square (α = 0.01) comparing the proportions of missing teeth between the two population types (1.675 in epidemiological samples compared to 1.987 in dental + orthodontic samples) detected a significant difference (P = 0.000, odds ratio [OR] = 1.2, 95% CI for OR = 1.154–1.249, Table 1). However, the difference between the numbers of absent teeth in orthodontic and non-orthodontic dental patients was marginally significant (P = 0.049, OR = 0.9589, 95% CI = 0.9198–0.9996, Table 1).

The effect of sample gender composition on the NMT was insignificant

The Spearman correlation coefficient showed a nonsignificant correlation between the mean NMT per person and the male-to-female ratio of the subjects enrolled in the evaluated studies (n = 27,

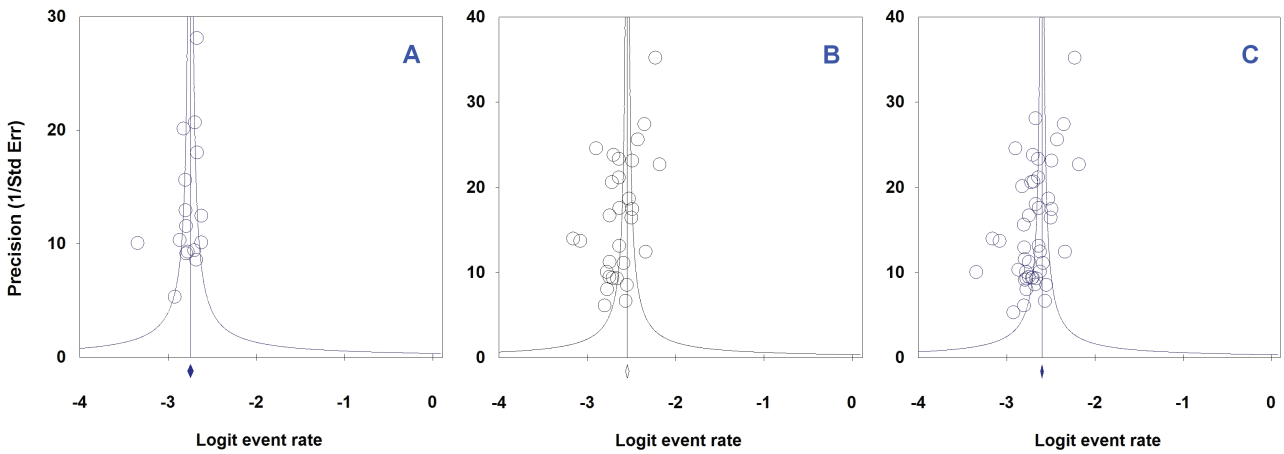

Figure 3. Funnel plots showing effect sizes against study precisions in the epidemiological samples (A), dental/orthodontic patients (B), and all the samples together (C).

Table 1. Contingency tables comparing the number of missing teeth with the number of teeth not missing, in different populations.

	Remaining teeth	Missing teeth	Total number of teeth	*P*
Sample types				
Epidemiological	55 625 (94.02%)	3539 (5.98%)	59 164 (100%)	**0.000**
Dental/orthodontic	132 330 (92.90%)	10 106 (7.10%)	142 436 (100%)	
Total	187 955 (93.23%)	13 645 (6.77%)	201 600 (100%)	
Sample types				
Dental	67 557 (92.73%)	5299 (7.27%)	72 856 (100%)	0.049
Orthodontic	57 890 (93.00%)	4354 (7.00%)	62 244 (100%)	
Total	125 447 (92.85%)	9653 (7.15%)	135 100 (100%)	
Ethnicities				
Negroids	2430 (93.32%)	174 (6.68%)	2604 (100%)	0.929
Mongoloids	77 099 (93.21%)	5613 (6.79%)	82 712 (100%)	
Caucasians	122 877 (93.25%)	8891 (6.75%)	131 768 (100%)	
Total	202 406 (93.24%)	14 678 (6.76%)	217 084 (100%)	

The number of missing teeth is subtracted from the total number of teeth to calculate the percentages of the missing and remaining teeth. Significant *P* values ($\alpha = 0.01$) in bold. Each person was assumed to have 28 permanent teeth. Hence, the total number of teeth equals the number of subjects suffering from CMT × 28 (as the expected number of permanent teeth excluding the third molars). Missing teeth: The collective number of teeth reported missing; Remaining teeth: The teeth not missing; or the total expected count of teeth (the number of affected patients × 28) subtracted by the number of the missing teeth.

$\rho = -0.216$ [more missing teeth per female], $P = 0.280$). The weighted least squares regression showed a nonsignificant correlation between the male-to-female ratio of the included subjects and the NMT per person ($\beta = -0.154$, $P = 0.444$).

There was no significant association between journal credits and the NMT

No significant correlations were found between the NMT per person and the publishing journals' scientific ranks using either the Spearman coefficient ($n = 48$, $\rho = 0.006$, $P = 0.968$) or the weighted least squares regression ($\beta = -0.040$, $P = 0.789$).

The minimum age of pooled subjects had a biasing effect

There was a significant correlation between the minimum age of the subjects included in different studies and the NMT per patient [$n = 35$, $\rho = -0.374$ (a greater NMT in younger children), $P = 0.027$]. The multiple weighted least squares regression indicated a significant role for the minimum age of patients [$n = 33$, $\beta = -0.376$ (favouring younger children), $P = 0.054$], correcting for the effect of population types ($\beta = -0.154$, $P = 0.418$).

The Welch *t*-test showed an overall decrease in the NMT by enrolling older subjects (Table 2). This was significant or borderline significant in the age range of 6–12 years [except for the age 7 ($P = 0.15$)], but not after 12 ($P = 0.2$) or at 5 ($P = 0.47$).

Larger samples might be associated with more missing teeth

The Spearman coefficient and the weighted least squares regression showed a marginally significant correlation [$n = 47$, Spearman $\rho = 0.268$ (more missing teeth per person reported in larger samples), $P = 0.069$] and a significant correlation [$\beta = 0.565$ (favouring larger samples), $P = 0.0001$], respectively, between the mean NMT per person and sample sizes.

To rule out the confounding effect of recent large studies on dental patients, the factor 'population type' was modelled as well. The analysis showed that sample size was still correlated with the NMT [$n = 44$, $\beta = 0.492$ (favouring larger samples), $P = 0.0003$], controlling for the sample type [$\beta = -0.298$ (more missing teeth per dental patient), $P = 0.0217$].

Table 2. Results of the Welch's *t*-test, comparing the mean numbers of missing teeth per person according to different minimum cutoff ages

	< Cutoff age		≥ Cutoff age			
Cutoff age (year)	*N*	Mean	*N*	Mean	Difference	*P*
6	12	2.07	23	1.70	−0.37	**0.024**
8	19	1.94	16	1.70	−0.23	0.069
9	22	1.93	13	1.65	−0.28	**0.021**
10	26	1.89	9	1.67	−0.22	0.083
11	29	1.88	6	1.59	−0.29	**0.040**
12	30	1.87	5	1.58	−0.29	0.078

N, number of studies. Only cutoff ages with *P* values ≤0.1 are shown. Significant *P* values ($\alpha = 0.05$) in bold.

In addition, the effect of sample size was significant [$n = 32$, $\beta = 0.482$ (larger samples had more missing teeth per person), $P = 0.002$] controlling for the effects of sample type ($\beta = -0.046$, $P = 0.887$) and patients' minimum age [which was significant as well: $\beta = -0.347$ (more missing teeth in younger children), $P = 0.049$].

Discussion

The results of this study indicated that CMT patients have an average of about 1.5 teeth missing per each person randomly selected from the population and an average of about two teeth missing among dental and orthodontic patients. The data were heterogeneous, meaning that there were other sources of error involved, aside from the variations reflecting inherent differences in the populations.

Does the average NMT per person differ between ethnicities or continents?

Overall, about 75–90% of populations usually have no more than two absent teeth (about 48% and 35% of patients might have one and two teeth missing, respectively) (4,5,7,8,12,17–19,25,33–36,38,39,42,44,45,47,52,58). Less than 10% of people might have three or more missing teeth (12,18,19,25), with slight variations [e.g. about 11.4% of Japanese had four and five teeth missing (3), and 16% of Germans had more than five teeth missing (11,25)]. Our results showed that there is virtually no difference among the numbers observed in different ethnicities. This was unlike the CMT prevalence, which might be affected by the factors ethnicity and region (18,21,24).

Has the NMT per person increased over time?

In primates, a decrease in the number of teeth has been identified through the evolutionary regression of mastication (52,59). A similar mechanism might account for a probable reduction in the number of dentition as an adaptation to the shrinking human jaws (1,21,60,61). Therefore, evolution has been suggested as an aetiology for CMT (2,8,13,19,21,60,62). Nevertheless, the tested periods are too short to anticipate any remarkable genetic alterations (21,23), although not all CMT cases are genetic, and factors such as diet changes might matter as well (22,23,42,62). Moreover, meta-analyses did not identify a significant, steady increase of CMT prevalence over time (21,23). The only significant association with time was observed by Polder *et al.* (18) who assessed the time span of 1936–2001 and identified a curvilinear increase in 1970s. In this study, after controlling for the sample types, there remained no correlation between the publication time and the number of missing dentition. We deduce that the increase observed might be attributed to the shift in recent methodologies from epidemiological designs to more ethical sampling approaches [i.e. using available radiographs of dental patients (8,25)]. It is also suggested to be attributable to improvements in imaging techniques and dental awareness (2,8,12,18,23).

Does the gender composition of the sample bias the results?

The role of gender on the NMT is unknown (4–8,13,17,22,28,33–36,38,58). CMT might be more prevalent in females, because of their smaller jaws, which might interfere with the dental bud formation (22,42). In addition, females with CMT might refer to dentists/orthodontists more than males (8,63), although, it is disputed (22). There were no sufficient data on this issue, as apart from a few, no studies had distinguished the NMT in girls from that in boys. However, we assumed that if a correlation existed between the proportion of pooled boys and girls with the total number of missing dentition in each study, it could imply that one gender might have more missing teeth per individual. Our analyses of 27 studies failed to detect a significant correlation, pointing to the need for larger meta-analyses.

Can the minimum age (as an inclusion criterion) affect the results?

Radiographic examination is necessary for the CMT diagnosis (3,8,25). Since radiographic evidence of tooth germs needs a certain level of calcification, the inclusion of excessively young patients might enter insufficiently calcified tooth buds into the sample. These can be mistakenly diagnosed as missing teeth on radiographs. Some authors have recommended the exclusion of children younger than 9 or 10 years old since dental calcification might be delayed, especially in the case of mandibular premolars and boys (3,7,8,17–19,25,50,52,58). This meta-analysis confirmed that pooling younger children might inflate the NMT. This problem almost resolves after the age 12, which accords with our previous finding on the CMT prevalence (25). Therefore, it is recommended to exclude children aged 12 years or younger.

Do dental patients exhibit more missing teeth?

There might be a higher chance for people with missing teeth to visit dentists (5,7,8,19,25,60). According to the findings of the present research, dental and orthodontic patients might have more missing teeth per patient compared to randomly selected subjects. Whereas, compared with epidemiological studies, the CMT frequency might be higher and lower, respectively, in patients visiting orthodontic and non-orthodontic dental offices (25). Conducting epidemiological X-ray studies is unethical in most situations (8,25). Therefore, these biases should be taken into account, in future non-epidemiological studies which are going to replace the conventional method.

Can the sample size bias the observed NMT?

The sample size might bias the CMT prevalence and the NMT in opposite directions. In a previous meta-analysis, it had been found that larger samples are associated with smaller CMT prevalence (25). The current study showed, however, that in larger samples, more cases of missing teeth per patient might be found. Perhaps, a tired and bored examiner assessing a large number of radiographs might start to skim over the images with less accuracy, and detect merely patients with relatively more severe cases of hypodontia. This will falsely reduce the prevalence of CMT (25), while inflating the NMT per person, just as observed. Perhaps a similar mechanism might also contribute to another finding that in larger samples, the examiner might focus on the absence of the premolars and relatively ignore the remainder (20).

Do greater numbers of missing teeth have a higher chance of being published?

It seems that neither the CMT prevalence (25), nor the NMT per person might determine the publication success.

Limitations and advantages

A limitation was the rather small number of available studies reporting certain variables such as the male-to-female ratio. Of the contacted authors, only one replied, sending the full text but refusing to detail on the points not available in their article. We tried to collect as many studies as possible, by relaxing the inclusion criteria and using second-hand information as well. A main study used to collect the information of older, unavailable studies clearly highlighted the inclusion of permanent-only missing teeth excluding the third molars, all diagnosed by radiographic means. However, the reference to the exclusion of syndromic CMT studies was indirect (26). As another limitation, articles with small samples were as well abstracted and analysed. Although the inclusion of indirect information and small studies might reduce the reliability of the results, they might also reduce the publication bias and favour the generalisability. Collecting all available studies also allowed the assessment of potential sources of bias, to be avoided in future research. Moreover, we analysed only studies with sample sizes available. This allowed us to weight them according to their sizes and precisions, which compounded with multivariable analyses, might improve the reliability.

Conclusions

The average NMT is about 1.5 teeth per randomly selected subject or 2.0 teeth per dental/orthodontic patient. This might not be affected by the area of residence, ethnicity, and time.

The NMT per person might be biased by the sample size and the minimum age of the pooled patients or participants. It is recommended to sample children above 12 years old, in order to avoid false positive errors introduced by the delayed dental bud development. It is as well worthwhile to investigate sufficiently large samples with the help of multiple observers, in order to reduce the error associated with large samples.

Given the size of the meta-sample, it was inconclusive if more teeth might be missing in a certain gender. Future meta-analyses with larger samples might adopt our method to assess this issue, indirectly. Moreover, future hypodontia researches are warranted to state the NMT in girls and boys, separately.

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Author contributions: VR conceived and designed the study, searched, reviewed, and abstracted the literature, specified and performed the statistical analyses, interpreted the findings, prepared the figures, and drafted/revised the article. HR searched, reviewed, and abstracted the literature, interpreted the findings, and drafted the article.

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