

Is Malocclusion Associated with Dental Caries among Children and Adolescents in the Permanent dentition? A Systematic Review

Abhinav Singh¹ and Bharathi Purohit²

¹Department of Dentistry, Regional Training Centre for Oral Health Promotion, All India Institute of Medical Sciences, Bhopal, India;

²Division of Public Health Dentistry, Centre for Dental Education and Research, WHO Collaborating Centre for Oral Health Promotion, All India Institute of Medical Sciences, New Delhi, India

Objective: To determine the association between malocclusion and the severity of dental caries among children and adolescents in the permanent dentition. **Method:** A search was conducted in Medline, Cochrane databases, Google scholar, Scopus and Web of Science through October 2020 for studies of malocclusion and dental caries among children and adolescents using the Dental Aesthetic Index (DAI) and the Decayed, Missing, Filled Teeth (DMFT) index. Quality was evaluated using the Newcastle-Ottawa tool for cross-sectional studies. Data were extracted using the Cochrane Collaboration guidelines. Meta-analysis used the Cochrane Program Review Manager Version 5. A random effects model was used to assess the association among different categories of malocclusion with dental caries. GRADE analysis assessed the certainty of evidence. **Results:** Five studies met the inclusion criteria. Handicapping malocclusion was significantly associated with higher mean DMFT scores (Mean difference: 1.03, 95% CI, 0.61, 1.44). Participants with severe malocclusion had higher mean DMFT when compared to subjects with normal occlusion (0.32, 95% CI, 0.13, 0.51). Definite malocclusion was also associated with higher mean DMFT scores (Mean difference: 0.19, 95% CI, 0.03, -0.35). **Conclusion:** Malocclusion is associated with dental caries in the permanent dentition. DMFT scores and the strength of the association increased with severity of malocclusion. Low to moderate certainty of evidence was observed for association between handicapping, severe, and definite malocclusion with dental caries.

Keywords: children, dental caries, meta-analysis, malocclusion

Background

Malocclusion, the departure from the normal relationship of teeth to other teeth in the same or opposing arch, affects a large segment of a population. Genetic, environmental, local factors, such as detrimental oral habits can cause malocclusion (Anthony *et al.*, 2018). Malocclusions have a profound impact on aesthetics and the behaviour of children and adolescents, consequently affecting their self-esteem and general well-being (Venete *et al.*, 2017) and quality of life (da Rosa *et al.*, 2016; Sardenberg *et al.*, 2017; Scapini *et al.*, 2017). Malocclusion is not a disease and is not life-threatening, but it may compromise the health of the oral tissues and can lead to psychological and social problems (Gaikwad *et al.*, 2014).

Despite significant achievements in oral health worldwide, dental caries still prevails among under-privileged groups in both developed and developing countries. The World Health Organization (WHO) Global Strategy for prevention and control of non-communicable diseases and the common risk factor approach is a strategy for managing prevention and control of oral diseases (Petersen *et al.*, 2005). The development of cost-effective prevention strategies also requires the recognition of risk factors.

Multiple studies have been conducted to determine whether malocclusion is associated with dental caries. However, inconsistent findings have been reported, and evidence remains inconclusive (Helm and Petersen, 1989;

Stahl and Grabowski, 2004; Disha *et al.*, 2017). A previous systematic review could not identify an association between malocclusion and dental caries (Hafez *et al.*, 2012). Studies reporting on the prevalence of crowding and dental caries without assessing their associations were excluded from this review. Although appropriate for systematic review, such studies should be excluded from pooling to estimate an association.

The Dental Aesthetic Index (DAI) is endorsed by WHO as an epidemiological and screening tool to record dentofacial anomalies, classify malocclusions, and determine orthodontic treatment needs (World Health Organization, 1997). Crowding and improper contacts between teeth make effective oral hygiene maintenance difficult and might increase the risk of dental caries. Pinto *et al.* (2018) conducted a meta-analysis and concluded that patients with lower Dental Aesthetic Index (DAI) score had lower Decayed, Missing, Filled Teeth (DMFT) values. However, the evidence was not conclusive as only three studies were included. Non-inclusion of appropriate studies threatens the internal validity of a review.

This systematic review aimed to determine the association between malocclusion and the severity of dental caries in the permanent dentition among children and adolescents. The review includes updated search criteria, a quality assessment for observational studies, and an assessment for the certainty of evidence.

Materials and Methods

Using the Population Exposure Comparison Outcome (PECO) format, the population was children and adolescents who were 11–20 years old, the exposure was malocclusion recorded by the Dental Aesthetic Index (DAI), the comparator was children and adolescents with no malocclusion, and the outcome was dental caries and treatment experience recorded as the number of decayed, missing and filled teeth (DMFT) in the permanent dentition. All observational studies including cross-sectional, prospective, retrospective, and case control studies assessing the association between malocclusion and dental caries based on the DAI and DMFT indices were to be included. The DAI has been endorsed by WHO as an epidemiological and screening tool to evaluate dentofacial anomalies, classify malocclusions, and determine orthodontic treatment needs (World Health Organization, 1997). DAI has demonstrated reliability and validity and compares favourably with other indices as it is more versatile, quicker, and simpler to use. Mathematically, DAI links clinical and aesthetic components of occlusion, including patient perception, to produce a single score, categorizing severity levels that approximate to treatment needs (Table 1). WHO (1997) recommend the DAI and DMFT indices for oral health surveys. To avoid methodological and clinical heterogeneity only studies using these indices were included. *In vitro* and animal studies, case reports, case series and studies among young people with special care needs were excluded. No language restrictions were stipulated.

Medline, Cochrane databases, Google Scholar, Scopus, and Web of Science for studies were searched through October 2020. The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Search keywords included malocclusion and dental caries, crowding, and dental caries and were combined with Boolean operators (See appendix). The search strategy was used for Medline and adapted for the other databases. References in the selected papers were reviewed manually and retrieved were relevant. Grey literature was searched through unpublished articles and manual searching of non-indexed journals at the institutional library at All India Institute of Medical Sciences (AIIMS), New Delhi (WHO Collaborating Centre for Oral Health Promotion) and AIIMS, Bhopal, and through abstracts, conference presentations, online clinical registries, including results of complete, but unpublished trials, but no articles were retrieved based on these criteria.

Table 1. Scoring criteria for the Dental Aesthetic Index

DAI Score	Severity and Treatment Need
≤ 25	No anomalies or minor malocclusion (no or slight treatment need)
26–30	Definite malocclusion (optional treatment)
31–35	Severe malocclusion (treatment highly desirable)
≥ 36	Very severe or handicapping malocclusion (treatment mandatory)

Studies were selected independently by the two investigators. The title and abstracts were screened to decide whether the studies would be retrieved in full. Retrieved articles were read before they were included. Differences between the two investigators were resolved by discussion. A third person with subject expertise assisted in cases of lack of consensus.

Data were extracted to a piloted worksheet. Data were extracted independently by the two investigators using the Cochrane Collaboration (2011) guidelines. Differences between the two investigators were resolved by discussion.

The Newcastle–Ottawa tool adapted for cross-sectional studies (Modesti *et al.*, 2016) was used to assess study quality on three domains (participant selection, comparability, and outcome). Scores of 0, 1 or 2 were awarded when criteria were not satisfied, satisfied or satisfied using a validated method or established model respectively. The sum of these scores categorised overall study quality as high (> 7), moderate (5–7), or low (< 5).

The certainty of evidence was determined using the GRADE assessment (Schünemann *et al.*, 2013), considering the type of included studies, risk of bias, consistency, directness of evidence, precision of results, risk of publication bias, magnitude of the effect, and influence of plausible residual confounding factors. GRADE assesses the quality of a body of evidence as high, moderate, low, or very low.

Meta-analysis was conducted using the Cochrane Program Review Manager Version 5. A random effects model determined the association between different categories of malocclusion with DMFT. Mean differences and 95% confidence intervals (CI) were calculated between groups. Chi- and I square (X^2 and I^2 , respectively) values were used to quantify heterogeneity. Statistical significance was set at $p < 0.05$.

Results

The search yielded 12 potentially relevant publications, of which five were included (Figure 1) (Baskaradoss *et al.*, 2013; Borzabadi-Farahani *et al.*, 2011; Feldens *et al.*, 2015; Gaikwad *et al.*, 2014; Singh *et al.*, 2012). Seven studies were excluded due to dissimilar primary outcomes, different assessment criteria or being investigated with children with special needs (Mtaya *et al.*, 2009; Borges *et al.*, 2010; Nalcaci *et al.*, 2012; Ukra *et al.*, 2013; Vellappally *et al.*, 2014; Feldens *et al.*, 2016; Kramer *et al.*, 2017).

Characteristics of the included studies are summarised in Table 2. Participants with definite malocclusion (≥ 36 DAI, $n = 717$), severe malocclusion (31–35 DAI, $n = 380$), 258 with handicapping malocclusion (26–30 DAI, $n = 258$), and participants with normal occlusion (≤ 25 DAI, $n = 3489$) were available for analysis. Four source studies reported associations between malocclusion and caries (Singh *et al.*, 2012; Baskaradoss *et al.*, 2013; Gaikwad *et al.*, 2013; Feldens *et al.*, 2015) and one reported non-significant but higher dental caries scores among young people with malocclusion (Borzabadi-Farahani *et al.*, 2011). More severe caries (higher DMFT) was related to more severe malocclusion, in a dose response effect by Singh *et al.* (2012), Gaikwad *et al.* (2013) and Feldens *et al.* (2015).

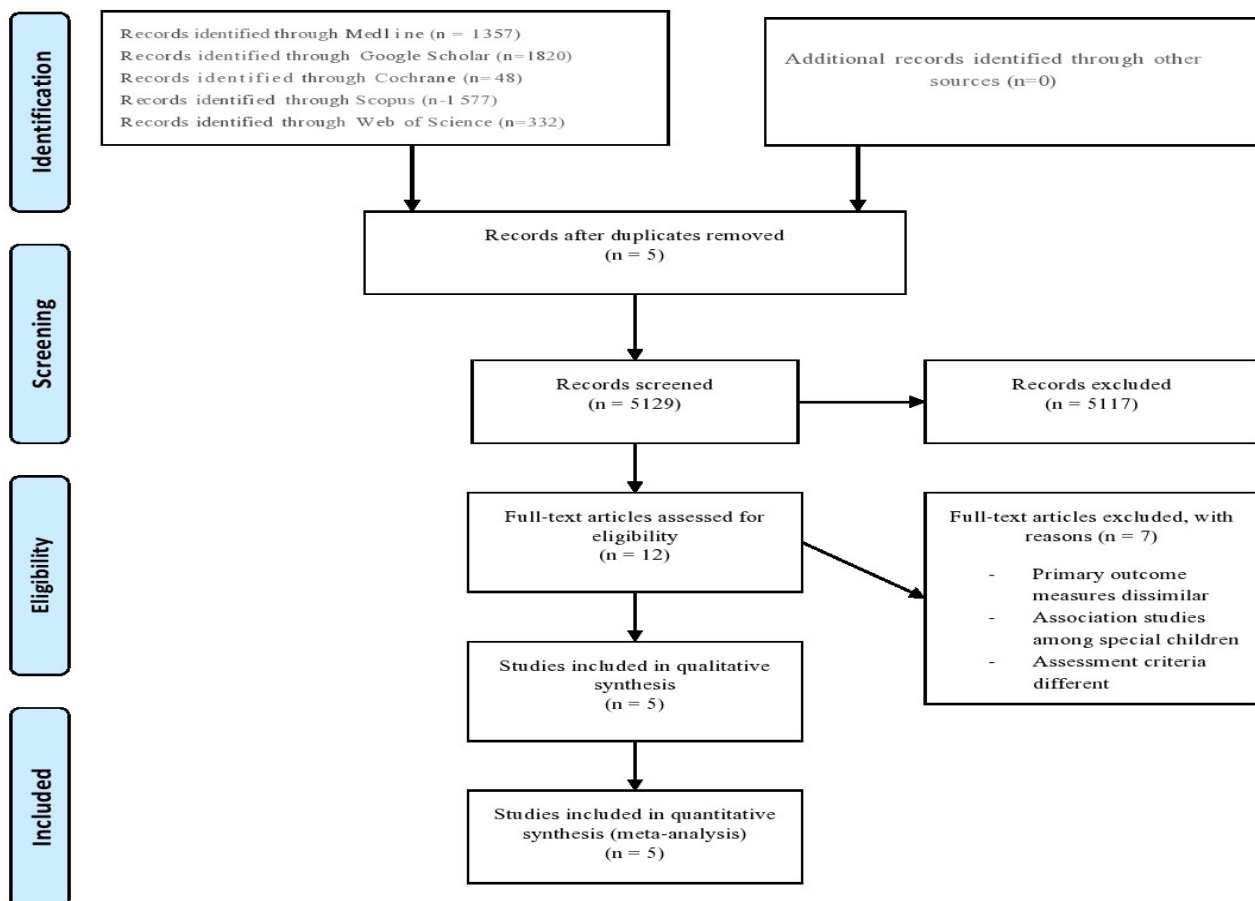


Figure 1. Flow diagram of study selection process

Table 2. Characteristics of included studies

Study; Location	Study Design; Setting	No. participants	Age range (y) Mean ± sd	% of participants in each DAI category	DMFT Mean ± sd
Borzabadi-Farahani et al, 2011 (Iran)	Cross sectional	728	11-20 15.11 ± 2.23	≤ 25 DAI: 54.5	4.77 ± 3.54
	Random selection			26-30 DAI: 23.6	5.23 ± 3.61
	Sample size estimated			31-35 DAI: 11	4.76 ± 3.49
	School-based			≥ 36 DAI: 10.9	5.44 ± 3.88
Singh et al, 2012 (Karnataka, India)	Cross sectional	927	12	≤ 25 DAI: 82	1.17 ± 1.53
	Random selection; Sample size estimated			26-30 DAI: 13	1.26 ± 1.41
	School-based			31-35 DAI: 3.2	1.77 ± 1.68
				≥ 36 DAI: 1.8	2.13 ± 1.83
Baskaradoss et al, 2013 (Tamil Nadu, India)	Cross sectional	1800	11-15 18.62 ± 6.2	≤ 25 DAI: 84.6	1.94 ± 1.25
	Random selection			26-30 DAI: 10.4	2.30 ± 1.71
	Sample size estimated			31-35 DAI: 3.3	2.31 ± 1.45
	School-based study			≥ 36 DAI: 1.6	3.46 ± 1.33
Gaikwad et al, 2014 (Maharashtra, India)	Cross sectional	880	12-15	≤ 25 DAI: 73	1.35 ± 1.44
	Random selection			26-30 DAI: 13.1	1.33 ± 1.56
	Sample size estimated			31-35 DAI: 18.1	1.60 ± 1.42
	School-based			≥ 36 DAI: 2.38	2.62 ± 1.91
Feldens et al, 2015 (Southern Brazil)	Cross sectional	509	11-14 12.4 ± 1.1	≤ 25 DAI: 32.4	4.77 ± 3.54
	Random selection			26-30 DAI: 24	5.23 ± 3.61
	Sample size estimated			31-35 DAI: 21.6	4.76 ± 3.49
	School-based			≥ 36 DAI: 22	5.44 ± 3.88

The studies were of moderate to high quality (Table 3). All addressed the confounding factor of age by matching among children with and without malocclusion. Singh et al. (2012) included children of similar socioeconomic status. Feldens et al. (2015) controlled for socioeconomic status in multivariate analysis.

The meta-analysis compared DMFT values among different severities of malocclusion (Figure 2). Handicapping malocclusion was associated with higher mean DMFT scores (Mean difference: 1.03; 95% CI 0.61–1.44). A low certainty of evidence was achieved for association between handicapping malocclusion with dental caries

(Table 4). Participants with severe malocclusion had higher mean DMFT when compared to normal occlusion (0.32; 95% CI 0.13–0.51) (Figure 3) with low certainty. Similarly, definite malocclusion was associated with presence of higher DMFT scores (0.19; 95% CI

0.03–0.35) (Figure 4) with moderate certainty. Moderate to low non-significant heterogeneity values of 49%, 0%, and 16% respectively were noted for comparisons of handicapping, severe, and definite malocclusion with normal occlusion (Figures 2–4).

Table 3. Quality Assessment: Newcastle-Ottawa scale

	Selection		Comparability			Outcome		Total	
	Representativeness	Sample size	Non-Respondents	Ascertainment of exposure	Control for age	Controls for other factors	Assessment		Statistical test
Borzabadi-Farahani, 2011	1	0	0	2	1	0	2	1	7
Singh, 2012	1	0	0	2	1	1	2	1	8
Baskaradoss, 2013	1	0	0	2	1	0	2	1	7
Gaikwad, 2014	1	0	0	2	1	0	2	1	7
Feldens, 2015	1	1	1	2	1	1	2	1	10

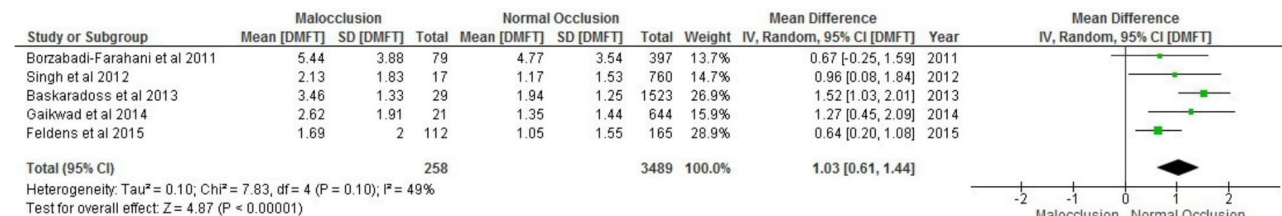


Figure 2. Meta-analysis of studies evaluating dental caries: handicapping malocclusion versus normal occlusion

Table 4. GRADE analysis for certainty of evidence for association between malocclusion and dental caries

No. studies	Design	Certainty assessment					Other considerations	No. participants		Mean Difference. Absolute (95% CI)	Effect Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Handicapping Malocclusion		Normal Occlusion			
Handicapping malocclusion											
5	Observational	Serious	Not serious	Not serious	Not serious	Strong association, all plausible residual confounding would suggest spurious effect	258	3489	1.03 higher (0.61-1.44)	⊕⊕○○ LOW	
Severe malocclusion											
5	Observational	Serious	Not serious	Not serious	Not serious	Strong association, all plausible residual confounding would suggest spurious effect	380	3489	0.32 higher (0.13-0.51)	⊕⊕○○ LOW	
Definite malocclusion											
5	Observational	Serious	Not serious	Not serious	Not serious	Strong association, all plausible residual confounding would suggest spurious effect	717	3489	0.19 higher (0.03-0.35)	⊕⊕⊕○ MODERATE	

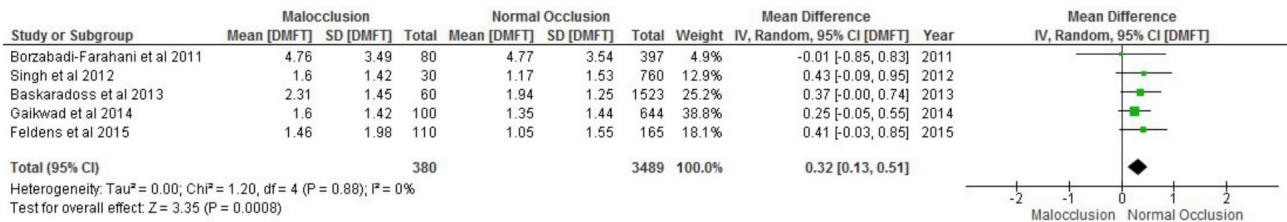


Figure 3. Meta-analysis of studies evaluating dental caries: severe malocclusion versus normal occlusion

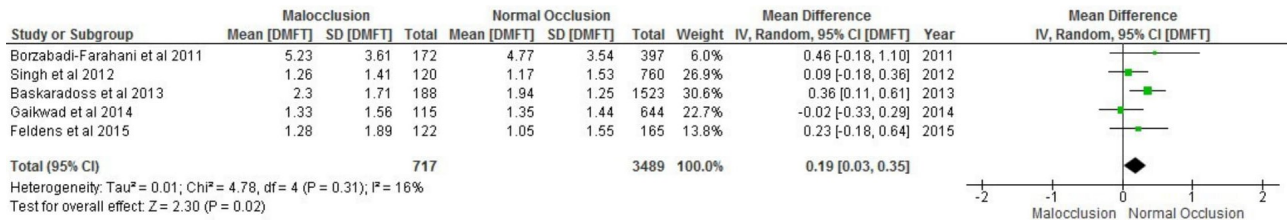


Figure 4. Meta-analysis of studies evaluating dental caries: definite malocclusion versus normal occlusion

Discussion

This review including five studies demonstrated an association between malocclusion and dental caries. There was a dose-response relationship more severe malocclusion severe levels being associated higher DMFT scores.

One pathway of causation between malocclusion and dental caries could be that malocclusion contributes towards greater plaque build-up by favouring its accumulation and obstructing its removal, which is further facilitated by severe malocclusion. However, dental caries leads to tooth loss and is a recognised risk factor for malocclusion (Sa-Pinto *et al.*, 2018). The association between malocclusion and dental caries may therefore be bidirectional. Unfortunately the cross-sectional design of the included studies does not allow the determination of the direction of the relationship (Feldens *et al.*, 2015). Any temporal relationship between caries and malocclusion remains inconclusive due to the study design.

An individual's socioeconomic circumstances can also influence their oral health, and thus the association found between malocclusion and caries may be partially due to confounding by this or other variables (Sa-Pinto *et al.*, 2018). However, the relationship persisted in Singh *et al.*'s (2012) study restricted to children of similar socioeconomic status.

An implication of these findings is that crowding and improper contacts between teeth may make effective oral hygiene difficult, which may increase plaque accumulation and predispose to caries development. Crowding could also inhibit the flow of fluoride into spaces. Crowding and buccal cross-bite have been associated with dental caries, whereas increased overjet and anterior open bite were associated with gingivitis (Kolawole and Folayan, 2019). A systematic preventive programme, including meticulous oral hygiene maintenance, diet management, and use of fluoride varnishes in practice, may be followed by people with malocclusion.

The association between malocclusion and dental caries is complex due to its potentially bidirectional

relationship.. However, this study determined the association between malocclusion and dental caries rather than etiological evidence. Limitations of the study include a low number of studies and no registration of the study protocol. The review could not establish a temporal relationship between malocclusion and dental caries. Only one tool to measure malocclusion was used, which may not have reflected the entire body of evidence. The DAI may under-record malocclusion as it prioritises aesthetic concerns rather than occlusal traits such as cross-bite. Nonetheless, it is still the most widely used index to assess malocclusion in surveys (WHO,1997). The DMFT index is simple to use but the values are not related to number of teeth at risk and may overestimate caries experience in teeth with preventive fillings. The effect of these two forms of misclassification would be to mask any relationship between malocclusion and caries. Nevertheless, that relationship persisted in these analyses. Three of the five included studies were from India and one each from Iran and Brazil. The results therefore are more generalizable to developing nations. Very few studies that assess association of malocclusion with dental caries in field settings have been identified; therefore, further observational studies, specifically cohort studies, are suggested for the future.

In summary, this systematic review associated malocclusion with dental caries with a seeming dose-response relationship in the permanent dentition. Low to moderate certainty of evidence was observed for association between handicapping, severe, and definite malocclusion with dental caries.

Appendix

Boolean operators used along with the whole string for search – ((“malocclusal”[All Fields] OR “malocclusion”[MeSH Terms] OR “malocclusion”[All Fields] OR “malocclusions”[All Fields] OR “malocclusive”[All Fields]) AND (“dental caries”[MeSH Terms] OR (“dental”[All Fields] AND “caries”[All

Fields]) OR “dental caries”[All Fields]) OR (“crowd s”[All Fields] OR “crowding”[MeSH Terms] OR “crowding”[All Fields] OR “crowd”[All Fields] OR “crowded”[All Fields] OR “crowds”[All Fields]) AND (“dental caries”[MeSH Terms] OR (“dental”[All Fields] AND “caries”[All Fields]) OR “dental caries”[All Fields])

Conflict of Interest

None to be declared

Funding

None

References

- Anthony, S., Zimba, K. and Subramanian, B. (2018): Impact of malocclusions on the oral health-related quality of life of early adolescents in Ndola, Zambia. *International Journal of Dentistry* **2018**, 7920973.
- Baskaradoss, K., Geevarghese, A., Roger, C. and Thaliath, A. (2013): Prevalence of malocclusion and its relationship with caries among school children aged 11–15 years in southern India. *Korean Journal of Orthodontics* **43**, 35–41.
- Borges, M., Peres, A. and Peres, G. (2010): Association between malocclusion and dissatisfaction with dental and gingival appearance: study with Brazilian adolescents. *Revista Brasileira de Epidemiologia* **13**, 713–23.
- Borzabadi-Farahani, A., Eslamipour, F. and Asgari, I. (2011): Association between orthodontic treatment need and caries experience. *Acta Odontologica Scandinavica* **69**:2–11.
- da Rosa, N., Del Fabro, P. and Tomazoni, F. (2016): Association of malocclusion, happiness, and oral health-related quality of life (OHRQoL) in schoolchildren. *Journal of Public Health Dentistry* **76**, 85–90.
- Disha, P., Poornima, P. and Pai, S. (2017): Malocclusion and dental caries experience among 8–9-year-old children in a city of South Indian region: A cross sectional survey. *Journal of Education and Health Promotion* **6**, 98.
- Feldens, A., Dos-Santos, I. and Kramer, F. (2015): Impact of malocclusion and dentofacial anomalies on the prevalence and severity of dental caries among adolescents. *Angle Orthodontics* **85**, 1027–34.
- Feldens, A., Ardenghi, M., Dos-Santos Dullius, I., Vargas-Ferreira, F., Hernandez, A. and Kramer, F. (2016): Clarifying the Impact of Untreated and Treated Dental Caries on Oral Health-Related Quality of Life among Adolescents. *Caries Research* **50**, 414–21.
- Gaikwad, S., Gheware, A., Kamatagi, L. (2014): Dental caries and its relationship to malocclusion in permanent dentition among 12-15-year-old school going children. *Journal of International Oral Health* **6**, 27–30.
- Hafez, S., Shaarawy, M. and Al-Sakiti, A. (2012): Dental crowding as caries risk factors: a systematic review. *American Journal of Orthodontics and Dentofacial Orthopedics* **142**: 443–50.
- Helm, S. and Petersen, P. (1989): Causal relation between malocclusion and caries. *Acta Odontologica Scandinavica* **47**, 217–21.
- Institute of Medicine, Division of health care services. (1980): Public policy options for better dental health. In: *Epidemiology and prevention of dental diseases – Malocclusion*. National Academy Press, Washington.
- Kim, Y., Park, E., Lee, J., Seo, J., Sheen, S. and Hahn, S. (2013): Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *Journal of Clinical Epidemiology* **66**, 408–14.
- Kolawole, K. and Folayan, M. (2019): Association between malocclusion, caries and oral hygiene in children 6 to 12 years old resident in suburban Nigeria. *BioMed Central Oral Health* **19**, 262.
- Kramer, F., Pereira, M., Ilha, C., Borges, S., Freitas, M. and Feldens, A. (2017): Exploring the impact of malocclusion and dentofacial anomalies on the occurrence of traumatic dental injuries in adolescents. *Angle Orthodontics* **87**, 816–823.
- Mtaya, M., Brudvik, P. and Astrøm, A. (2009): Prevalence of malocclusion and its relationship with socio-demographic factors, dental caries, and oral hygiene in 12- to 14-year-old Tanzanian schoolchildren. *European Journal of Orthodontics* **31**, 467–76.
- Modesti, A., Reboldi, G., Cappuccio, P., Agyemang, C., Remuzzi, G., Rapi, S., Perruolo, E. and Parati, G. (2016): ESH working group on CV risk in low resource settings. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. *PLoS One* **11**, e0147601.
- Nalcaci, R., Demirer, S., Ozturk, F., Altan, A., Sokucu, O. and Bostanci, V. (2012): The relationship of orthodontic treatment need with periodontal status, dental caries and sociodemographic factors. *Scientific World Journal* **2012**, 498012.
- Petersen, E., Bourgeois, D. and Ogawa, H. (2005): The global burden of oral diseases and risks to oral health. *Bulletin of the World Health Organization* **83**, 661–9.
- Sa-Pinto, A., Rego, T. and Marques, L. (2018): Association between malocclusion and dental caries in adolescents: a systematic review and meta-analysis. *European Archives of Paediatric Dentistry* **19**, 7382.
- Sardenberg, F., Martins, T. and Bendo, B. (2013): Malocclusion and oral health-related quality of life in Brazilian school children. *Angle Orthodontist* **83**, 83–9.
- Scapini, A., Feldens, A. and Ardenghi, M. (2013): Malocclusion impacts adolescents’ oral health-related quality of life. *Angle Orthodontist* **83**, 512–8.
- Schünemann, H., Brozek, J., Guyatt, G. and Oxman, A. (2013): *The GRADE handbook*. Available at: “<https://training.cochrane.org/resource/grade-handbook>”. Accessed June 5, 2020.
- Singh, A., Purohit, B. and Sequeira, P. (2012): Malocclusion and orthodontic treatment need measured by the Dental Aesthetic Index and its association with dental caries in Indian schoolchildren. *Community Dental Health* **29**, 2.
- Stahl, F. and Grabowski, R. (2004): Malocclusion and caries prevalence: is there a connection in the primary and mixed dentitions? *Clinical Oral Investigations* **8**, 86–90.
- The Cochrane Collaboration. (2011): *Selecting studies and collecting data: General methods of Cochrane reviews, Part 2*. Cochrane handbook for systematic reviews of interventions. Available at: “<http://handbook.cochrane.org>” Accessed May 10, 2020.
- Ukra, A., Foster, A., Thomson, M., Farella, M., Tawse-Smith, A. and Beck, V. (2013): Impact of malocclusion on quality of life among New Zealand adolescents. *New Zealand Dental Journal* **109**, 18–23.
- Vellappally, S., Gardens, J., Kheraif, A., Krishna, M., Babu, S., Hashem, M., Jacob, V. and Anil, S. (2014): The prevalence of malocclusion and its association with dental caries among 12-18-year-old disabled adolescents. *BioMed Central Oral Health* **14**:123.
- Venete, A., Trillo-Lumbreras, E. and Prado-Gascó, V. (2017): Relationship between the psychosocial impact of dental aesthetics and perfectionism and self-esteem. *Journal of Clinical and Experimental Dentistry* **9**, e1453–e1458.
- World Health Organization. (1997): *Oral health surveys – Basic methods, 4th ed.* Geneva: World Health Organization.