Evaluation of Treatments Available for Class I, II and III Malocclusion in Children, Adolescents, and Adults

Emma Sepide Bakh

RESEARCH QUESTION

To evaluate the benefits and harms in available treatments for patients with Class I, II and III malocclusion.

BACKGROUND

Disease Definition and Risk Factors

Malocclusion is the abnormal alignment of teeth, and involves the way in which upper and lower teeth are fitted together (1). In normal occlusion, the upper teeth are fitted in a way so that they slightly overlap the lower teeth. This allows the teeth to fit into the corresponding depression of the opposite tooth (2). Proper alignment of teeth is very important for chewing and equally distributed force. When chewing, over 150 pounds of force is applied to the molars, and an unequally distributed force leads to damage and loosening of teeth (1).

Edward H. Angle was the first to publish classifications of malocclusion in 1890 (3, 4) He suggested that it was the upper first molars that were the key of occlusion, and that the classifications of occlusion are based on the relationship between the mesiobuccal cusp of the maxillary first molar and the buccal groove of the mandibular first molar (5). Malocclusion is distinguished in three different classifications, depending on the relationship of the teeth and their positioning, as seen in Figure 1 (5). In Class I malocclusion a normal relationship exists between the molars, but the line of occlusion is compromized due to misaligned teeth, or crowding(6). Class II malocclusion subdivided into two divisions. Class II Division 1 involves proclination of anterior maxillary teeth, resulting in a large overjet. While Class II Division 2 involves retroclination of maxillary anterior teeth, resulting in a deep overbite (7), (8), (5). In Class III malocclusion there is a posterior occlusion of the mesiobuccal cusp of the maxillary first molar, to the groove of the mandibular first molar. The line of occlusion may or may not be regular (5). Class II and Class III malocclusion can be either dental, skeletal, or in some cases both (5).

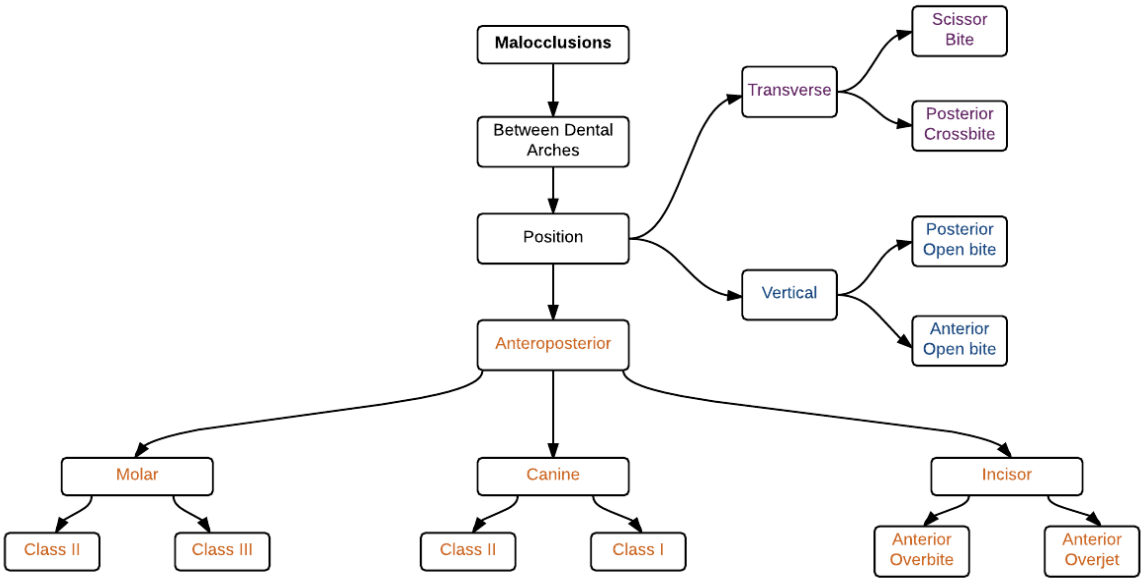

Figure 1: Visualization of the classification of different types of malocclusion. Class I, II and II malocclusion occur in the anteroposterior position and involves the molars, canine and incisors. Malocclusion in the transverse position involves scissor bite and posterior crossbite. Vertical malocclusion involves posterior open bite and anterior open bite.
This diagram was produced by repurposing a diagram by Getano et al. 2015 (9)

The cause of malocclusion has been attributed to several different factors, the most significant of which include; non-nutritive sucking habits (pacifier use or digits) in children, mouth breathing, and genetic factors have also been shown to play a role (10, 11). Several studies have reported the impact of non-nutritive sucking habits on development of malocclusion (10, 11), (12, 13). These studies have shown that children with pacifier or digit sucking habits are significantly more likely to develop anterior open bite, overjet, anterior displacement of the maxilla, and posterior crossbite. Pacifiers are used by 75-95% of infants in their first two years of life (10). The study by Nihi et al. 2015, showed a clear association between prolonged use of pacifiers and development of malocclusion, and they showed that anterior open bite was the predominantly developing characteristic of malocclusion (10). A study by E. Gois et al. 2008, showed that breathing pattern and enlarged adenoids may also have an impact on the development of malocclusion. Breathing pattern has an effect on growth and orofacial development, which may influence crossbite and malocclusion. They showed that mouth breathing children had a 10.9 times greater chance of developing malocclusion and anterior open bite. Since enlarged adenoids tend to lead to mouth breathing, this is also considered a risk factor (13).

Development of malocclusion is not only affected by environmental factors, but also genetics. Genetic studies on class III malocclusion have identified several loci involved with malocclusion in Asian and Hispanic families (14), (15)
Da Fontoura et al. 2015 evaluated facial skeletal variations and malocclusion with craniofacial candidate genes. Their study, although limited by small sample size, showed significant associations between several genes and malocclusion. They identified SNAI3 and TWIST1 genes as particularly suggestive for craniofacial variation. SNAI3 was associated with severely concave to convex profiles, and TWIST1 was associated with variation from short to long mandibular bodies.
They also showed that single nucleotide polymorphism (SNP) within genes FGFR2, EDN1, TBX5 and COL1A1 were associated with skeletal malocclusion, particularly class II malocclusion (16)

Disease Burden/Social Impact

Malocclusion has been shown to have detrimental consequences on maxillofacial development and oral health related quality of life (OHRQoL) (16). Not only can oral health be impaired by the development of malocclusion, but it can result in impaired aesthetic function, leading to psychological problems in adolescents, as well as adults (4, (17). Personal dissatisfaction with malocclusion has an impact on the quality of life, from functional and aesthetic aspects, to low self-esteem because of bullying (17), (18). The link between malocclusion and the OHRQoL depends on perception of self and functional aspects like speech, chewing, mouth breathing. As malocclusion increases, the OHRQoL decreases progressively (8). The most common impact of malocclusion on QoL is emotional and social behavior. Adolescents with malocclusion experience 30% more negative effects on OHRQoL, by for example, not showing teeth, not laughing and talking with others (8). Few studies have investigated a relationship between deteriorating QoL and prevalence of malocclusion (19, 20). However, there is a general lack of available data showing this relationship. Socio-dental research is lacking in contribution to determining the detrimental effects that malocclusion may have on patients (21).
Studies by De Oliveira et al. 2003 and Liu et al. 2009 showed that orthognathic surgery or orthodontic treatment in patients with malocclusion significantly improved their QoL by having less impact on their daily activities and improving their self perception (20, 22). A study by Kiyak et al. 2008 investigated the post-orthognathic surgery psychological effect on patients, and discovered that there was a significant reduction in the number of complaints, from 84.6% to 5.1% 24 months after surgery, and that overall body image had improved(23). The treatment process may however also have a temporary impact on the QoL of the patient, as it can interfere with eating and speaking (20)

Prevalence

The prevalence of malocclusion ranges from 20% to 70%, and varies depending on the population studied (11; 17). Dimberg et al. 2015, reported that 43-78% of school children develop malocclusion. A study by Bilgic et al. 2015 evaluated the prevalence of malocclusion in 2329 randomly chosen Turkish adolescents between the age of 12.5 to 16.2 years. They found that class II malocclusion was the most predominant (44%), while class I was 34.9% and class III occlusion rate was 10.3%. This study also showed that anterior open bite was the most common, with 73.5% and mostly observed in girls (24), which is also confirmed in other studies (17).

Their findings for class II malocclusion were interesting, when compared to occlusion rates in studies from other European countries. For example, English school children were found to have a 12.5% class II malocclusion rate (25), Colombian children had a 14.9% rate (26), and Italian children had a 36.3% occlusion rate(27). Surprisingly, a study conducted on Swedish children showed a malocclusion rate of 48% (28).

Although these studies suggest that class II malocclusion is the most prevalent class of malocclusion in adolescents, there is a lack of data available through official bodies, regarding prevalence of malocclusion from wide-spread national/international studies and surveys.

Treatment options available

Treatment of malocclusion is normally initiated once a child, normally between the age of 10-12, is referred to an orthodontist. Early treatment is important, however it holds a disadvantage of gradually diminishing compliance and uncertain growth prediction (29). Malocclusion is most often treated with orthodontics. Orthodontics work by applying a constant pressure over a prolonged period of time, slowly correcting the dental and facial structure (30). Although orthodontics are the most commonly used treatment, especially in children, other forms of treatment may be necessary depending on the type and severity of the malocclusion. Class I malocclusion is characterized by a normal molar relationship, but with some degree of overcrowding and malpositioned teeth (8) This is usually treated with orthodontics and fixed appliance like cervical anchorage in more severe cases (31). Treatment of Class II malocclusion depends on the particular discrepancy. In Class II division 1 malocclusion, which is characterized by a lack of contact between opposing teeth (open bite), treatment most commonly involves the use of functional appliances, multibracket therapy and bite blocks (32).

In Class II division 2 malocclusion, the discrepancy is characterized by retroclination of the maxillary incisors, leading to a deep overbite. This can be treated with functional appliance therapy, or removal appliance therapy that reduces overbite. Extraction and non-extraction treatments must be considered. Generally, non-extraction therapy is favored due to the soft tissue changes that may follow tooth extraction, and extraction is only performed to aid in surgery when there is severe crowding of the teeth (33).

Class III malocclusion can involve many different types of discrepancies, depending on the positioning of the maxilla. Due to the severity of Class III malocclusion, surgical intervention may be necessary. Orthognathic surgery (corrective jaw surgery) is commonly used to correct the maxillary or mandibular position. For example, for mandibular prognathism, mandibular surgery (sagittal split ramus osteotomy) alone is enough to correct the malocclusion. When there is maxillary and mandibular excess, surgery on both will be required, like anterior segment osteotomy. In hyperplasia of the maxilla, Le Fort osteotomies are most commonly used to correct the positioning of the upper lip (34).

METHODS

The following text will identify the criteria for considering studies in this review.

Types of studies

Randomized controlled trials (RCTs), WHO trials and Clinical trials will be included. Only studies reported as full text and abstract only will be included.

Types of Participants

This study will include children and adults with class I, II, III malocclusion, as well as randomized controlled trials of different treatment modalities for different classes of malocclusion.

Types of interventions

We will include trials that involve/compare orthognathic surgery techniques and orthodontic treatment of different classes of malocclusions in children, adolescents and adults.

Types of outcome measures

Primary outcomes

1. Effect of treatment

- Short term result of treatment and occlusal characteristic 3 months post treatment.
- Long term result of treatment and relapse of malocclusion.

2. Adverse effects of treatment

- Soft tissue changes in response to hard tissue movement 3 months post treatment.

3. Impact on Oral Health Related Quality of Life (OHRQoL) (using any validated scale)

- Short term improvement in quality of life (QoL) (three months post treatment)
- Long term improvement in QoL (more than three months post treatment)

The above clinical outcomes are based on the necessity to assess the short and long term results of orthodontic treatment/orthognathic surgery and their success rate. We must also assess the occlusal outcome, proper occlusion, as well as improved OHRQoL in patients. Studies will be included irrespective of whether they report OHRQoL and soft tissue changes.

Search methods for identification of studies

Electronic searches:
A literature search will be performed in order to identify all published randomized clinical trials. The literature search will identify all potential international studies published in English. The following electronic databases will be searched for identification of potential studies

1. MEDLINE (Appendix 1)
2. EMBASE (Appendix 2)
3. The Cochrane Central Register of Controlled Trials (Appendix 3)
4. ClinicalTrials.gov; Appendix 4)
5. World Health Organization - International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp.en/; Appendix 5)

Other resources:
The reference list of primary studies and review articles will be checked for additional references.

Data collection and analysis

Selection of studies:
Titles and abstracts will be screened for inclusion of all potential studies that are identified as a result of the search strategy. Full text studies will be retrieved and reviewed in order to identify studies for inclusion. The reason for exclusion of ineligible studies will be identified and recorded. This selection process and characteristics of excluded studies will be recorded in the 'characteristics of excluded studies' table.

Data extraction and management
A standard data collection form for study characteristics and outcome data will be used. The study characteristics will be extracted from included studies and detailed in 'characteristics of included studies' table.
The following study characteristics will be extracted:

1. Methods
2. Participants:
    - Number of participants
    - Mean age
    - Age range
    - Gender
    - Class of malocclusion
    - Type of discrepancy

3. Treatment: treatment, comparisons,
4. Outcomes: primary outcomes specified, reported time points

Outcome data from included studies will be extracted, and all randomized participants for short term and long term outcomes (e.g. OHQoL) will be included.
If outcome data is reported in an unusable way, it will be noted in the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies
The risk of bias will be assessed for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* available on www.cochrane-handbook.org.
Risk of bias is assessed according to the following points:

1. Random sequence generation
2. Allocation of concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

Each potential source of bias is graded as high, low or unclear risk of bias and evidence for this judgment will be reported in the 'Risk of bias' table. For treatment effects, the risk of bias for the studies that report that outcome will be considered.

Assessment of bias in conducting the systematic review
The review will be conducted according to the published protocol. Where there are deviations from the protocol, this will be reported in the 'Difference between protocol and review' section of the review.

Measuring treatment effect
Binary outcomes of adverse events (e.g. soft tissue change occurrence) is extracted in two or more groups. The data extracted includes the total number of patients with the event and the total number of patients in each group. If data is missing, the author will be contacted to obtain the missing information or percentages will be used to convert to a whole number using a percentage sheet form. If this is not possible, an alternative analysis must be used, or the exclusion of the data from the meta-analysis must be considered.
Ordinal outcomes, like class of malocclusion and OHRQoL will be extracted differently depending on whether it is treated as dichotomous or continuous data.

Dichotomous data (e.g. resolution of malocclusion vs. no resolution of malocclusion) is analyzed as risk ratio (95% CI). This will only be done if there are few categories. Continuous data (numerous categories of QoL) is analyzed as mean difference (95% CI), when outcomes are reported in same units in all trials, or as standardized mean difference when different scales are used for measuring the outcomes.
Data extraction for ordinal outcomes depends on how the meta-analysis will be performed. If there are few categories, the data can be dichotemized, in which case the data will be extracted as for binary outcomes. If the data is treated as continuous data, it will be extracted as continuous outcomes (e.g. in OHRQoL). A sensitivity analysis will be performed to test the effect of the different ways of combining the categories.
Meta-analysis will only be performed if it is meaningful, as in when treatment, participants and the underlying clinical questions are similar enough.
In cases where multiple treatment arms are reported in the same trial, only the relevant arms will be included. The control group will be included in cases where there are two comparisons (e.g extraction treatment versus non-extraction treatments), in order to avoid double counting.

Unit of Analysis Issues
The unit of analysis will be the individual participants undergoing treatment for malocclusion. Cluster-randomized trials are not anticipated for this comparison, however, if such trials are obtained, the effect estimate adjusted for the clustering effect will be obtained as well, if available. If this is not available, the trial will be excluded from the meta-analysis.

Dealing with Missing Data
Missing numerical outcome data will be obtained by contacting study authors or sponsors. If this is not successful, the mean will be imputed from the median (i.e. consider the median as the mean), standard deviation from standard error, interquartile range or P values according to the *Cochrane Handbook for Systematic Reviews of Interventions (35).* The impact of including such studies will be assessed by a sensitivity analysis.

Assessment of Heterogeneity
The I^2 statistical test will be used to measure heterogeneity across the trials in each analysis. If the result percentage of variability is higher than 50-60%, indicating a substantial amount of heterogeneity (as specified by the *Cochrane Handbook for Systematic Reviews of Interventions),* the pre-specified subgroup analysis will be performed to explore this further.

Assessment of Reporting Biases
In studies where the missing data is thought to introduce bias, the authors of such studies will be contacted to provide the missing data. If this is not possible, the impact of inclusion of such studies will be assessed using the sensitivity analysis.

Summary of Findings Table
A summary of findings table will be created using all the outcomes. The five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) will be used to assess the quality of a body of evidence, related to the studies used in the meta-analyses. The methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (34) will be used, as well as GRADEpro software.

Subgroup Analysis
We plan to conduct the following subgroup analysis

1. Different classes of malocclusion
    - Class I
    - Class II
    - Class III
2. Different types of treatment for each class of malocclusion
    - Orthodontics
    - Surgical interventions

3. Treatment start at different stages of dentition (age)
    - Children
    - Adolescent
    - Adults

All outcomes will be used in the subgroup analyses. The Chi^2 test will be used to assess subgroup differences and interactions.

Sensitivity analysis
Sensitivity will be analyzed in order to assess the relevance of the conclusion. The sensitivity analysis will involve the following:

1. Excluding trials that are of high or unclear risk of bias.
2. Exclude trials where the mean and/or standard deviation have been imputed.
3. Exclude cluster RCTs where the adjusted effect estimates are not reported

Reaching Conclusions
Conclusions will purely be based on the quantitative and qualitative studies included in this review. Recommendations of clinical practice will be avoided. Implications for research will guide the reader and provide clarity for where future research should be.

APPENDICES

Appendix 1 MEDLINE Search Strategy
1. exp Malocclusion/
2. exp Prognathism/
3. exp Retrognathia/
4. (Malocclusion or malocclusions or crossbite or crossbites or "cross bites" or underbite or overbite or "tooth crowding" or retrognathism or retrognathia or prognathism or prognathia or overjet or neutrocclusion or distocclusion or mesiocclusion or "Tooth size discrepancy" or "Tooth size discrepancies" or "horizontal discrepancy" or "horizontal discrepancies" or "vertical discrepancy" or "vertical discrepancies").ti,ab.
5. 1 or 2 or 3 or 4
6. randomized controlled trial.pt.
7. controlled clinical trial.pt.
8. randomized.ab.
9. placebo.ab.
10. drug therapy.fs.
11. randomly.ab.
12. trial.ab.
13. groups.ab.
14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp animals/ not humans.sh.
16. 14 not 15
17. 5 and 16

Appendix 2. EMBASE Search Strategy
1. exp malocclusion/
2. exp prognathia/
3. exp retrognathia/
4. (Malocclusion or malocclusions or crossbite or crossbites or "cross bites" or underbite or overbite or "tooth crowding" or retrognathism or retrognathia or prognathism or prognathia or overjet or neutrocclusion or distocclusion or mesiocclusion or "Tooth size

discrepancy" or "Tooth size discrepancies" or "horizontal discrepancy" or "horizontal discrepancies" or "vertical discrepancy" or "vertical discrepancies").ti,ab.
5. 1 or 2 or 3 or 4
6. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/
7. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af.
8. 6 or 7
9. 5 and 8

Appendix 3. The Cochrane Central Register of Controlled Trials Search Strategy

#1 MeSH descriptor: [Malocclusion] explode all trees
#2 MeSH descriptor: [Prognathism] explode all trees
#3 MeSH descriptor: [Retrognathia] explode all trees
#4 (Malocclusion or malocclusions or crossbite or crossbites or "cross bites" or underbite or overbite or "tooth crowding" or retrognathism or retrognathia or prognathism or prognathia or overjet or neutrocclusion or distocclusion or mesiocclusion or "Tooth size discrepancy" or "Tooth size discrepancies" or "horizontal discrepancy" or "horizontal discrepancies" or "vertical discrepancy" or "vertical discrepancies")
#5 #1 or #2 or #3 or #4

Appendix 4. ClinicalTrials.gov Search Strategy

Interventional Studies | Malocclusion OR retrognathism OR retrognathia OR prognathism OR prognathia | Phase 2, 3, 4

Appendix 5. WHO ICTRP Search Strategy

Malocclusion or retrognathism or retrognathia or prognathism or prognathia

REFERENCES

1. Malocclusion *MSD Manual Consumer Version*. Available at: https://www.msdmanuals.com/home/mouth-and-dental-disorders/symptoms-of-oral-and-dental-disorders/malocclusion [Accessed March 23, 2016].

2. Malocclusion *MSD Manual Consumer Version*. Available at: https://www.msdmanuals.com/home/mouth-and-dental-disorders/symptoms-of-oral-and-dental-disorders/malocclusion [Accessed March 17, 2016].

3. Angle EH (1900) *Treatment of Malocclusion of the Teeth and Fractures of the Maxillæ: Angle's System*.

4. Asbell MB (1990) A brief history of orthodontics. *Am J Orthod Dentofacial Orthop* 98(3):206–213.

5. ANGLE'S CLASSIFICATION OF MALOCCLUSION (2015) *DENTODONTICS*. Available at: http://dentodontics.com/2015/09/09/angles-classification-of-malocclusion/ [Accessed March 27, 2016].

6. Angle's Class I - Dental Clinic Help Available at: http://www.geemboomba.com/home/classifications/angle-s-classification/angles-class-i [Accessed March 27, 2016].

7. Angle's Class I - Dental Clinic Help Available at: http://www.geemboomba.com/home/classifications/angle-s-classification/angles-class-i [Accessed March 27, 2016].

8. Angle's classification of malocclusion *TheFreeDictionary.com*. Available at: http://medical-dictionary.thefreedictionary.com/Angle%27s+classification+of+malocclusion [Accessed March 27, 2016].

9. Gateno J, Alfi D, Xia JJ, Teichgraeber JF (2015) A Geometric Classification of Jaw Deformities. *J Oral Maxillofac Surg* 73(12 Suppl):S26–31.

10. Nihi VSC, et al. (2015) Pacifier-sucking habit duration and frequency on occlusal and myofunctional alterations in preschool children. *Braz Oral Res* 29(1):00–00.

11. Wagner Y, Heinrich-Weltzien R (2015) Occlusal characteristics in 3-year-old children – results of a birth cohort study. *BMC Oral Health* 15. doi:10.1186/s12903-015-0080-0.

12. Larsson E Artificial sucking habits: etiology, prevalence and effect on occlusion. - PubMed - NCBI. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9055659 [Accessed March 17, 2016].

13. Elton Geraldo Oliveira Góisa, Humberto Campos Ribeiro-Júniorb, Miriam Pimenta

Parreira Valec, Saul Martins Paivac, Júnia Maria Cheib Serra-Negrad, Maria Letícia Ramos-Jorgee, and Isabela Almeida Pordeusf (2008) Influence of Nonnutritive Sucking Habits, Breathing Pattern and Adenoid Size on the Development of Malocclusion. *The Angle Orthodontist* 78. Available at: http://www.angle.org/doi/10.2319/0003-3219(2008)078[0647:IONSHB]2.0.CO;2?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed [Accessed March 17, 2016].

14. Yamaguchi T, Park SB, Narita A, Maki K, Inoue I (2005) Genome-wide Linkage Analysis of Mandibular Prognathism in Korean and Japanese Patients. *J Dent Res* 84(3):255–259.

15. Frazier-Bowers S, Rincon-Rodriguez R, Zhou J, Alexander K, Lange E (2009) Evidence of Linkage in a Hispanic Cohort with a Class III Dentofacial Phenotype. *J Dent Res* 88(1):56–60.

16. da Fontoura CSG, et al. (2015) Candidate Gene Analyses of Skeletal Variation in Malocclusion. *J Dent Res* 94(7):913–920.

17. Dimberg L, Arnrup K, Bondemark L (2015) The impact of malocclusion on the quality of life among children and adolescents: a systematic review of quantitative studies. *Eur J Orthod* 37(3):238–247.

18. Scapinia A, Feldensb CA, Ardenghic TM, Kramerb PF (2013) Malocclusion impacts adolescents' oral health–related quality of life. *The Angle Orthodontist* 83. doi:10.2319/062012-509.1.

19. de Oliveira CM and Sheiham A The relationship between normative orthodontic treatment need and oral health-related quality of life. - PubMed - NCBI. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14986910?access_num=14986910&link_type=MED&dopt=Abstract [Accessed March 20, 2016].

20. De Oliveira CM, Sheiham A (2003) The relationship between normative orthodontic treatment need and oral health- related quality of life. *Community Dent Oral Epidemiol* 31(6):426–436.

21. Burden DJ, Holmes A (1994) The need for orthodontic treatment in the child population of the United Kingdom. *Eur J Orthod* 16(5):395–399.

22. Liu Z, McGrath C, Hägg U (2009) The Impact of Malocclusion/Orthodontic Treatment Need on the Quality of Life. doi:10.2319/042108-224.1.

23. H.Asuman Kiyak, PhD, ∗ , Thomas Hohl, DDS†, Roger A. West, DDS†, R.William Mc (2008) Psychologic changes in orthognathic surgery patients: A 24-month follow up. 42(8):506–512.

24. Bilgic F, Gelgor IE, Celebi AA (2015) Malocclusion prevalence and orthodontic treatment need in central Anatolian adolescents compared to European and other nations' adolescents. *Dental Press J Orthod* 20(6):75.

25. Haynes S The prevalence of malocclusion in English children aged 11-12 years. - PubMed - NCBI. Available at: http://www.ncbi.nlm.nih.gov/pubmed/5287526 [Accessed March 17, 2016].

26. Thilander B E al Prevalence of malocclusion and orthodontic treatment need in children and adolescents in Bogota, Colombia. An epidemiological study related to diff... - PubMed - NCBI. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11398553 [Accessed March 17, 2016].

27. Perillo L E al Prevalence of orthodontic treatment need in southern Italian schoolchildren. - PubMed - NCBI. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19706641 [Accessed March 17, 2016].

28. Josefsson E E al Malocclusion frequency in Swedish and immigrant adolescents--influence of origin on orthodontic treatment need. - PubMed - NCBI. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17290019 [Accessed March 17, 2016].

29. Eve Tausche Olaf Luck (2004) Prevalence of malocclusion in early mixed dentition and orthodontic treatment need. *European Journal of Orthodontics*. Available at: http://ejo.oxfordjournals.org/content/eortho/26/3/237.full.pdf [Accessed March 17, 2016].

30. Malocclusion - symptoms, Definition, Description, Demographics, Causes and symptoms, Diagnosis, Treatment Available at: http://www.healthofchildren.com/M/Malocclusion.html [Accessed April 2, 2016].

31. Langberg BJ, Todd A (2004) Treatment of a class I malocclusion with severe bimaxillary protrusion. *Am J Orthod Dentofacial Orthop* 126(6):739–746.

32. Paola Cozzaa, Manuela Mucederob, Tiziano Baccettic, and Lorenzo Franchi (2005) Early Orthodontic Treatment of Skeletal Open-bite Malocclusion. *The Angle Orthodontist* 75:707–713.

33. Millett DT, Cunningham SJ, O'Brien KD, Benson PE, de Oliveira CM (2012) Treatment and stability of Class II Division 2 malocclusion in children and adolescents: A systematic review. *Am J Orthod Dentofacial Orthop* 142(2):159–169.e9.

34. Je Uk Park, Baik DDS S (2001) Classification of Angle Class III malocclusion and its treatment modalities. *The International Journal of Adult Orthodontics & Orthognathic Surgery* 16. Available at: http://www.quintpub.com/PDFs/aoos/aoos/aoos_16_1_park2.pdf [Accessed April 2, 2016].

35. Julian P T Higgins And ed. (2011) *Cochrane Handbook for Systematic Reviews of Interventions* (The Cochrane Collaboration).