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Malocclusion's Risk Factors: A Systematic Review

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Abstract

Aim: This systematic review aimed to determine the risk factors for malocclusions. **Methods:** A comprehensive search for publications in electronic databases such as PubMed, Medline, Embase, Cochrane, Google scholar, Scopus and Web of science was conducted in order to identify and choose the literature for this paper. 13 articles were selected, and their level of methodological quality was appraised using the STROBE quality assessment tool. **Results:** The analysis of these articles allowed us to identify the major risk factors in the development of malocclusions. We have classified these factors into general and local factors. General factors were age, gender and genetic background. Local factors were preterm birth, breastfeeding habits, oral health, quality of life and socio-economic status, dysfunctions such as mouth ventilation, and parafunctions such as finger sucking. **Conclusion:** The risk factors for the development of malocclusion have been identified. Understanding these local and general risk factors will help orthodontists adopt a preventive and interceptive approach when managing these malocclusions.

Subject Areas

Dentistry

Keywords

Malocclusion, Corrective Orthodontics, Class I, II and III, Risk Factors, Orthodontics

1. Introduction

The World Health Organization (WHO) defines malocclusion as a handicapping dento-facial defect that involves aberrant occlusion and/or altered craniofacial in-

teractions. It can impact facial harmony, function, aesthetic appearance, and psychosocial well-being [1]. The "father of modern orthodontics," Dr. Edward Hartley Angle, created three classifications of malocclusion based on where the upper first molar's mesiobuccal cusp is in relation to the lower first molar's buccal groove. The mesiobuccal cusp of the maxillary first molar obstructs the buccal groove of the mandibular first molar, resulting in the classification of the tooth as an angle class I molar, also referred to as neutroclusion. The maxillary first molar's mesiobuccal cusp, which obstructs the mandibular first molar's buccal groove mesially, classifies it as a class II molar. Lastly, a class III molar is identified by the maxillary first molar's mesiobuccal cusp obstructing distal to the mandibular first molar's buccal groove [2]. The relationships between skeletal bases in the anteroposterior direction are defined by the Ballard classification, which is a skeletal classification. Because these relationships do not always align with occlusal relations, Ballard suggested a classification of skeletal base relationships to supplement the Angle classification. Class I skeletal structure: harmonious jaw relations. Skeletal class II: the mandible's too posterior position. Skeletal class III: excessively anterior mandibular position [3]. Many etiological theories have been proposed for malocclusion. The primary causes in this instance include ethnic, environmental, and genetic factors. There is a substantial correlation between genetics and malocclusion because some types of malocclusions, such as Class III relationships, run in families. An example of this is the bimaxillary protrusion, which is more prevalent in African-born people than in other ethnic groups. On the other hand, a range of malocclusion problems can result from functional adaptation to external stimuli that affect anatomical elements such as soft tissue, bone, and teeth. Malocclusion might therefore be seen as a complex problem with no currently recognized cause [4]. Deformities can be prevented from developing or getting worse by identifying the risk factors for malocclusion and implementing early intervention. Determine the risk factors for this multifactorial disease in order to discover inherited/genetic risks, aid in the early detection of the causes, and identify unsafe oral practices such as mouth breathing, tongue pushing, and thumb sucking [5]. Additionally, the significance is in avoiding future issues such as tooth cavities, crowding, spacing, etc. Finally, correcting these malocclusions early on aids in the patient's longer-term psychosocial well-being and helps select the best approach to treatment [6].

The purpose of this systematic review was to determine the risk factors for malocclusion in order to prevent its progression and its effects by implementing early diagnosis, prevention and interception.

2. Methods

2.1. Protocol and Registration

The protocol for this review was registered on 2nd March 2024 on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) under the following registration number: INPLASY202430010. This review was carried out using PRISMA (Preferred Reporting Items for Systematic

Reviews and Meta Analyses) protocols [7].

2.2. Search Strategy

The literature for this paper was identified and selected by performing a thorough search in electronic databases like PubMed, Medline, Embase, Cochrane, Google Scholar, Scopus, and Web of Science published over the past decade (October 2013 - October 2023) by using of keywords such as Malocclusion, Corrective orthodontics, Class I, II and III, Risk factors and Orthodontics. This search was based on the PICO (problem/patient/population, intervention/indicator, comparison, and outcome) elements (**Table 1**).

Table 1. Description of the PICO elements.

PICOS	Description
Population	Patients with malocclusions without age or gender restrictions
Intervention	Literature research to identify potential risk factors for malocclusions
Comparison	Control group
Outcomes	Identification of potential risk factors related to malocclusion
Study design	Retrospective study, cohort study, case-control study, randomized controlled trials (RCT)
Research question	What are the risk factors for the development of dental and skeletal malocclusions?

The search strategy resulted in the collection of 5695 articles, duplicates were removed and filters were used (date, type of article), the remaining articles were then left at the number of 1040, then reviewed the titles and abstracts of potentially relevant studies to exclude off-topic articles that did not meet the inclusion criteria. In cases of doubt, studies were included, and full texts were assessed for eligibility.

2.3. Criteria for Study Selection

a. Inclusion criteria:

Articles meeting the following criteria were included:

- Studies on risk factors and predisposing factors for malocclusions.
- Randomized and non-randomized clinical trials.
- Descriptive and analytical observational studies: case-control, cohort and cross-sectional studies as well as retrospective studies.
- Articles published between 2013 and 2023.

b. Exclusion criteria:

Articles that met any of the following exclusion criteria were excluded:

- Articles judged to be case studies, expert reports, letters, commentaries, editorials.
- Articles not meeting the objectives of our work based on abstract reading and critical reading of the full text.
- Articles in languages other than English and French.

After applying these criteria's, the number of articles were further reduced to

13, representing a database for the systematic analysis. These articles were critically assessed after referring the guidelines of STROBE (Strengthening the Reporting of Observational studies in Epidemiology). The "STROBE Statement" is a checklist and assessment tool whose content validity enables the following: reporting the methodological aspects of observational studies in the health sciences, including retrospective and prospective cohort studies, case-control studies, and cross-sectional studies; and identifying the key characteristic elements. The 40 methodological components that make up the observational study-specific combined STROBE checklist are divided into 22 categories [8].

3. Results

13 research articles were included and analyzed for quantitative data (**Figure 1**). We classified these factors into general and local factors. General factors were age, gender and genetic background. Local factors were preterm birth, breastfeeding habits, oral health, quality of life and socio-economic status, dysfunctions such as mouth ventilation, and parafunctions such as finger sucking.

All of these articles were analyzed with a data extraction as presented in **Table 2.** The Strobe tool was used to analyze the included studies, allowing for the assessment their methodological quality. Only one study had "poor" methodological quality [18], while seven were deemed to be of "good" quality [9] [13] [15] [17] [19]-[21]. The full analysis was presented in **Table 3**.

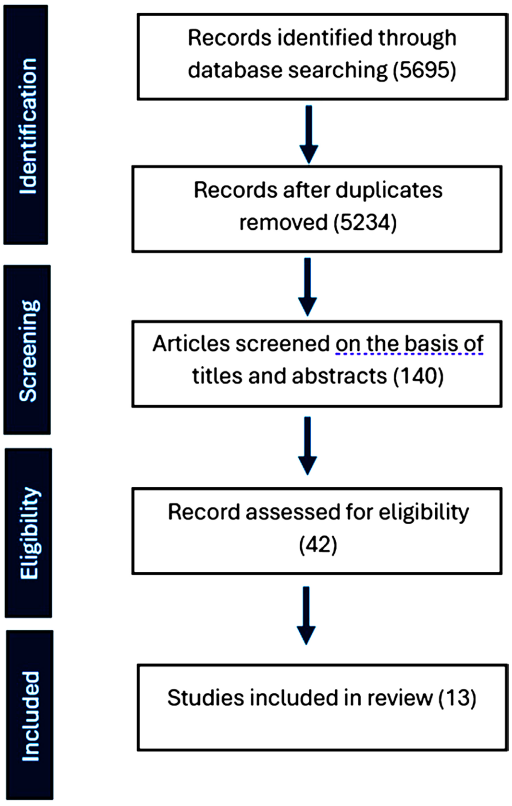

Figure 1. Flow chart for article selection.

Table 2. The general characteristics of selected studies.

Title	Author/ Year	Type of Study	Means of Acquisition	Sample	Gender	Potential Risk Factors	Critical Analysis Strategy	Conclusion
Longitudinal study of habits leading to malocclusion development in childhood. [9]	Moimaz SA *et al* **(2014)**	Prospective cohort study	Intra oral examinations	80 mother-child pair	----------	-Pacifier sucking -Finger sucking -Nocturnal mouth breathing -Bottle feeding -Low rates of breastfeeding	-Chi-square test -Fischer's test	Between the ages of 12 and 30 months, children who were bottle fed and mouth breathers were associated with posterior bite, but children who sucked their fingers or used pacifiers were more likely to exhibit an open bite and an overjet at 12, 18, and 30 months. Malocclusion was linked to poor breastfeeding rates, sucking behavior, and nighttime breathing.
The prevalence of malocclusion and oral habits among 5 - 7-year-old children. [10]	Kaspara-viciene K *et al* **(2014)**	Cross sectional study	Clinical examination of occlusion, extra-oral assessment combined with a questionnaire for parents	503 preschool children	M: 260 F: 243	-Mouth breathing -Digit sucking -Infantile type of swallowing -Tongue thrust swallowing	-Chi square test -Bland and Altman analysis for quantitative measure-ments	Anterior open bite and posterior crossbite were more common among finger suckers. Anterior open bite and infantile swallowing pattern were revealed to be significantly correlated. Preschoolers who practiced tongue thrust swallowing and non-nutritive sucking behaviors were at developing anterior open bite and posterior crossbite.
Down syndrome. A risk factor for malocclusion severity. [11]	Marques LS *et al* **(2015)**	Cross-sectional study	-Interviews Assessments of medical charts -Oral examination	120 G1: 60 with DS G2: 60 with no physical or mental impairment	M:37 F:23 Control group M:19 F:41	-Vertical and transversal occlusal alteration -Insufficient bone development -Mouth breathing patterns due to orofacial muscle hypotonia and absence of lip seal -Abnormal positioning of the tongue -Craniofacial deformities -Dental alterations (number and size of teeth) -Muscle disorders -Premature birth -Altered breathing pattern	Chi-square test Statistical Package for Social Sci-ences (SPSS)	The most prevalent malocclusions among people with Down syndrome were transversal and vertical changes that affected the form of the arch and the position of the teeth, such as mandibular protrusion, anterior open bite, and posterior crossbite. Patients with DS had increased rates of lip incompetence and missing teeth. Short facial patterns and angle class III malocclusion were more prevalent.

Continued

Association between malocclusion and contextual factors of quality of life and socioeconomic status. [12]	Vedovello SA *et al* **(2015)**	Cross-sectional study	Structured questionnaires and clinical examinations	1256 children	M:484 F:547	-Socioeconomic Status -Low quality of life	-Logistic regression analysis -Bivariate analysis	The development of malocclusions was significantly influenced by age and socioeconomic status. The condition that was thought to have the biggest impact on quality of life was increased overjet. Children from lower-income families were more susceptible to environmental factors associated with malocclusions.
Effects of breast-feeding duration, bottle feeding and non-nutritive sucking habits on the occlusal characteristics of primary dentition. [13]	Chen X *et al* **(2015)**	Cross sectional study	Oral health examination	734 children	M:398 F:336	-Bottle feeding for longer than 18 months -Pacifier sucking habit -Demographic factors: maternal age, level of education about breastfeeding	Chi square test	Open bites were more common in kids who sucked their fingers. Even in the absence of non-nutritive sucking behaviors, prolonged inadequate breastfeeding can negatively affect the development of the maxillary arch and cause malocclusion in the form of a posterior crossbite.
Early risk factors for posterior crossbite and anterior open bite in the primary dentition. [14]	Germa A *et al* **(2016)**	Cross-sectional study	Interview during the mother's pregnancy + Oral examination	422 children	M:211 F:211	-Non-nutritive sucking: pacifier or thumb sucking -Mouth breathing -Inadequate tongue capacity -Neurological immaturity in the case of preterm birth -Neurological impairment	-Chi square test	Persistent sucking behaviors seemed to be linked to early posterior crossbite. Early posterior crossbite seemed to be associated with preterm birth.
Prevalence and factors related to malocclusion, normative and perceived orthodontic treatment need among children and adolescents in Bangladesh [15]	Sultana S *et al* **(2018)**	Cross sectional study	Oral examinations + Questionnaire	800 children	M:403 F:397	-Breast feeding -Non-nutritive sucking habits -Reported extractions of deciduous teeth -Caries in the deciduous teeth	Chi square test	Long-term non-nutritive sucking behaviors, parental education level, and caries experiences had a significant relationship with the development of malocclusions

Continued

Is premature birth an orthodontic risk factor? A controlled epidemiological clinical study. [16]	Objois C *et al* **(2019)**	Cross-sectional comparative epidemiological study	Panoramic radiography and cephalometric analyses	197 patients: Preterm group:47 Control group: 150	M:62 F:88	-Respiratory system immaturity -The use of oral and nasogastric probes for prematurely born children -Increased number of premature triggered births -Difficulties in the coordination of sucking and swallowing -Increased used of medically assisted procreation	-Chi-square test and Student test	There were noticeably more dental inclusions and retentions in infants born extremely and very preterm. Additionally, transverse deficits of the maxilla and a reduction in the perimeters of the maxillary and mandibular arches were linked to prematurity, which resulted in insufficient space for teeth to emerge naturally. Diastemas, overbite, anterior open bite, and palatal anomalies were all present in premature newborns.
Association between oral habits, mouth breathing, and malocclusions in Italian preschoolers. [17]	Paolantonio EG *et al* **(2019)**	Cross -sectional study	Baby ROMA index carried out by calibrated operators	1616 children	M: 808 F:808	-Thumb and lip sucking -Bruxism -Mouth breathing -Tongue thrusting -The persistence of the deleterious parafunctions -open bite, crossbite, increased overjet and displacement -Persistent non-nutritive sucking habits	-Chi-square test -Fischer test -K test	Mouth breathing was present in more than half of preschoolers with malocclusions, and it was closely associated with malocclusion. Sucking habits and oral breathing were strongly associated with some malocclusions (overjet, anterior open bite).
Orthodontic treatment need and timing: Assessment of evolutive malocclusion conditions and associated risk factors. [18]	Grippaudo MM *et al* **(2020)**	Cross-sectional study	Clinical observation	4422 patients	M:2078 F:2341	-Mouth breathing -Poor oral hygiene -Age -Non-nutritive sucking habits -Mouth breathing -Oral breathing and obstructive sleep apnea -Postural or orthopedic problems -Alteration of the exfoliation sequence -Medical or auxological conditions -Caries and early loss of deciduous teeth -Congenital syndromes and malformations -Familial tendency for malocclusions -Parafunctions (bruxism) -Facial or mandibular asymmetries -Outcomes of trauma or surgery	Chi-square test	Malocclusion became worse by certain risk factors that emerged during growth. In order to prevent the issue from getting more severe, it was crucial to address those factors with an early orthodontic intervention. Some malocclusions were less affected by environmental risk factors. In certain situations, it could be better to postpone treatment until adolescence.

Continued

Prevalence of caries and associated risk factors in a representative group of preschool children from and urban area with high income in Milan province, Italy [19]	Nota A *et al* **(2020)**	Cross-sectional study	Questionnaire and oral health examination	160 children	M:78 F:82	-Oral habits -Oral hygiene -Diet and lifestyle -Breathing pattern	Chi square test Regression test	It should be mentioned that the development of malocclusions was linked to a number of factors, including lack breastfeeding, non-nutritive sucking behavior, mouth breathing patterns, pacifier use, lack of lifestyle/sport activities, and poor dental hygiene practices.
Relationship between dental caries, oral hygiene and malocclusion among Syrian refugee children and adolescents. [20]	Salim NA *et al.* **(2021)**	Cross sectional study	Dental examinations using a basic disposable mirror and a WHO periodontal probe	606 patients	F: 326 M:280	-Psychological distress -Gender -Low quality of life -Poor periodontal conditions -Discomfort -Epilepsy -Allergies -Weak oral hygiene practices -Limited financial resources -Limited accessibility to proper nutrition and clean water -Being in a community outside the healthcare system -Lack of education -Ethnic differences -Regional economic differences	Chi square test One way ANOVA Welch test Post hoc testing (Gabriel and Games Howell) Sample t-test	Malocclusions were closely linked to poor oral hygiene and a lower quality of life.
Prevalence and influencing factors of malocclusion in adolescents in Shanghai, China. [21]	Yin J *et al* **(2023)**	Cross-sectional study	Oral examination Questionnaire	1799 adolescents	M:955 F:844	-Dietary habits -Increasing prevalence of dental caries -Increasingly refined diet -Premature loss of deciduous teeth -Inadequate chewing function -Dental caries -Premature extraction of deciduous teeth	Chi-square test Stepwise binary logistic regression	Extended periods of inadequate nursing might negatively affect the development of the maxillary arch and cause a posterior crossbite.

4. Discussion

A systematic literature review was conducted to highlight risk factors for malocclusions. With no discernible gender differences, about half of all children and adolescents globally experience some form of malocclusion. With the slight exception of Africa (48%), this high frequency did not drop below 50% on any of the continents of the world. According to research, malocclusion is most common

in early childhood during the phase of deciduous dentition (54%), and it stays the same during the permanent dentition (54%) [3]. In their primary and permanent dentitions, about two-thirds of the world's population had a Class I dental condition. In both the permanent and primary dentition, Class II was three times more common than Class III in the remaining one-third of the population. Class I predominance seems to decrease from primary to mixed and permanent dentition, most likely as a result of environmental conditioning or genetic manifestation, while Angle's Classes II and III remain relatively constant over all three dentitions [22]. In a study of 1000 schoolchildren in Casablanca, Morocco, ages 8 to 12, the prevalence of malocclusions and the need for orthodontic treatment were examined. The findings revealed that 61.4% of the subjects had Angle Class I malocclusions, 24% had Class II malocclusions, and 10% had Class III malocclusions; in total, 84.2% of the subjects needed some orthodontic treatment, while 15.8% did not [23]. The midline shift, which occurs with a prevalence of 27% in the primary dentition and 28% in the permanent one, is another malocclusion characteristic that is largely consistent across dentition stages. On the other hand, some malocclusion traits, such crowding of teeth and scissor bite, grew from primary to permanent dentitions. Dental crowding increased from 16 to 39%, while scissor bite climbed from 0.4 to 5% [3]. Only two malocclusion features—the posterior crossbite and the upper anterior diastema—decreased from primary to permanent dentitions. Its frequency was reduced from 35% to 5% by the diastema. The smaller interdental gap was probably caused by permanent incisors' larger dimensional size compared to their deciduous counterpart. Similar to diastema, crossbite has decreased from 14% to 7% [3].

Regarding gender differences in malocclusion prevalence, some studies indicated variations, while others did not find significant differences. In support of Onyeaso *et al.*'s [24] findings that males had significantly more Class II and III molar connections than females, Satish *et al.* reported a higher prevalence of Class II and Class III malocclusions among boys [25]. There were not significant differences in the occurrence of malocclusion across genders, according to the research of Arabiun *et al.* [26] and Grewe *et al.* [27].

Antecedent investigations into occlusal features, such as maxillary and mandibular arch length and width, have yielded estimations of the relative genetic and environmental contributions. According to specific research [28] [29], genetic factors significantly impact the shape of the dentoalveolar arches, the degree of dental crowding and spacing, and the degree of overbite. Study undertaken by Watanabe *et al.*, had found a substantial genetic propensity for Class III malocclusion, particularly in situations of mandibular prognathia [30]. This syndrome, frequently associated with Class III malocclusion, is believed to have a major genetic component. The anterior growth rotation associated with Class II division 2 malocclusion was also impacted by hereditary factors. Moreover, compared to horizontal development patterns, vertical growth patterns were found to be more genetically controlled [31].

Table 3. Quality assessment using the Strobe tool.

	Studies	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18]	[19]	[20]	[21]
STROBE Item:	1-a	1	1	1	1	1	1	1	1	1	0	1	1	1
	1-b	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	1	1	0	1	0	1	1	1	1	0	1	1	1
	3	1	1	1	1	1	1	1	0	1	0	0	1	0
	4	1	1	1	1	1	1	1	1	1	0	1	1	1
	5	1	1	0	1	0	1	1	1	1	0	1	1	1
	6-a	1	1	1	1	1	1	1	1	1	1	1	1	1
	6-b	1	1	1	1	1	1	1	1	1	1	1	0	1
	7	1	0	0	1	1	0	1	0	0	0	0	1	0
	8	1	0	1	1	1	1	1	1	1	1	1	1	1
	9	0	0	0	0	1	1	0	1	0	0	0	0	1
	10	1	1	0	1	1	0	1	1	1	1	1	1	1
	11	1	1	1	1	1	0	1	1	1	1	1	1	1
	12-a	1	1	0	1	1	1	1	1	1	1	1	1	1
	12-b	1	1	1	0	1	1	1	0	1	0	1	1	1
	12-c	0	0	0	1	0	0	1	0	1	0	1	1	1
	12-d	1	0	1	0	1	1	1	1	1	0	1	1	1
	12-e	0	0	0	0	0	0	0	0	0	0	0	0	0
	13-a	1	1	0	1	1	1	1	1	0	1	1	1	1
	13-b	1	1	0	0	1	0	1	0	0	0	0	1	1
	13-c	0	0	0	0	1	0	0	0	0	0	0	0	0
	14-a	0	0	1	0	0	1	0	0	1	0	1	1	1
	14-b	0	0	0	0	1	1	0	0	1	1	1	0	1
	14-c	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	15	1	1	1	1	0	0	1	1	1	1	1	1	1
	16-a	1	1	0	0	1	1	1	1	1	1	0	1	1
	16-b	0	0	0	0	1	0	0	1	1	0	1	0	0
	16-c	0	1	1	1	1	1	1	1	1	0	1	0	1
	17	0	0	1	1	1	1	1	0	0	0	0	0	0
	18	1	0	1	1	1	1	1	1	1	0	1	1	1
	19	1	1	1	0	0	0	1	1	1	1	1	1	1
	20	1	1	1	1	1	1	1	1	0	1	1	1	1
	21	1	1	1	1	1	1	1	1	1	1	1	1	1
	22	1	0	0	1	0	0	0	0	1	1	0	0	1
Total		24	20	18	22	25	22	26	22	25	15	24	24	27
Percent		70.58	58.82	52.94	64.70	73.53	64.70	76.47	64.70	73.53	44.11	70.58	70.58	79.41
Methodological quality grade		Good	Average	Average	Average	Good	Average	Good	Average	Good	Poor	Good	Good	Good

Environmental factors were also considered as risk factors in the development of malocclusions, including lack of breastfeeding. One of the earliest and most important experiences for a baby's healthy facial development is breastfeeding. It has been shown that nursing significantly reduces the risk of anterior open bite. The findings also showed that nursing for extended periods of time protects against anterior open bite and non-specific malocclusion [32]. Breastfed newborns display higher levels of face muscle activity compared to bottle-fed babies.

This increased muscle activity promotes healthy maturation of the craniofacial structure and jawbone development [32]. According to Moimaz *et al.* [9], overbite was shown to be more common in subjects who had been breastfed for more than a year. Conversely, Sum *et al.* [33] failed to find any link between vertical disparity and breastfeeding. Long-term use of bottles and pacifiers can induce changes in the oral cavity and cause deformities in the dental arch, which can then affect essential processes including swallowing, mastication, and speech articulation [34]. A child's craniofacial development may be significantly impacted by this, leading to skeletal and dental abnormalities that disrupt vital oral functions and may also exacerbate psychological discomfort and misery brought on by misaligned dentition [35].

Particularly in early infants, poor oral habits include tongue swallowing, mouth breathing, and finger sucking. Mouth breathing is another typical unfavorable oral behavior that is associated with the onset of malocclusion, especially when it occurs during sleep [36]. According to research by Moimaz *et al.* [9], Sousa *et al.* [37], and Chen *et al.* [13], oral dysfunctions were linked to malocclusions such as anterior open bite, posterior crossbite, and Class II or Class III molar/canine connections. In the past, it has been believed that the main environmental factor causing malocclusion is bad oral habits. However, other studies indicate that malocclusion may also be related to dietary status [38] [39]. Crowding may have an indirect relationship to nutritional status through poor odontogenesis, which delays dental eruption and increases the risk of caries, which leads to tooth loss. Such occurrences may alter the dental arch's structure, impairing maxillomandibular development because there aren't enough masticatory cues [38]. Nutrition influences the development of orofacial features, according to the review by Barao *et al.* [40], subjects following a soft diet developed narrow jaws as a result of underdeveloped muscles and supporting systems, and there was a positive correlation between the incidence of Class II malocclusion and the avoidance of course and fibrous foods. Furthermore, consuming more soft foods may lead to the development of malocclusion or tooth crowding, according to Saghiri *et al.* [41] mastication can encourage the face bones to expand, especially in the transverse dimension, which can lead to wider mandibular and maxillary arches.

The development of several tissues and organs throughout the body, including the teeth and bones of the face, might be affected by premature delivery. In a systematic review of oral problems resulting from preterm birth, Paulsson *et al.* [42] discovered evidence of palate morphological abnormalities. They came to the conclusion that one risk factor for these alterations is orotracheal intubation, a standard technique for preterm neonates. Malocclusion can develop as a result of changes in tooth placement and palate morphology [42]. Neiva and Leone [43] showed that employing a gloved finger to stimulate non-nutritive sucking was more successful than using a pacifier in enhancing the sucking skills of preterm neonates.

5. Conclusion

Through a systematic assessment of the literature, the risk factors for the development of malocclusion have been identified. These local and general characteristics enable practitioners to detect the risks of malocclusions, hence offering the opportunity for early intervention to prevent or lessen the consequences.

Conflicts of Interest

The authors declare no conflicts of interest.

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