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The effect of premature extraction of primary teeth on the subsequent need for orthodontic treatment: a systematic review

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Abstract:

Aim: This was primarily to examine the effect of Premature Extraction of Primary Teeth (PEPT) on subsequent malocclusion and need for orthodontic treatment in the permanent dentition. The secondary aim was to correlate the effect of PEPT with loss of space in the primary and mixed dentitions.

Methods: A predefined protocol was developed and registered prospectively with PROSPERO database. The electronic databases searched were MEDLINE, EMBASE, PubMed and Cochrane Central Register of Controlled Trials. The study designs considered for inclusion were controlled trials, cohort and case-control studies. Risk of bias was assessed using a validated quality assessment tool.

Results: 513 studies were identified. Sixteen studies were included in the systematic review, one study reported on malocclusion and 15 studies reported on space changes. Narrative synthesis was undertaken owing to the heterogeneity of the included studies. No study examined the effect of PEPT on orthodontic need. Most studies reported on space dimensions used a split-mouth design and were at a high risk of bias.

Conclusions: The included literature identified that PEPT led to various features of malocclusion and space loss in the mixed and permanent dentition. No studies, that met the inclusion criteria, described the effect of PEPT on the subsequent need for orthodontic treatment.

The effect of premature extraction of primary teeth on the subsequent need for orthodontic treatment: a systematic review

Introduction

There are a wide variety of definitions for Premature Extraction/ loss of Primary Teeth (PEPT) according to published literature including; missing a primary tooth on examination when the permanent successor could not be palpated (Bjork, 1964; Ronnerman, 1977; Pedersen et al., 1978), the loss of primary canines and first primary molars during, or prior to, first school grade; and the loss of primary second molars during, or prior to, the "second school grade" (Hoffding and Kisling, 1978a; 1978b) missing a primary tooth for at least six months prior to the loss of the contralateral tooth in the same arch (Kronfeld, 1953) or a missing primary tooth on two successive examinations approximately a year apart (Northway et al., 1984).

A definition of PEPT is difficult to describe as eruption patterns of the permanent teeth can deviate for either genetic or environmental reasons. An appropriate definition should consider the dental age of a child, as the chronological age may not accurately predict a child's stage of dental development. For the purpose of this systematic review, PEPT was defined as *any primary tooth that was extracted prior to the natural exfoliation of the tooth.*

Prevalence of PEPT varies in a paediatric population depending upon a number of factors including: water fluoridation, socio-economic status, prevalence of dental caries and the treatment philosophy of dentists. PEPT following dental caries is a common finding in child populations and studies have reported a range of 20-65% (Hoffding and Kisling, 1978a; 1978b; Pedersen et al., 1978; Northway and Wainwright, 1980; Melsen and Terp, 1982). A recent national oral health survey of children undertaken in England shows that almost a third of 5-year-olds and nearly half of the 8-year-olds had obvious dental decay in primary dentition and the percentages of primary teeth extracted were 5% and 17% in these age groups respectively (Health and Social Care Information Centre, March 2015).

While dental caries was the most common factor for PEPT other causes include: congenital disorders, premature exfoliation of primary teeth particularly of primary canines as a result of eruption of permanent canines, ectopic eruption of permanent teeth especially of first permanent molars, dental trauma and orthodontic extractions either as interceptive treatment to alleviate or prevent malocclusion (Willet, 1933; Durward, 2000; British Society of Paediatric Dentistry, 2002). There has been no systematic review to date to assess the orthodontic effects of premature extraction of primary teeth.

The effect of PEPT on malocclusion is an important consideration when discussing treatment options for carious teeth in the primary and mixed dentition. Three national bodies, the British Society of Paediatric Dentistry (2001), American Association of Pediatric Dentistry (2015) and Royal College of Surgeons of England (2015) have identified that alignment of permanent teeth may be affected by premature extraction of primary teeth. A possible biological mechanism by which PEPT may influence future orthodontic need is shown in figure 1.

The aetiology of malocclusion is complex with involvement of both genetic and environmental factors and has been described as polygenic multifactorial (Mitchell, 2007). The potential loss of space following PEPT is a contributing environmental factor that has the potential to cause or exacerbate malocclusion and thus may lead to an increase in orthodontic need. One other systematic review was identified in this search which examined the effect of premature extraction of first primary molars on short term space loss (Tunison et al., 2008). This review concluded that the space loss was clinically insignificant. However, it has to be borne in mind that the national guideline by the British Society of Paediatric Dentistry (2002) have recognised that extraction of a second primary molar is more likely to lead or exacerbate further potential malocclusion and measuring space between primary canines and second molars would concentrate on space loss in a specific quadrant rather than the space changes in the full arch. In addition, this systematic review did not examine the longer-term effect of the premature extraction of a first primary molar on orthodontic need.

The aim of this systematic review was primarily to examine the effect of PEPT on subsequent malocclusion and need for orthodontic treatment in the permanent dentition. The secondary aim was to correlate the effect of PEPT with loss of space in the primary and mixed dentitions.

Methods

Search strategy

To capture as many potential studies as possible, a structured electronic search, reference list screening and search for unpublished studies was undertaken. Electronic databases searched were MEDLINE (1st Jan 1946 to week 3 of March 2013), EMBASE and EMBASE classic (1st Jan 1947 to 3rd April 2013), PubMed (1st Jan 1996 to week 3 of April 2013) and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms using keywords and subject headings included in the review were detailed in the published protocol which is available online on PROSPERO international prospective register of systematic reviews (Bhujel et al., 2013).

Inclusion criteria

Language

The language of the publications analysed was restricted to English.

Study Type

Controlled trials, cohort studies and case control studies that assessed the effects of premature extraction/loss of primary teeth were included in the review. For the primary objective, all studies that had a comparison group to the PEPT group were considered. For the secondary objective, split-mouth study design comparing unilateral loss of primary teeth with the intact intra-arch quadrant as a control was also included in the review and analysed separately.

Participants

Studies with participants affected by PEPT in the primary or mixed dentition were included in this systematic review. All participants with age groups consistent with the primary and mixed dentitions were considered. For assessment of malocclusion, the age group of the children had to be consistent with the eruption of the full permanent dentition. Thus, the study had to follow-up the children from the time of PEPT until the eruption of their full permanent dentitions at approximately 12 years of age. For the assessment of space changes, any age group of participants in the primary or mixed dentition were included.

Intervention

The intervention group (PEPT) was where the extraction had occurred prior to the natural exfoliation of the tooth or teeth. The comparator group was children who had not suffered PEPT. For split-mouth study design with intra-arch comparison, PEPT in a quadrant was compared to the contra-lateral control quadrant without PEPT.

Outcome measures

The possible orthodontic outcomes included:

- Any measure of orthodontic need (Pedersen et al., 1978; Melsen and Terp, 1982). The most appropriate and robust method for assessing orthodontic need was the use of a recognised index such as the Index of Orthodontic Need (Brook and Shaw, 1989). This index was developed in the 1980s and is widely used in the UK to prioritise orthodontic treatment to those with the greatest orthodontic need (British Orthodontic Society, 2009).

- Complexity of orthodontic treatment (for example duration of orthodontic treatment or need for permanent tooth extractions as part of orthodontic treatment (Pedersen et al., 1978; Melsen and Terp, 1982).
- Malocclusion based on Angle's Class I, Class II and Class III malocclusion with additional features like overbite and overjet (Hoffding and Kisling, 1978a; 1978b; Pedersen et al., 1978).
- Crowding, malalignment, rotation of teeth, ectopic eruption and jaw displacements.

A number of outcomes were used to investigate space loss. These could include:

- Arch perimeter, hemi-perimeter,
- Arch length,
- Arch width,
- Incisor inclination and incisor position,
- The first and second primary molar space defined by Northway et al. (1984) as the distance between the mesial midpoint of the first permanent molar (or distal midpoint of the second primary molar) has been reported to be easily defined and monitored. Since the definition of first and second primary molar space by Northway et al. (1984), further split- mouth studies have reported on this measurement (Lin and Chang, 1998; Park et al., 2009; Lin et al., 2011).
- Soft tissue maxillary features such as the incisive papilla and palatal rugae to provide stable landmarks for measurements (Linder-Aronson, 1960; Northway et al., 1984; Park et al., 2009).

Data Collection and Analysis

All studies identified by the search strategy that appeared to fulfil the inclusion criteria were reviewed based on their title and abstracts. For those with relevant titles and abstracts, the full text article was obtained and assessed for inclusion. A data extraction form was used to collect pertinent study information following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement which is endorsed by the World Health Organization (von Elm et al., 2007).

Electronic searching, reference list searching and grey literature search was carried out by the principal author (NB). Two authors (NB and PS) independently read the titles and abstracts and when uncertain the full article prior to excluding those that were unrelated studies. For included studies, two reviewers (NB and PS) independently undertook the data extraction. Any disagreement was resolved by consensus and then in consultation with a third reviewer (PD). Risk of bias assessment was based on the Cochrane Risk of Bias Tool (Higgins and Green, 2011) using five criteria: selection, performance, detection, attrition and reporting biases. The risk of bias was assessed independently by two reviewers (NB and PS) and any disagreement resolved by consensus and in consultation with a third reviewer (PD).

Results

Search Results

There were 490 studies identified by the electronic search strategy and 23 added by reference list searching after the primary filtering process. After the screening and filtering process, 25 studies were appraised in this review (see figure 2). Two studies were unpublished Master's degree thesis, one awarded by University of Montreal (1977) and one by University of Toronto (1949). The former, was also published as a research article (Northway et al., 1984), thus it was treated as a duplicate publication with more information added from the thesis. The latter, was requested from the British Library but they did not hold a copy.

It was not possible to perform a meta-analysis owing to the heterogeneity of the outcome measures reported. A narrative synthesis was provided from the included studies structured around assessment and quantification of orthodontic need and space loss.

Malocclusion

Two studies were identified which were part of a two-part series by the same authors; Hoffding and Kisling (1978a; 1978b). These studies were of a case control design. These two papers did not report on changes to orthodontic need following PEPT.

Hoffding and Kisling (1978a; 1978b) conducted a retrospective case control study of 550 children. The aim of this study was to evaluate the effects of PEPT on occlusion and space conditions in the permanent dentition. Of the 550 children, 327 children had a history of PEPT and 223 had no history of PEPT. Children with a history of premature extractions of permanent teeth and or orthodontic extractions were excluded from the study, thus the PEPT group was reduced to a final number of 231 children. In the PEPT group, extractions involved the maxillary arch in 32 children, mandibular arch in 97 children and both arches in 102 children. Although it was reported that age at the time of survey was 13 to 14 years, mean age of the participants was not reported. Ethnicity of the participants was not reported.

The primary outcome for this systematic review was any feature of malocclusion. This information was collected from epidemiological surveys and features of malocclusion used in this study were maxillary overjet, sagittal molar relationship and space conditions in incisor and posterior segments. Molar occlusion was registered for both sides of the mouth and was judged to be deviated from normal if there was half a unit or more of either Class II or Class III relationship as per Angle's classification. While assessing space conditions, crowding was registered if there was a space deficiency of 2 mm or more within an arch.

When any sign of malocclusion described above was considered, the frequency of malocclusion in cases of PEPT was 90% compared to 80% where there was no history of PEPT. This difference was statistically significant. When features of malocclusion were assessed individually, PEPT was not significantly associated with maxillary overjet and distal molar occlusion (Angle's molar classification Class II). However PEPT was significantly associated with mesial molar occlusion (Angle's molar classification Class III). Frequency of crowding was also statistically higher in PEPT group with 49% in comparison to 29% in the control arch. Key findings: PEPT increased the frequency of at least one feature of malocclusion (features of malocclusion included were maxillary overjet ≥ 6 mm, class II malocclusion of at least half unit, class III malocclusion of at least half unit, spacing discrepancy of at least 2 mm). The frequency of crowding was also increased with the previous history of PEPT.

Space Changes

Six studies assessed space loss following PEPT. Two published studies reported the same data set (Ronnerman, 1965; Ronnerman, 1977), thus the results were amalgamated into one study for this systematic review. One randomised controlled trial (Kau et al., 2004) and one controlled trial (Sayin and Turkkahraman, 2006) were identified. Both of these studies investigated the effects of premature extraction of both lower primary canines. The remaining two studies used a cohort design (Clinch and Healy, 1959; Leighton, 1981). A summary of these studies and their key findings is shown in Table 1.

Key findings: PEPT lead to space loss on the affected side of the arch. Bilateral loss of primary canines led to reduction of the arch perimeter.

Split-Mouth Design

Ten studies were identified which used a split-mouth design assessing the effect of PEPT in a quadrant and comparing this to the opposite quadrant within the same arch where there were no premature extractions. This allowed intra-arch comparison. A summary of these studies and their key findings is shown in Table 2.

Key findings: Split-mouth studies were difficult to compare with each other as the criteria used to measure space loss varied and not all studies reported the same outcome. The first and second primary molar space was the most frequently used outcome measure used in four out of 10 studies and three of these studies showed reduction in space following PEPT.

Risk of bias

The risk of bias for all included studies is reported in Table 3. Only one study included in the review was identified as low risk of bias across all the domains (Kau et al., 2004). The remaining studies were frequently at high risk of bias across all the domains. None of the studies reported a power calculation. The methods used to reduce confounding was poorly described in most studies leading to high risk of performance bias. All studies reported on had at least one or more outcomes assessed. Although the duration of follow-up period was limited in most studies, attrition bias was low in both the controlled trials and most of the split-mouth studies.

Discussion

The results of this systematic review showed that PEPT led to various features of malocclusion and space loss in the permanent dentition. However, no studies were identified which assessed the consequences of PEPT and orthodontic need in the permanent dentition. The studies which assessed space changes following PEPT, concluded that space loss was a frequent consequence.

Methodology

All the included studies reported on an intervention group of PEPT with a comparator group of children who had not suffered PEPT. Any study reported without a comparison group was excluded from this systematic review, as the estimation effect for such studies is unlikely to be accurate. This is because dental arch measurements are not static and change systematically during periods of normal growth and development. However split-mouth studies where the extraction side or quadrant was compared to the non-extraction side were included. These studies were included to facilitate estimations of space changes although it was recognised that these studies would have limited value in studying the effects of PEPT on malocclusion as intra-arch relationship such as midline shift and ectopic eruption are also features of malocclusion. A recent meta-epidemiological study looking at intervention effects in split-mouth and parallel-arm randomised control trials did not find significant differences between the two study designs despite the nesting of data within the split mouth design which is not found in the parallel arm group (Smail-Faugeron et al., 2014).

Most studies included in this systematic review were identified from electronic databases such as MEDLINE and EMBASE. Indexing for these electronic databases have evolved with more subject heading are being introduced on a regular basis. For example, IOTN is now a Medical Subject Heading (MeSH) in MEDLINE since 2012, which was previously indexed under MeSH 'dental health surveys' and 'malocclusion' from 1975 to 2011. This review may have missed important studies prior to the development of MEDLINE (prior to 1946) and EMBASE (prior to 1947). Thus reference list searching and use of another electronic resource, PUBMED were also utilised. Free terms search using 'premature loss of primary teeth' in PUBMED identified four more studies that were not included in either MEDLINE or EMBASE. This could be because PUBMED also holds citations prior to 1966 that have not been updated with current MeSH headings (US National Library of Medicine, 2013).

Language of publication considered in this review was restricted to English. Restriction to English language only was chosen for pragmatic financial reasons. This may have led to a language bias. A recently published review concluded that there was no evidence of systematic bias where systematic reviews were restricted to English when assessing medical interventions (Morrison et al., 2012).

Quality of papers

Twenty-five studies were appraised for this review, of which seven were cross-sectional in their design. Cross-sectional studies were excluded from this review, as there is no temporal relationship of exposure to outcome. Time of exposure was particularly important for the subject of this systematic review as there was a defined period for PEPT depending on the dental age of the patient.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was developed in 2007 for the reporting of observational research (von Elm et al., 2007). STROBE was the most appropriate guideline as most of the included studies used an observational design rather than a randomised controlled design. None of the studies included in this review were adequately reported in comparison to CONSORT or STROBE statements. Many studies, however, were carried out prior to the development of these guidelines. Significant information was not reported in almost all studies identified and appraised in this review. Examples of these are the null hypothesis statement, selection criteria, sample size calculation, information about blinding of researchers or participants and levels of agreement (intra or inter examiner agreement. None of the studies included a flow diagram to show the number of participants at each stage of the study). Therefore this information was difficult to extract from these studies.

In this systematic review, it was evident that most of the studies did not have adequate follow-up periods. Only one study reporting on malocclusion had a follow-up period of approximately seven years. This was a case control study where information of PEPT was collected retrospectively by reviewing dental records (Hoffding and Kisling, 1978a; 1978b). Space studies using a split mouth design described follow-up periods ranging from one year (Sayin and Turkkahraman, 2006) to 10 years or more (Clinch and Healy, 1959; Leighton, 1981). Most of the split-mouth studies were followed for a short period of time, 5-12 months. The outcomes reported for these short follow-up periods must therefore be viewed with caution. However, an advantage of these shorter follow up periods was the reduction in attrition bias which was likely to increase with longer follow-up times.

The number participants included in the studies in this review ranged from 13 children (Padma Kumari and Retnakumari, 2006; Lin et al., 2011) to 550 children (Hoffding and Kisling, 1978a; 1978b). None of the studies reported a sample size calculation or outcomes based on the gender or ethnicity. The only exception was Northway et al. (1984) which included only French Canadian subjects which they defined as where three out of four grandparents were of that origin. Features of malocclusion depend on ethnicity, race and gender (El-Mangoury and Mostafa, 1990; Proffit et al., 2007). For example, Class II malocclusion was more prevalent among Europeans when compared to Oriental populations and Class III malocclusion was more prevalent among African and Oriental populations (Proffit et al., 2007). Class III malocclusion was three times more prevalent among males as compared to females in a population of 18 to 25 year old Egyptians (El-Mangoury and Mostafa, 1990).

All space change studies comparing PEPT with non-extraction comparator group included in this systematic review reported on crowding in the experimental group (Clinch and Healy, 1959; Ronnerman, 1977; Leighton, 1981; Kau et al., 2004). Split-mouth design studies mainly reported on the first and second primary molar space comparing the extraction side to the contralateral control side. Some of these studies reported on arch perimeter, thus allowing intra-arch comparison (Lin and Chang, 1998; Padma Kumari and Retnakumari, 2006; Park et al., 2009; Lin et al., 2011). There was one split-mouth study reporting on hemi-perimeter to compare the extraction side to the control side (Macena et al., 2011). Two studies (Venkaiah et al., 1974; Ronnerman and Thailander, 1977) concluded that the difference in space closure was insignificant. Split- mouth studies have a limited value as orthodontic need indices such as IOTN assess not only intra-arch discrepancies but also inter-arch discrepancies.

Northway et al. (1984) reported that the first and second primary molar space could be easily defined and monitored. However, other factors such as 'Leeway space of Nance' (Nance, 1947) could not be taken into account when reporting the first and second primary molar space. Similarly primate spaces are normal in the primary dentition, presenting mesial to the maxillary canines and distal to the mandibular canines (Baume, 1950). Thus, measuring the first and second primary molar space in mandibular arch does not take account of the primate space.

It was evident that various parameters used to report space loss, made comparison between studies difficult. It also remains unknown whether quantification of space using measurements such as arch perimeter and arch length were valid while undergoing normal dental and facial development especially during the mixed dentition phase (Moorrees and Chadha, 1965). However these measurements do provide information on the entire dental arch rather than an individual component of the dental arch. As a result of the inconsistent criteria used in the space studies, varied study designs and differing outcome measures used it was not appropriate to undertake a meta-analysis of the study results. Therefore a narrative synthesis was undertaken to enable comparison of the results for the space and split mouth studies.

The risk of bias assessment identified that most of the studies were at high risk of bias for each of the five specific criteria used. This means that significant caution is required in interpreting the results of these high risk studies. The Cochrane risk of bias quality assessment tool was easy to use, with disagreements between the reviewers rare (NB and PS) and resolved by discussion.

Discussion of results

No study examined the effect of PEPT on orthodontic need. Only one study met the inclusion criteria for this systematic review which studied the effects of PEPT on malocclusion. Hoffding and Kisling (1978a, 1978b) study looked at various features of malocclusion including maxillary overjet $\geq$ 6 mm, class II malocclusion of at least half unit, class III malocclusion at least half unit, spacing discrepancy of at least 2 mm.. However, malocclusion was not quantified using any established and validated index. Clinically, the most relevant and appropriate method of reporting orthodontic need would be to use an index such as the IOTN. This would provide clinically important conclusions based on a set of outcomes that are well recognised and used widely by clinicians. However, IOTN was only developed in 1989 and the only study reporting on malocclusion included in this review was prior to this date.

Comparison of the studies with PEPT group compared to non-extraction group was difficult as none of the studies reported on the same outcome measure permitting comparison between studies. The intervention group also varied as some studies were reporting specific cases such as two controlled trails reported on bilateral extraction of lower primary canines and consequences of this (Kau et al., 2004; Sayin and Turkkahraman, 2006). Both of these studies reported that PEPT related to bilateral mandibular primary canines led to reduced arch perimeter and mandibular incisor crowding. Other studies agreed with this finding space loss and hence crowding report when comparing the PEPT group with the non-extraction group. Most of these studies reported on more than one outcome measure but none of them specified which outcome was used as the primary outcome.

Reporting of the split-mouth studies was more consistent and many of the studies in this group reported on the primary molar space. However, these studies had limited value as they were unable to describe normal dental arch changes within an arch. Thus these split-mouth studies may have led to overestimation of the effect of PEPT on space. It has been established that a small amount of mandibular incisor crowding during eruption of these teeth is considered normal (Moorrees and Chadha, 1965). Some of these studies reported that arch perimeter increased following PEPT (Park et al., 2009; Lin et al., 2011). This shows the difficulty in describing the effect of PEPT from normal physiological growth and development. Furthermore occlusal factors such as crowding and lack of space, drifting patterns of various teeth and intercuspation of first permanent molars could potentially affect space loss and its resultant consequences.

Future work

The results of this systematic review showed the need for further well-designed studies to evaluate the effects of PEPT on malocclusion in the permanent dentition. This would need to cover a long follow up period of approximately 10 years. Where possible any underlying malocclusion in the primary dentition should be recorded prior to PEPT as these can influence future malocclusion in the permanent dentition (Peres et al., 2015). Observational study designs such as prospective cohort would be most appropriate although there are significant costs in recruiting and maintaining a suitable cohort. An alternative design, such as a randomised controlled trial, would be appropriate when studying the benefits and disadvantages of space maintenance or extraction versus restoration of primary teeth. Such studies would therefore require a long follow up period and use reliable and validated outcome measures such as IOTN.

Conclusions and Recommendations

The studies assessing the consequences on developing dentition following PEPT were mostly either cross-sectional or cohort studies using small samples. There have been no randomised controlled studies looking at the effects of PEPT on malocclusion and subsequently on orthodontic need resulting from PEPT. There has been a lack of standardised, valid and reproducible methods to quantify space loss.

SIGN guidelines available from http://www.sign.ac.uk were used for evidence statements and grades of recommendations. The following recommendations are drawn from the basis of this systematic review.

- No study examined the effect of PEPT on orthodontic need.

- PEPT increased the frequency of at least one feature of malocclusion (features of malocclusion included were maxillary overjet ≥ 6 mm, class II malocclusion of at least half unit, class III malocclusion at least half unit, spacing discrepancy of at least 2 mm) (Evidence level 2+, Recommendation grade C).
- PEPT increased the frequency of crowding in the permanent dentition (Evidence level 2+, Recommendation grade C).
- PEPT lead to space loss on the affected side of the arch (Evidence level 2+, Recommendation grade C).
- PEPT of lower primary canines bilaterally led to reduced arch perimeter (Evidence level 1+, Recommendation grade B).

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Figure Legends

Figure 1. Flowchart illustrating the effect of premature extraction of primary teeth (PEPT) leading to malocclusion.

Figure 2. Flowchart of the study selection process for PEPT and malocclusion

Table legends

Table 1. Summary characteristics of the space studies comparing Premature Extraction of Primary Teeth (PEPT) with non-extraction as the comparator group.

Table 2. Summary characteristics of the space studies comparing Premature Extraction of Primary Teeth (PEPT) with the non-extraction group with split mouth design.

Table 3. Risk of bias of the included studies.

Figure 1. Flowchart illustrating the effect of premature extraction of primary teeth (PEPT) leading to malocclusion.

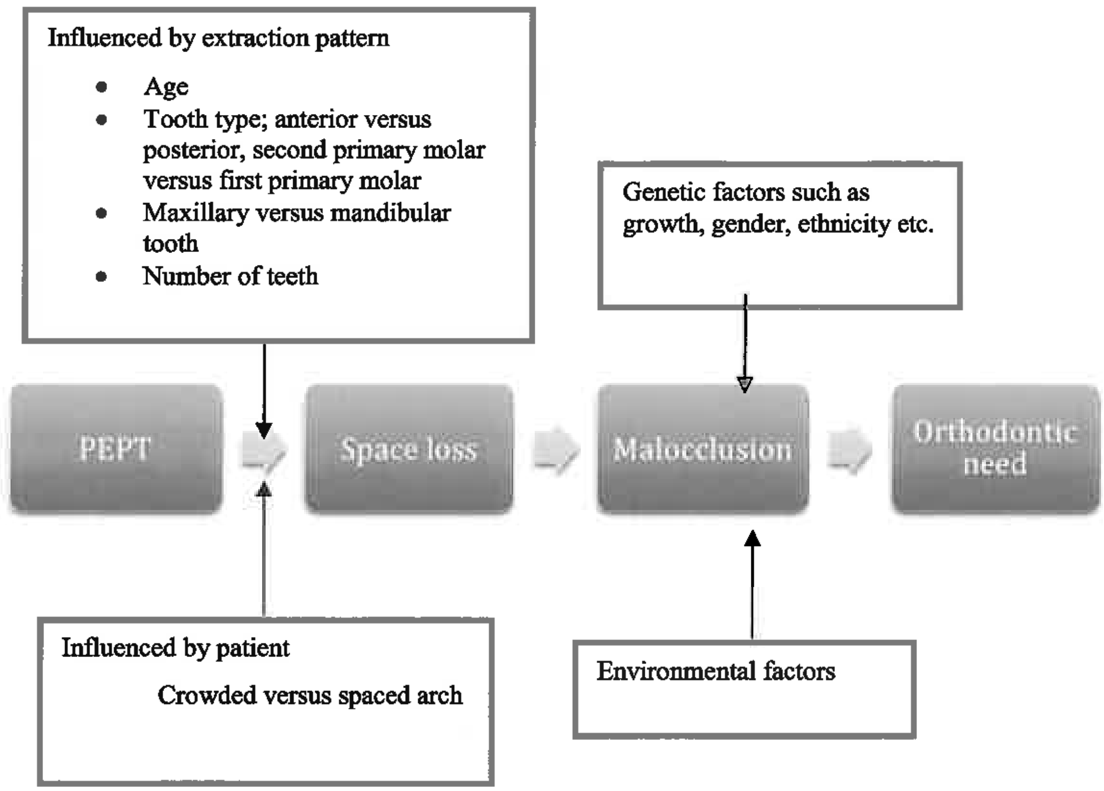

Figure 2. Flowchart of the study selection process for Premature Extraction of Primary Teeth (PEPT) and malocclusion

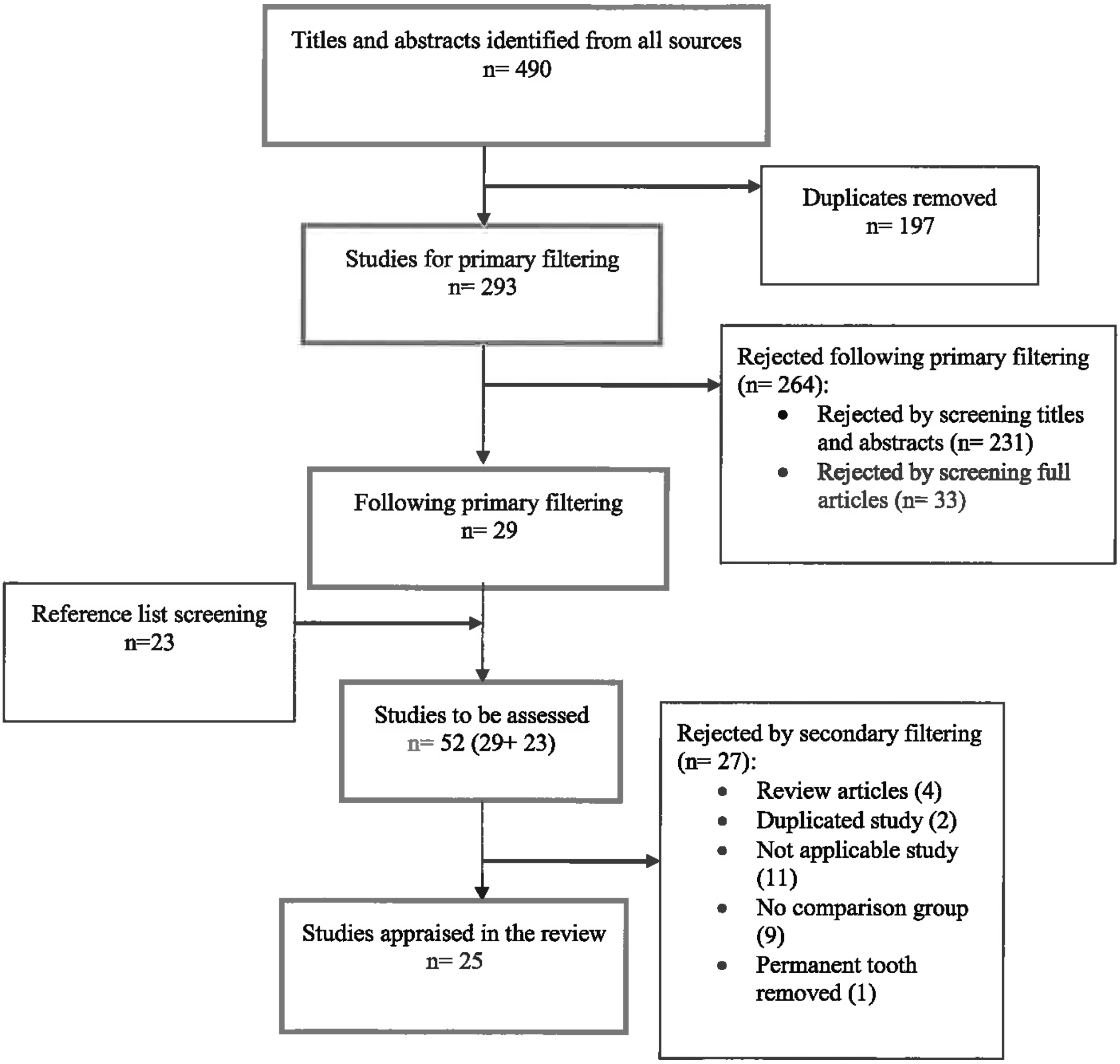

Table 1. Summary characteristics of the space studies comparing Premature Extraction of Primary Teeth (PEPT) with non-extraction as the comparator group.
PC = prospective cohort; RCT = randomised controlled trial; RC = retrospective cohort; CT= controlled trial

Author	Design	No of subjects	Age (Years)	Follow-up period	Intervention	Outcomes	Main findings
Clinch and Healy (1959)	PC	59	3-4	9-11 years	History of PEPT of primary first and/or primary second molar. (29/59 children)	Space loss.	Early extraction cases in maxillary premolar-molar segment lost an average of 6.18 mm when compared to late loss (after the age of 3-4 years) of 3.52 mm. Corresponding results for mandibular arch were 3.93 mm, 3.99 mm respectively.
Ronnerman (1965, 1977)	RC	187	12.9	-	History of PEPT of primary molars. (161/187 children)	Space loss. Incidence of crowding.	Loss of one primary molar in a quadrant when a tooth was lost before 7.5 years resulted in less relative space compared to when a tooth was lost after 7.5 years. The proportion of children with severe crowding (>3.5mm) was greater in the intervention group. Maxillary arch 24% compared to control group of 13% and mandibular arch 27% compared to control group of 8%.
Leighton (1981)	PC	36	3-4	13-22 years	History of PEPT of mandibular primary molars. (18/36 children)	Arch perimeter. Space.	Arch perimeter showed significant changes in the intervention group, -5.07 mm compared to the control -3.26 mm. The intervention group showed reduction in space, -3.13 mm compared to the control -0.34 mm.
Kau et al. (2004)	RCT	97	8-9	1 year (min)	Premature extraction of both mandibular primary canines. (55/97 children)	Arch perimeter. Crowding index.	Arch perimeter reduced more in the extraction group, 2.95 mm compared to the control 1.51 mm. The crowding difference was significant at 6.03 mm in the extraction group compared to 1.27 mm control group.
Sayin and Turkkahraman (2006)	CT	32	8.91	1 year (min)	Premature extraction of both lower primary canines. (16/32 children)	Arch length. Intermolar width. Interalveolar width. Molar position.	Mandibular incisors were significantly more retruded in the intervention group. Changes in arch length, intermolar width and interalveolar width were similar between the intervention and control group.

Table 2. Summary characteristics of the space studies comparing Premature Extraction of Primary Teeth (PEPT) with the non-extraction group with split mouth design.

PC = prospective cohort; RCT = randomised controlled trial; RC = retrospective cohort

Author	Design	No of subjects	Age (Years)	Follow-up	Intervention	Outcomes	Main findings
Linder-Aronson (1960)	RC	41	14-15	-	Unilateral loss of primary canine, first primary molar and/or second primary molar	Arch hemi-perimeter	Hemi-perimeter on extraction side (mean -0.40+/-0.38mm) compared to control side (mean 0.16+/-0.34) was not significantly different.
Venkaiah et al. (1974)	PC	30	8-11	5 months	Unilateral extraction of first primary molars.	Extraction space. (poorly defined)	Difference in space closure in the extraction group compared to the control group was statistically insignificant (Mean of 0.85mm vs 0.65mm in the maxillary arch and mean of 0.60 vs 0.60mm in the mandibular arch).
Ronnerman and Thailander (1977)	PC	65	-	9, 11 & 13 years	27 cases of unilateral loss of first primary molar and 38 cases of unilateral loss of second primary molar.	Incisor and canine-premolar segment.	Unilateral loss of maxillary first molar led to significantly less space at 9 yrs compared to the control. At the age of 13 yrs, the difference was insignificant.
de Boer (1982)	PC	446	5	9-10 years	21 maxillary and 27 mandibular arches with unilateral molar loss.	Space between lateral incisor to first permanent molar	Extraction of second primary molar at the age of 5-6 years led to space loss; 8 mm in maxillary arch and 6.5 mm in mandibular arch.
Northway et al. (1984)	PC	107	-	5.9 years	71 children with premature extractions of primary molar/s compared to the contralateral non-extraction quadrant.	first and second primary molar space.	Maxillary arch: average yearly first and second primary molar space loss were 0.3 mm, 0.7 mm and 0.9 mm for first primary molar loss, second primary molar loss and both primary molar loss respectively. By the age of 8 years, extraction groups were significantly shorter than the controls By the age of 6 years, all maxillary extraction groups were significantly shorter than the controls (t=2.2 for first primary molar loss, 4.2 for second primary molars loss and 3.5 for both primary molars loss). Mandibular arch: 0.5 mm, 0.9 mm and 0.7 mm respectively. All extraction groups significantly shorter than the controls.
Lin and Chang (1998)	PC	21	6-7	8 months	Unilateral loss of mandibular first primary molar.	Arch perimeter, arch length, arch width and first and second primary molar space.	First and second primary molar space was significantly shorter on the extraction side after 8 months (16.84± 1.86mm) than the control side (17.83± 1.3mm).
Padma Kumari and Retnakumari (2006)	PC	30	6-9	8 months	Unilateral loss of mandibular first molar.	Arch perimeter, arch length, arch width and extraction space.	Mandibular first molar 'space' in extracted side showed significant reduction at 2, 4, 6 and 8 months, values were 7.77 mm, 7.03 mm, 6.62 mm, 6.4 mm (Vs 8.33 mm, 8.32 mm, 8.33 mm and 8.2mm for the control sides).
Park et al. (2009)	PC	13	7-8	8-23 months	Unilateral loss maxillary first primary molar.	Arch perimeter, arch length, arch width and first	The mean first and second primary molar space change on the extraction and control side was 0.57± 0.83 mm and 0.31± 0.38 mm respectively (not statistically significant.)

						and second primary molar space.	
Lin et al. (2011)	PC	13	6	12 months	Unilateral loss of maxillary first primary molar.	Arch perimeter, arch length, arch width and first and second primary molar space.	First and second primary molar space was significantly shorter on extraction side than control after 12 months (15.84 mm vs 16.92 mm).
Macena et al. (2011)	PC	55	8-9	10 months	Unilateral loss of first and/ or second primary molar.	Arch hemi-perimeter and arch length.	Arch hemi-perimeter following extraction of lower second primary molars reduced significantly in 10 months (differences in mean 0.6+/-0.6mm vs 0.1+/-0.6mm).

Table 3. Risk of bias of the included studies

Author	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
Clinch and Healy (1959)	High	High	High	High	High
Linder-Aronson (1960)	High	High	High	High	High
Ronnerman (1965) Ronnerman (1977)	High	High	High	Unclear	High
Venkaiah et al. (1974)	High	High	High	Low	High
Ronnerman and Thilander (1977)	High	High	High	Unclear	High
Hoffding and Kisling (1978)	High	Unclear	High	Unclear	High
Leighton (1981)	High	High	High	Unclear	High
de Boer (1982)	High	High	High	Unclear	High
Northway et al. (1984)	High	Low	Low	Low	Low
Lin and Chang (1998)	High	Low	High	Low	Low
Kau et al. (2004)	Low	Low	Low	Low	Low
Padma Kumari and Retnakumari (2006)	High	High	High	High	Low
Park et al. (2009)	High	Low	High	Low	Low
Lin et al. (2011)	High	Low	Low	Low	Low
Macena et al. (2011)	High	Low	Low	Low	Low

(High) = high risk of bias; (Unclear) = unclear risk of bias; (Low) = low risk of bias