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Prevalence of hypodontia and associated factors: A Systematic Review

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INTRODUCTION

Hypodontia, also known as selective tooth agenesis or congenital tooth absence, is the developmental absence of at least one permanent tooth and is a common dental anomaly in man (Endo et al. 2006). Hypodontia may occur either as part of a syndrome or as a non-syndromic form. Non-syndromic hypodontia is more common, with varying numbers of teeth that can be involved; however, the incisor-premolar type predominates (Nieminen et al. 1995). The permanent dentition is much more affected than the primary, where hypodontia is reported to be rare (Cobourne, 2007). Oligodontia is defined as the congenital absence of six or more teeth, excluding third molars. Anodontia is the most severe form of hypodontia and involves absence of the entire permanent or primary dentition. It is very rare without an accompanying genetic syndrome, such as ectodermal dysplasia (Gorlin et al. 1980).

Previous meta-analysis have shown high variation in the prevalence of hypodontia between populations, which differs significantly between males and females. In the majority of the examined studies, females were more often affected by hypodontia than males and the highest prevalence was found in the Chinese population (7.7% in women and 6.1% in men). In contrast to this trend, the lowest prevalence rate of 2.2% was found in the Saudi Arabian women (Mattheeuws et al. 2004; Polder et al. 2004)

Brook's unifying aetiological explanation for anomalies of tooth number and size (Brook, 1984; Brook et al. 2009a) suggests that developmental dental anomalies such as hypodontia are caused by a number of complex interactions between genetic, epigenetic and environmental factors during the process of dental development. Some environmental factors which cause tooth anomalies (not necessarily hypodontia) include fluoride, tetracycline, low birth mass, malnutrition, vitamin D deficiency, infections and metabolic disorders (Winter, 1996; Brook et al. 2009a). The developmental anomaly tends not to be specific in relation to the environmental insult encountered (*e.g.* a toxin) but rather is dependent on the timing,

magnitude and duration of the insult, as well as the degree of dental development and the host susceptibility (Brook et al. 2009a).

Several studies (Keene, 1966; Boruchov and Green, 1971; Alaluusua et al. 2004; Marec-Berard et al. 2005; Keller et al. 2007; Yamaguchi et al. 2008; Parkin et al. 2009; Pedersen et al. 2012) have indicated that environmental factors (allergy, dioxin, chemotherapy, maternal illness and birth weight) may affect the prevalence of hypodontia. The observation that certain teeth tend to be affected in hypodontia cases and that these anomalies are often present in more than one family member suggests a prominent role for genes in hypodontia (Cobourne, 2007). Further evidence for the roles of genetic factors in the aetiology of hypodontia has been provided by many other studies (Erpenstein and Pfeiffer, 1967; Alvesalo and Portin, 1969; Vastardis et al. 1996; Ahmad et al. 1998; Goldenberg et al. 2000; Arte et al. 2001; Pirinen et al. 2001; Thesleff, 2006; Nieminen, 2009).

The purpose of this systematic review was to determine the prevalence of hypodontia and associated factors. Specifically, we aimed to update the meta-analyses by Polder et al. 2004 and Mattheeuws et al. 2004.

MATERIAL AND METHODS

For the assessment of the revealed studies we followed the STROBE guidelines for reporting observational studies (von Elm et al. 2007). PRISMA guidelines were followed when conducting this systematic review (Moher et al. 2009).

Types of Publications

Only studies concerning hypodontia of the permanent dentition were included, due to the fact that hypodontia is rare in the primary dentition and is not considered to be an important clinical issue to address. Studies on the prevalence of hypodontia related to genetic conditions, such as Down syndrome and van der Woude syndrome, ectodermal dysplasia and

cleft lip and palate were also excluded if no control subjects without these conditions were compared. The prevalence of hypodontia associated with the third molars was also excluded because of the high prevalence of this condition, with at least one third molar missing in 20-30% in European populations (Grahnen, 1956; Haavikko, 1971; Neal and Bowden, 1988).

This review was limited to articles published after 2002 because the meta-analyses by Polder et al. 2004 and Mattheeuws et al. 2004 summarised previous publications. For articles which were not published in the English language, data was taken from the English abstract where possible. The following publication types were excluded: letters, editorials, post-graduate theses, case reports, randomised controlled trials and reviews.

Outcome Measures

Primary outcome_The primary outcome measure of this review was overall prevalence of hypodontia, excluding third molars.

Additional outcomes_Prevalence of hypodontia by other factors, including population type, continent, gender, type of malocclusion, number of missing teeth, type of missing teeth, upper and lower jaws, geographic region, patients with cleft lip and palate, patients with systematic conditions, patients with a family history and race.

Literature Search

The electronic literature search on the prevalence of hypodontia was carried out for papers published from 2002 to August 2012 using two databases – MEDLINE and Embase, with the intention of retrieving all original reports since 2002 that were relevant to the aims and objectives of this study. The keywords used for the search were 'hypodontia' or 'anodontia' or 'oligodontia' or 'agenesis' and 'prevalence' or 'incidence' or 'epidemiology' and 'teeth' or 'tooth' or 'dental' (See Appendix 1 for detailed search strategy). The search was also limited to studies of humans. The original MEDLINE search was adapted to EMBASE. Selected results from each database were combined and the duplicates were removed.

Following the search of MEDLINE and Embase, a Google search was conducted to find any relevant papers, which might have been missed. Hand searching of reference lists in selected articles was also carried out. Only papers with an abstract in the English language were included and for full articles not published in the English language, data was taken from the English abstract where possible.

Data collection

Two reviewers independently read the abstracts of all reports retrieved through the electronic searches. Each reviewer classified articles as selected, not selected, or unsure if information from the title and abstract was not sufficient to make a decision. These results were compared between the two reviewers and, where there were disagreements, they were discussed and a final decision was made. Full texts were obtained for each study that met the inclusion criteria based on the abstract and these were further assessed for eligibility for inclusion in the systematic review.

Data Extraction

For all selected studies, data were extracted using a specially designed data extraction form. The data included first author, year of publication, country of study, study design, characteristics of the study population, the method of measurement (radiographic, clinical, both), number of participants, gender distribution, age, participation rate and prevalence of hypodontia overall and by age, gender or distribution of missing teeth in the jaw.

Quality Assessment

Quality assessment of the selected original studies was conducted using a specially designed form based on the STROBE guidelines for reporting observational studies (von Elm et al. 2007). The form contained eighteen elements which aimed to assess the reporting of aims and objectives of the study, study design, sample size, participant selection process and criteria, as well as the statistical methods employed, principal findings and validity and reliability of

the results reported. The options for each element were 'yes', 'no' or 'unable to determine'. Quality assessment of reviews and meta-analyses was carried out according to the PRISMA statement (Moher et al. 2009).

Statistical Analysis

Information from data extraction forms and quality assessment data were entered in a specially designed spreadsheet and analysed statistically using IBM SPSS Statistics version 20 (2011). Meta-analysis of the prevalence of hypodontia was conducted using comprehensive meta-analysis software (Borenstein et al. 2005).

The main outcome measure (prevalence of hypodontia) was reported as an event rate (and 95% CI). We investigated the relationship between hypodontia and other factors using Risk Ratio (RR) and 95% CI. The random effects model was used for combining the results of studies in the meta-analysis to account for within-study and between-study variation as it was considered to be more conservative than a fixed effects model and was appropriate in the presence of such high heterogeneity. Heterogeneity of data was evaluated using the I^2 statistic, which estimates the percent of observed between-study variability due to heterogeneity rather than to chance and ranges from 0 to 100%. A value of 0% indicates no observed heterogeneity whilst 100% indicates significant heterogeneity. For this review, we determined that I^2 values above 90% were indicative of significant heterogeneity warranting analysis with a random effects model as opposed to the fixed effects model to adjust for the observed variability. Confidence intervals for I^2 statistics were calculated using the method described by Thorlund et al. 2012.

RESULTS

Search results

Search results are presented in Figure 1. Following the literature search strategy described previously, the database MEDLINE revealed 138 results and EMBASE 147, respectively. Additionally, the Google search added 12 and the hand search provided a further 6 articles, summing up to a total of 303 potentially relevant papers. After excluding the duplicates and scanning the titles and abstracts for relevance, 76 papers remained in the selection. The full texts of the articles were assessed and 15 articles were excluded because either no full texts in the English language were available and their abstracts did not provide sufficient information, or the full texts were rated as not relevant. Seven out of 61 studies were reviews and therefore were excluded. Fifty four studies were finally included for this review of which, 3 were not written in the English language but because their abstracts provided sufficient information on the prevalence of hypodontia, those studies were evaluated where possible.

Description of studies

A total of 93 studies were included in this review, of which 39 studies were taken from the previous two systematic reviews on this subject (Mattheeuws et al. 2004; Polder et al. 2004) (Table 1). The full texts of three studies were not available in the English language but the abstracts were included and the information analysed where possible. The participation rate was presented in only 4 out of 53 examined studies. In the majority of the studies the participation rate was not applicable because medical records, such as radiographic views and dental casts were examined at time points earlier in the participants' history. In some studies, the number of radiographic views excluded due to insufficient quality was presented but not included in the participation rate analysis because these numbers did not reflect the participants' willingness to take part in a study. Two out of the 4 studies which gave information on the participation rate were cross- sectional studies in two populations (Chalothorn et al. 2008; Saeves et al. 2012) one retrospective cohort study (Keller et al. 2007)

and one cross- sectional study (Goren et al. 2005) in which the number of participants out of the total number of randomly chosen army recruits was mentioned in its abstract.

The majority of the studies (94%) were designed as cross-sectional. Four studies (4.3%) were cross-sectional studies with two populations and were not included in the prevalence analysis but were considered when examining factors associated with hypodontia. In those studies the prevalence of hypodontia was investigated in people with one of the following features: Prader- Willi syndrome (Saeves et al. 2012), at least one missing third molar (Cantekin et al. 2012), cleft lip and palate (Camporesi et al. 2010), or epithelial ovarian cancer (EOC) (Chalothorn et al. 2008), was compared to a group without these conditions. One retrospective cohort study (1%) (Alaluusua et al. 2004) examined the risk of tooth agenesis in humans exposed to high levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in childhood to those of unexposed regions. One case-control study (1%) conducted cephalometric and area measurements in individuals with hypodontia and compared them with an age- matched group from the Bolton growth study. The participants were recruited from schools in 31% of all studies, followed by orthodontic clinics (30%) and dental surgeries (22%). Students and army recruits were selected in three studies (3%), each. In four studies (4%) the study population was not stated and in six studies (7%) the study design implicated that two or more groups were compared and selected from different sources of the population. Most of the studies were conducted in European countries (43%), the Asian region (32%) and Northern America (14%). Four studies were conducted in Latin America and Caribbean, two in Oceania and one in Africa. In three studies the country was not described.

Almost 50% of the studies were published after 2005. The sample size of selected studies varied from 89 to 100577, with a median of 1291. The age of the study participants ranged from 3 to 71 years. The prevalence showed a high variation between the studies. The

lowest prevalence was 0.10% and the highest 73.40% with a median of 6.10%. For this analysis only cross-sectional studies with one population were considered. Studies which reported only the agenesis of specific teeth and all studies which included missing third molars in their reported prevalence were excluded.

Quality assessment

Results of quality assessment are presented in Table 2. All abstracts summarised the main content and results of the study whereas the title or abstract provided no apparent information about the study design in 57% of all articles. The research question was clearly defined in all papers and in 98% of the articles the design was rated as appropriate for the specific objectives. The study setting was described in 44 papers. The method of participant selection as well as sample size and gender distribution, and study population type were described in most of the studies, with 72%, 87% and 93%, respectively. However, the majority of articles (85%) did not provide information about the justification for sample size. The diagnostic criteria and outcome measurements were clearly described in 32 papers (59%) regarding the possible modifiers and confounders such as missing teeth due to extraction. There was an almost equal number of papers which gave information about the validity and reliability of the examination methods (46%) and which did not (48%). The methods used in the statistical analyses were mentioned in 38 articles (70%) and the majority of studies reported the number of subjects analysed (94%). The main study findings were most often described in relation to the original aims and objectives (96%), and 44 papers (82%) discussed the external validity of the findings. A lack of information was found for the reporting of the results with a 95% confidence interval (CI) (24%), the referring to any limitations within the study and its results (33%) and a statement about the source of funding and competing interest of the authors.

Factors considered

Studies reported different factors related to the prevalence of hypodontia (Table 3). Three abstracts (full papers not in the English language) were excluded because they did not provide sufficient information. In five out of the total of 51 papers the prevalence of hypodontia was described by age group. Most of the studies (86%) gave separate data for males and females. The type of jaw (maxilla/ mandible) or right/ left side in which hypodontia occured was reported in 34 papers (67%) and in some the number of tooth agenesis was compared between the locations.

In 39% of the papers subjects with missing teeth were categorized in groups showing the severity of hypodontia raising from 1,2,3,4,5 to 6 or more missing teeth in the individual jaw. A detailed description of which teeth were missing in the jaws of the affected individuals was found in 53% of all studies, mostly using the World Dental Federation notation for presenting their findings.

Other dental anomalies were examined in 19 studies such as hyperdontia, impaction, dilacerations, microdontia, ectopic eruption, transposition and transmigration. In addition to this, some studies explored other oral findings including salivary flow rate, dental caries, enamel defects and gingival inflammation. Five studies concentrated on the agenesis of specific teeth such as the lateral incisors, canines or second molars. The occurrence of tooth agenesis in people living in different geographic regions were compared in four studies of which, one examined people living in a region with a high TCDD exposure after a dioxin accident with people of another unexposed area. One study compared hypodontia rates in people with black and white skin colour. The malocclusion type was considered in seven papers, and one paper reported the distribution of the selected orthodontic treatment option (space opening or space closure). Cephalometric and area measurements were made in one study and the general health status was considered in one further paper in which allergy was reported in people with hypodontia and without. Furthermore two studies compared the

number of people with hypodontia in cleft lip and palate patients with those without. Moreover, one study examined if people with missing third molars have a higher risk for the agenesis of further teeth. One study concentrated on the genetic reason for the occurrence of hypodontia and its association with ovarian cancer.

Prevalence by population type

Figures 2-4 show the prevalence of hypodontia by population type. Sixty nine papers were divided into the categories of schoolchildren, orthodontic patients or dental patients. Three studies which were assumed to contain both dental and orthodontic patients were allocated to the orthodontic group (Gabris et al. 2006; Abu Shakra and Alqaqaa, 2008; Aktan et al. 2010). Studies that were not considered in these categories were: 6 studies with a design of not cross-sectional in one population, 3 studies examining army recruits and 3 students, 5 studies which concentrated on the absence of specific teeth, 4 in which the population type was not mentioned and 3 which only gave prevalence figures of hypodontia including missing third molars.

Due to a high heterogeneity between studies (I^2>90%) a random effect model was used for combining results of studies in the meta-analysis. The combined prevalence in schoolchildren, dental patients and orthodontic patients was found to be 6.4% (CI: 5.6-7.3%), 6.7% (CI: 4.7-9.4%) and 6.0% (CI: 4.2-8.7%) respectively. There was no statistically significant difference in prevalence between the 3 groups (Q=0.175, P=0.916). Therefore, we combined the populations (overall prevalence 6.4% (CI: 5.7, 7.2%) in order to investigate other factors.

A Funnel plot and Kendall's Tau showed some evidence of publication bias (-0.23; P=0.005).

Prevalence by continent

There was a statistically significant difference in the prevalence of hypodontia by continent (Q=34.18, P<0.001). The prevalence of hypodontia was highest in Africa (13.4%, CI: 9.7-18.0%) but this was based on one study only (Maatouk et al. 2008). This was followed by Europe (7%, CI: 6.0-8.0%), Asia (6.3%, CI: 4.4-9.1%) and Australia (6.3%, CI: 5.3-7.4%) with a lower prevalence in North America (5.0%, CI: 4.1-5.9%) and Latin America and Caribbean (4.4%, CI: 3.2-6.1%).

Prevalence by gender

Females had a higher prevalence compared to males (Figure 5). The combined odds ratio (OR) for the prevalence of hypodontia in females compared to males was found to be 1.22 (CI: 1.14-1.30).

Prevalence by type of malocclusion

The prevalence of hypodontia by malocclusion type is given in Table 4. Only 5 studies provided sufficient information. Al-Moherat et al. 2009 examined the distribution of hypodontia cases with one to three missing teeth between the malocclusion classes 1-3 and found a significant relationship between the number of absent teeth and the type of malocclusion. All studies, but one (Kim, 2011) showed a higher prevalence in Class III. The combined OR for Class III compared to class I or II was 2.15 (95% CI 0.78, 5.89).

Prevalence by number of missing teeth

Table 5 summarises the studies which give information on the number of people with 1, 2, 3, 4, 5, 6 and more missing teeth. The prevalence of persons with missing 1, 2, 3, 4, 5, 6 or more was found to be 41.9% (CI: 36.1-48.0%), 39.7% (CI: 0.35-44.5%), 7.2% (CI: 6.1-8.5%), 5.4% (CI: 4.2-7.0%), 1.7% (CI: 0.9-3.2%) and 3.1% (CI: 1.5-6.4%), respectively.

Prevalence by type of missing teeth

Table 6 shows a detailed distribution of the missing teeth in both jaws and only included studies which presented data on the detailed distribution of missing teeth and studies which

concentrated on the absence of single teeth like the lateral incisors. The most commonly missing teeth were found to be in descending order L5 (29.9%), U2 (24.3%), U5 (13.7%), L1 (6.1%), L2 (4.3%), U4 (3.6%), L4 (2.7%), U3 (2.5%), L7 (1.8%), U7 (1.5%), L3 (1.3%), U6 (1.1%), L6 (1%), U1 (1%)

Table 7 is similar to Table 6, but the results of studies listed in this table were given as the percentage of people with missing teeth by tooth type as a proportion of the total number of subjects with tooth agenesis.

Prevalence by upper and lower jaws

Table 8 shows the location of missing teeth in the maxilla and mandible. A higher percentage of missing teeth were located in the maxilla (combined prevalence of 53.2% (CI: 49.3-57%) compared with 46.8% (CI: 43-50.7%) in the mandible).

Prevalence by geographic region

Behr et al. 2011 compared the prevalence of hypodontia in subjects from Regensburg, Germany, with those from various geographic regions outside Regensburg, and found statistically significant differences. Alaluusua et al. 2004 who concentrated on the impact of dioxin exposure in childhood on the dental germ in the permanent dentition concluded that hypodontia was associated with TCDD exposure in childhood. The paper by Kim, 2011 evaluated patients from two geographically separated orthodontic clinics, one private local clinic and the other a general hospital. He did not find statistically different prevalence rates between both clinics (95% CI for odds ratio: 0.966, 1.513). Aktan et al. 2010 included patients from 6 different regions of Turkey and detected relationships between congenitally missing teeth, gender and region.

Prevalence in patients with cleft lip and palate

Behr et al. 2011 collected data on the prevalence of cleft lip and medical syndromes (ectodermal dysplasia, Down syndrome, Goldenhar syndrome and Apert syndrome) and data

on hypodontia in the study sample but did not present a prevalence ratio. The study by Camporesi et al. 2010 compared the prevalence of dental abnormalities such as hypodontia in children with unilateral (UCLP) and bilateral cleft of the lip and palate (BCLP), with a control group. Their results showed that the absence of lateral incisors was significantly greater in UCLP and BCLP groups when compared with the control group without cleft lip and palate.

Prevalence in patients with systematic conditions

The paper by Yamaguchi et al. 2008 reported a significant positive correlation between hypodontia and the presence of at least one health problem or allergy. A significant difference in the prevalence of hypodontia was found between epithelial ovarian cancer (EOC) patients and controls, with an 8.1 risk increase in EOC patients (Chalothorn et al. 2008). Hypodontia in subjects with Prader- Willi syndrome (PWS) was significantly more common in comparison to a control group ($p<0.001$) (Saeves et al. 2012).

Prevalence of hypodontia in patients with a family history

A family survey on hypodontia conducted in Sayada, Tunisia (Maatouk et al. 2008) has shown that congenitally missing teeth was likely to be transmitted as an autosomal dominant inheritance trait. However, this study had some limitations due to the incomplete family trees detected in the study. In the study by Spahic-Dizdarevic et al. 2011 no reliable results could be provided for the inheritance of hypodontia. Chalothorn et al. 2008 reported that EOC patients had more often a family history of hypodontia and ovarian cancer ($p= 0.0001$) and ($p=0.0031$), respectively. These statistically significant findings indicate a possible molecular link between hypodontia and EOC in specific genes.

Prevalence of hypodontia by race

A significantly lower prevalence of hypodontia was found in black than in white people in the study by Harris and Clark, 2008 (odds ratio 2.52). They concluded that study results of white subjects did not readily apply to American blacks or, potentially, to other racial groups.

Within Asia, there was no statistically significant difference (Q=1.683; P=0.431) between oriental countries (China, Hong King, Japan and South Korea; 7 studies) and the rest (Saudi Arabia, Jordan, Turkey, Iran India and Pakistan; 18 studies) (7.5% CI 5.8-9.6 and 6.0% CI 3.8-9.4, respectively).

Prevalence of hypodontia by time

Figure 6 shows meta-regression of year of publication on prevalence. There was a very small decrease in the prevalence of hypodontia over time (slope -0.002, P<0.001).

DISCUSSION

Our findings confirm that the prevalence of hypodontia shows high variation between previous studies and that females had higher prevalence than males. This meta-analysis included data from the meta-analysis by Polder et al. 2004 which also showed large variation in the prevalence of hypodontia– ranging from 0.3% (Rosenzweig and Garbarski, 1965) to 36.5% (Mahaney et al. 1990). The large variation in the reported prevalence may be explained by differences in the methods of sampling and examination, as well as the distribution of age, sex, and racial origin of the subjects, or by the multi-factorial aetiology of hypodontia including environmental and genetic factors.

Following application of the inclusion and exclusion criteria, Polder et al. 2004 were left with 31 studies. This meant that the number of individuals in the meta-analysis was still large enough to make valid conclusions on a number of key issues in relation to the prevalence of hypodontia. Polder et al. 2004 showed that tooth agenesis varied between populations and between genders. European and Australian individuals had a significantly

higher prevalence of hypodontia than North Americans. This was also found in our systematic review and furthermore it was found that African individuals had a significantly higher prevalence of hypodontia than Europeans, Asian and Australians, North Americans and Latin Americans and Caribbeans. However, the prevalence of hypodontia in Africa was based on one study only (Maatouk et al. 2008). This may provide further evidence for the hypothesis that racial background is a vital determinant of the prevalence of congenital absence of teeth (Niswander and Sujaku, 1963; Rosenzweig and Garbarski, 1965; Eidelman et al. 1973; Simons et al. 1993; Harris and Clark, 2008). When comparing the figures of the prevalence of hypodontia in Polder et al. 2004 study and our systematic review it appears that the prevalence of hypodontia has increased over time in Asia (from 4.7% to 6.3%), Europe (from 5.5% to 7%) and to some degree in North America (from 3.9% to 5%). This small increase in the prevalence of hypodontia may most probably be attributed to the inclusion of more studies reporting the prevalence of hypodontia in our systematic review. Another reason to the differences found between Polder et al. 2004 and our study may be due to the exclusion of studies of orthodontic patients in Polder et al. 2004 study. However, in our systematic review we found no statistically significant differences in the prevalence of hypodontia between population type i.e. schoolchildren, dental and orthodontic patients. Polder et al. 2004 also postulated a link between aetiological factors in Scandinavian and Swiss populations based on a higher prevalence found in studies from these countries in the years 1971-1980 than was reported in other countries. However this was a speculation, rather than a fact backed up with statistical analysis.

When comparing the sexes across schoolchildren and dental populations Polder et al. 2004 found that females had a prevalence value of 1.37 times higher than males with the difference was found to be statistically significant (RR= 1.37 95% CI for RR= 1.28–1.45). A similar finding was reported by Rose, 1966 in a large survey of congenitally missing teeth in

6000 orthodontic patients. Our study which analysed sex differences across all populations supports this finding where it was found that females had a prevalence of 1.22 times higher than males with the difference was found to be statistically significant (OR= 1.22, 95% CI for OR= 1.14-1.30). Most previous investigations have also found such sex differences in the prevalence of hypodontia, but these differences were found to be neither clinically nor statistically significant (Grahnen, 1956; Muller et al. 1970; Brook, 1974; Mattheeuws et al. 2004).

The third permanent molar is the most frequently affected tooth in association with hypodontia and it has been reported that at least one third molar is congenitally absent in 20-30% of the European population (Grahnen, 1956; Haavikko, 1971; Neal and Bowden, 1988). However, third molars are generally excluded from hypodontia studies due to the high frequency of their absence. After excluding third molars, the mandibular second premolar was found to be the most affected tooth, followed by the maxillary lateral incisor then the maxillary second premolar. Maxillary central incisors, mandibular canines, maxillary and mandibular first molars were found to be the least affected teeth. This distribution of congenitally missing teeth was also found by Polder et al. 2004. Other studies (Eidelman et al. 1973; Hunstadbraten, 1973; Davis, 1987; Schalk-van der Weide et al. 1992; Simons et al. 1993) have found a different pattern of the type of missing teeth. This difference may be attributed to the differences in sampling techniques including the sample size, type of population studied, type and accuracy of the examination carried out and the way in which the results were analysed. The congenital absence of maxillary central incisors, mandibular canines, maxillary and mandibular first molars has been rarely reported in hypodontia patients (Simons et al. 1993; Endo et al. 2006) and if these teeth were reported to be congenitally absent they tended to be in conjunction with syndromic oligodontia. Overall,

the prevalence of hypodontia in the mandible and maxilla were found to be comparable. A finding which was also reported by Polder et al. 2004.

In the current systematic review it was found that mild hypodontia (congenitally missing 1 or 2 teeth) was the most common (81.6%) followed by moderate hypodontia (congenitally missing 3 to 5 teeth) 14.3% and finally followed by severe hypodontia (Oligodontia: congenitally missing 6 or more teeth) 3.1%. The corresponding figures found by Polder et al. 2004 were 82.9%, 14.4% and 2.6% which were drawn from a graph presented in their study, as no detailed description was provided in the text of the manuscript. Also, it seems that the reported figure of more than 6 missing permanent teeth in Polder et al. 2004 study (0.14%) and stated in the text was not correct as the figure calculated from the graph showed this figure to be 2.6%. Similar figures of the prevalence of hypodontia reported here in our study were also reported in other previous investigations (Kirzioğlu et al. 2005; Larmour et al. 2005; Harris and clark, 2008).

Our systematic review and meta-analysis provided a timely update to the meta-analysis conducted by Polder et al. 2004 that was carried out in 2002 with the inclusion of more up to date epidemiological studies on the prevalence of hypodontia. Furthermore, our study was carried out and reported in a much more thorough manner (following the PRISMA statement) than the previous meta-analysis (Polder et al. 2004), including a detailed description of the included studies, quality assessment of the selected original studies using a specially designed form based on the STROBE guidelines for reporting observational studies and the investigation of more factors that were associated with the prevalence of hypodontia. However, it is important to point out to the limitations and potential sources of bias in our study that may explain the very high heterogeneity detected between studies. The greater uncertainty which this may have added to our estimate was reflected in the method of estimation and calculation of the confidence intervals using a random effects model. The

results of our systematic review apply to non-syndromic hypodontia. But, the majority of the studies included in our systematic review were reported by clinicians who may have been unaware of the associated medical conditions in patients with tooth agenesis, especially those of a mild form such as very mild ectodermal dysplasias. However, it is unlikely that patients who were reported to have mild or moderate hypodontia to have associated undiagnosed syndromes. Eighty five percent of the studies included in our systematic review did not justify the sample size with a reported large variation which may have introduced an information bias as the observed prevalence of hypodontia may have varied with sample size. Large studies may have underestimated the prevalence of hypodontia and small studies reporting a small prevalence of hypodontia were less likely to be submitted/ accepted for publication, thus introducing a publication bias. Another possible source of bias was the large variation of the age of the participants in the included studies (3 to 71 years). A false-positive diagnosis of hypodontia of the lower second premolars could have been made in younger patients (less than 7 years old) due to a possible much later onset of the mineralization of their tooth buds than the reported average dates of 3-3.5 years. However, Polder et al. 2004 reported no significant correlation between the prevalence of hypodontia and sample size or age of patients. Moreover, postgraduate theses were excluded from our meta-analysis due to limited resources which could have excluded some useful data.

As can be seen from the above, mild hypodontia (congenitally missing 1 or 2 teeth) is a fairly common dental anomaly. As the most commonly missing teeth were found to be the mandibular second premolars and the maxillary lateral incisors, and due to the other dental anomalies that are commonly associated with hypodontia such as microdontia, abnormal tooth shape, palatally impacted upper canines, abnormal tooth eruption and irregularities in tooth position (Schalk-van der Weide et al. 1992; Goodman et al. 1994; Peck et al. 1996; Baccetti, 1998; Arte et al. 2001; Peck et al. Peck et al. 2002; Brook et al. 2009a; Brook et al.

2009b; Gupta et al. 2011;), this dental condition often cause aesthetic concerns by patients as well as functional and psychological issues (Meaney et al. 2012). Therefore patients with hypodontia were deemed to have a greater need for orthodontic treatment than those with the full complement of teeth (Ringqvist and Thilander, 1969; Thilander and Myrberg, 1973). The management of such patients will require multidisciplinary care (McNamara et al. 2006; Hu et al. 2011; Valle et al. 2011)which is very costly for health care providers especially in those with severe hypodontia (Murdock et al. 2005). Thus it is important to have an up to date knowledge of the prevalence of this condition to plan and prioritize funding the provision of health care including those with hypodontia.

CONCLUSIONS

- There was a statistically significant difference in the prevalence of hypodontia by continent. Prevalence of hypodontia was the highest in Africa (13.4%), followed by Europe (7%), Asia (6.3%) and Australia (6.3%) with a lower prevalence in North America (5.0%) and Latin America and Caribbean (4.4%).
- Females were found to have a higher prevalence than males (combined OR 1.22; 95% CI 1.14, 1.30).
- The most commonly affected teeth were found to be the mandibular second premolars followed by the maxillary lateral incisors and the maxillary second premolars. The least affected teeth were found to be the maxillary central incisors, the maxillary and mandibular first molars and the mandibular canines.
- There was no difference in the prevalence of hypodontia between the maxilla and mandible.
- The prevalence of mild, moderate and severe hypodontia was found to be 81.6%, 14.3% and 3.1% respectively.

- There was some evidence of a very small decrease in the prevalence of hypodontia over time (slope -0.002, $P<0.001$).
- More studies in the prevalence of hypodontia are needed especially in non-Europian patients with sound designs in terms of sample size estimation, well defined and sound inclusion and exclusion criteria especially age selection, clear description of the validity and reliability of the measurements and representation of the results with 95% CI.

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Table 1. Description of included studies

Characteristic	N	%
Previous reviews	39	41.9
Current search	54	58.1
Total included	93	100
Publication year		
1936-1945	3	3.2
1946-1955	0	0
1956-1965	6	6.5
1966-1975	17	18.3
1976-1985	3	3.2
1986-1995	8	8.6
1996-2005	10	10.8
2006-2012	46	49.5
Country		
Europe	40	43.0
Switzerland	2	2.2
Sweden	7	7.5
Norway	6	6.5
Finland	1	1.1
Austria	1	1.1
United Kingdom	1	1.1
Germany	1	1.1
Hungary	3	3.2
Slovenia	1	1.1
Romania	2	2.2
Bosnia	2	2.2
Iceland	2	2.2
Denmark	3	3.2
Italy	4	4.3
Spain	1	1.1
Portugal	2	2.2
Croatia	1	1.1
Northern America	13	14.0
USA	11	11.8
Canada	2	2.2
Latin America and Caribbean	4	4.3
Brazil	2	2.2
Mexico	1	1.1
Venezuela	1	1.1
Asia	30	32.3

Saudi Arabia	2	2.2
China	2	2.2
Turkey	9	9.7
India	1	1.1
Iran	3	3.2
South Korea	2	2.2
Japan	4	4.3
Jordan	4	4.3
Israel	1	1.1
Pakistan	2	2.2
Africa	1	1.1
Tunisia	1	1.1
Oceania	2	2.2
Australia	2	2.2
Not stated	3	3.2
Study type		
Cross-sectional	87	93.6
Cross-sectional with two population	4	4.3
Case-control	1	1.1
Retrospective cohort study	1	1.1
Population (cross- sectional studies n=87)		
Schoolchildren	29	33.3
Students	3	3.5
Orthodontic Patients	28	32.2
Dental patients	20	23.0
Army recruits	3	3.5
Not stated	4	4.6
Sample size		
Median (Range)	1291 (89, 100 577)	
Not stated	1	
Prevalence		
Median (Range)	6.10% (0.1%- 73.4%)	
Not included	14	
Participation rate (n=54)		
Median (Range)	69.5% (51%, 94%)	
Not stated or not applicable	50	

Table 2. Quality assessment

Item	*Yes*	*No*	*Unable to determine*
1 Abstract summarises what was done and findings	54 (100%)	-	-
2 Study design clearly stated in title or abstract section	23 (42.6%)	31 (57.4%)	-
3 Research question/specific objectives/ any hypothesis clearly stated	54 (100%)	-	-
4 Design appropriate for the research question/ specific objectives	53 (98.1%)	-	1 (1.9%)
5 Study setting, location and dates conducted described	44 (81.5%)	8 (14.8%)	2 (3.7%)
6 Method of participant selection and inclusion/ exclusion criteria clearly enumerated	39 (72.2%)	12 (22.2%)	3 (5.6%)
7 Sample (population) size and gender distribution clearly described	47 (87.0%)	6 (11.1%)	1 (1.9%)
8 Reason for sample size described	5 (9.3%)	46 (85.2%)	3 (5.6%)
9 Study population type clearly described	50 (92.6%)	3 (5.6%)	1 (1.9%)
10 Diagnostic criteria and outcome measurements clearly described including modifiers/ confounders	32 (59.3%)	19 (35.2%)	3 (5.6%)
11Validity and reliability of measurements clearly described	25 (46.3%)	26 (48.1%)	3 (5.6%)
12 Statistical method of analysis clearly stated	38 (70.4%)	13 (24.1%)	3 (5.6%)
13 Report number of records/ subjects analysed	51 (94.4%)	1 (1.9%)	2 (3.7%)
14 Results presented with 95% CI	13 (24.1%)	38 (70.4%)	3 (5.6%)
15 Main study findings described in relation to original aims and objectives	52 (96.3%)	-	2 (3.7%)
16 Any limitations clearly stated	18 (33.3%)	33 (61.1%)	3 (5.6%)
17 External validity of research results (generalisability) was clearly discussed	44 (81.5%)	10 (18.5%)	-
18 Source of funding and any competing interest stated	7 (13.0%)	44 (81.5%)	3 (5.6%)

Table 3. Factors considered in published papers

Factor	N (Total 51)	%
Age group	5	9.8
Gender	44	86.3
Genetic disorders	2	3.9
Jaw side	34	66.7
Number of missing teeth	20	39.2
Intra oral distribution (detailed)	27	52.5
People with missing 3rd molars as cases	1	2
Other dental anomalies	19	37.3
Other oral findings	4	7.8
Region	4	7.8
Participants with Cleft lip as cases or comparison group	2	3.9
Malocclusion type	7	13.7
Special teeth agenesis	5	9.8
Race/ ethnicity	1	2
General health status	1	2
Family history	3	5.9
Choice of treatment	1	2
Dioxin exposure	1	2
Cephalometric and area measurements	1	2
Ovarian cancer patients as cases	1	2

Table 4. Prevalence of hypodontia by type of malocclusion

Year	*1st Author*	*% of hypodontia cases by malocclusion type*				*OR (95% CI)*
		Class 1	*Class II1*	*Class II2*	*Class 3*	*Class 3 vs Class I/II*
2009	Uslu	22.6 (81/358)	19.4 (63/325)	17.6 (9/51)	24.7 (41/166)	1.25 (0.84, 1.85)
2008	Chung	9.5 (103/1082)	6.9 (19/275)		13.8 (60/436)	1.62 (1.16, 2.25)
2010	Vahid-Dastjerdi	6.4 (37/576)	6.7 (71/1060)		45.2 (52/115)	11.68 (7.71, 17.70)
2011	Kim	12.5 (123/985)	10.2 (105/1030)	16.7 (12/82)	10.7 (104/968)	0.93 (0.73, 1.19)
Combined estimate (random effect estimate) I^2=97.2						2.15 (0.78, 5.89)

Table 5. Distribution of persons with missing teeth, by number of teeth that are missing

Year	1st Author	Sample size	Affected people	No of missing teeth per person (%)					
				1	2	3	4	5	6+
2002	Nordgarden	9532	430	49.1	37	5.9	6	0.5	1.9
2007	Sisman	2413	182	35.7	47.3	6.6	6.6	1.7	2.2
2008	Yamaguchi	3683	215	45.6	41.4	10.7	0.9	0.5	1.0
2008	Goya	2072	202	38.6	29.2	6.9	5.9	5.4	13.9
2009	Rølling	8138	601	51.6	32.9	7.2	5.7	1	1.7
2009	Peker	139	102	30.4	52	7.8	2	1	6.9
2010	Aslam	1185	51	60.7	33.3	1.9	1.9	1.9	0
2010	Stefania	1206	78	23.1	44.9	6.4	9	3.9	3.9
2011	Bud	804	55	36	45	7	5	2	4
2012	Medina	607	25	52	40	4	4	0	0
Combined				**41.9 (36.1, 48.0)**	**39.7 (0.35, 44.5)**	**7.2 (6.1, 8.5)**	**5.4 (4.2, 7.0)**	**1.7 (0.9, 3.2)**	**3.1 (1.5, 6.4)**

Table 6. Distribution of missing teeth by tooth type in % of all missing teeth

					Specific Teeth (% of total missing teeth)													
Year	1st Author	Sample size	Affected people	Total teeth missing	U1	U2	U3	U4	U5	U6	U7	L1	L2	L3	L4	L5	L6	L7
2002	Nordgarden	9532	430	774	0	19.9	1.16	2.07	20.03	0	0.65	1.94	2.2	0.13	1.55	46.12	0.52	3.75
2005	Fekonja	212	24	48	0	54.1	2.1	2.1	18.8	0	0	6.2	0	0	0	14.6	0	2.1
2006	Endo	3358	286	696	0	12.4	6.5	4.9	15.7	4	2.4	7.1	13.2	1.6	2.4	27	0.2	2.4
2006	Rahardjo	1012	24	53	?	15.1	?	?	13.2	?	?	?	24.5	?	?	28.3	?	?
2007	Sisman	2413	182	377	2.7	27.3	2.1	4.2	10.9	4.8	1.3	6.6	3.4	0.3	3.7	25.2	6.1	1.3
2008	Chung	1622	182	329	1.5	10.6	6.1	11.3	14.3	0	0.6	6.4	20.4	1.5	5.8	20.4	0	1.2
2008	Maatouk	262	35	62	1.6	16.1	4.8	6.4	17.7	1.6	1.6	1.6	1.6	4.8	8.1	30.6	1.6	1.6
2008	Kűchler	975	45	78	0	17.9	1.3	0	23	0	0	5.2	12.8	2.6	2.6	34.6	0	0
2009	Rølling	8138	601	1070	0.09	19.8	1.4	2	20.3	0.7	1.2	3.27	3.45	0.19	0.56	44.9	0.2	2.1
2009	Peker	139	102	256	0.8	33.2	3.9	7.4	12.5	0.8	5.1	7	2.3	0.8	2.3	18.8	1.6	3.5
2009	Al-Moherat	1726	123	197	1.5	44.2	0.5	0	12.7	0	0	12.7	0	0	0.5	27.9	0	0
2010	Ajami	600	54	94	1.1	26.6	0	4.3	8.5	0	0	16	0	0	0	43.6	0	0
2010	Vahid-Dastjerdi	1751	160	197	?	35.6	?	?	13	?	?	?	9.6	?	?	8.2	?	?
2010	Celikoglu	3341	154	329	?	46.5	?	?	?	?	?	13.4	?	?	?	22.5	?	?
2010	Aslam	1185	51	77	3.9	23.4	2.6	9.1	5.2	1.3	0	11.7	5.2	1.3	5.2	27.3	3.9	0
2010	Stefania	1206	78	172	0.6	30.2	0.6	5.8	12.8	2.3	1.2	7	2.9	1.2	4.7	16.9	1.7	1.2
2010	Aktan	100577	1471	3147	0.7	38.2	1.9	2.2	12.9	0.1	0.9	4.6	2.7	0.8	1	32.4	0.4	1
2011	Topkara	2761	187	375	0.27	35.5	1.9	1.3	9.9	0.5	3.2	7.5	10.7	0.5	2.1	24.5	0.5	1.6
2011	Behr	1353	171	693	0.4	14.9	4	4.3	11.8	1.2	3	5.3	3.6	2	3.8	21.5	1.2	3.8
2011	Bud	804	55	114	?	24.5	?	?	19	?	?	10.5	?	?	?	30.7	?	?
2012	Cantekin	1291	80	135	0	15.6	3	1.5	3	0.7	0	3	5.2	1.5	3.7	62.2	1.5	0
2012	Sogra	1590	159	?	?	37	?	?	?	?	?	?	?	?	?	8	?	?
Combined (no CI presented due to lack of space)					**1.0**	**24.3**	**2.5**	**3.6**	**13.7**	**1.1**	**1.5**	**6.1**	**4.3**	**1.3**	**2.7**	**29.9**	**1.0**	**1.8**

Table 7. Distribution of missing teeth by tooth type in % of the total of dental agenesis cases

year	1st Author	Sample size	Affected	Total teeth missing	Specific Teeth (% of total missing teeth)													
					U1	U2	U3	U4	U5	U6	U7	L1	L2	L3	L4	L5	L6	L7
2011	Gupta	1123	47	78	12.8	40.4	0	0	12.8	?	?	14.9	0	0	0	10.6	?	?
2008	Harris	1700	88	198	0.5	35.4	1	3.5	14.6	1	1.5	8.6	4	1	3.5	31.8	0	2
2008	Goya	2072	202	574	0.5	5	0	0	2.5	0	0	3	6.9	0.5	0.5	19.8	0	0.5
2006	Albashaireh	1005	55	93	0	30.1	0	0	26.9	0	0	4.3	2.2	0	0	36.6	0	0
2008	Shakra	1524	67	67	0	61.2	1.5	3	10.4	0	1.5	26.9	9	1.5	3	28.4	0	1.5
2006	Gábris	2219	326	n.r.	?	71.17	?	?	48.16	?	?	21.17	?	?	?	63.8	?	?
2005	Abu Alhaija	1003	60	n.r.	0	40	0	0	?	0	0	8.33	0	0	0	?	0	0
2009	Fujita	1375	(l.o.) 100	(l.o.) 133	n.r.	38.35	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	61.65	n.r.	n.r.	n.r.	n.r.	n.r.

Table 8. Location of missing teeth in the maxilla and mandible

					Location of missing teeth (%)	
Year	1st Author	**Sample size**	*Affected*	*Total teeth missing*	*Maxilla (%)*	*Mandible (%)*
2002	Tavajohi-Kermani	89	all	108	42.3	57.7
2003	Silva Meza	668	18	n.r.	45	55
2005	Fekonja	212	24	48	77.1	22.9
2007	Bondemark	1543	2nd molars only	n.r.	34.8	65.2
2007	Sisman	2413	182	377	53.3	46.7
2008	Chung	1622	182	329	44.4	55.6
2008	Harris	1700	88	198	57.6	42.4
2008	Maatouk	262	35	62	49.8	50.2
2008	Goya	2072	202	574	42.3	57.7
2009	Rølling	8138	601	1070	45.4	54.6
2009	Peker	139	102	256	64.5	35.5
2009	Al-Moherat	1726	123	197	58.9	41.1
2010	Vahid-Dastjerdi	1751	160	197	71	29
2010	Celikoglu	3341	145	329	60.2	39.8
2010	Gomes	1049	66	108	59.2	40.8
2010	Aslam	1185	51	77	45.5	54.5
2010	Stefania	1206	78	172	53.5	46.5
2010	Amin	230	14	25	44	56
2010	Aktan	100577	1471	3147	57	43
2011	Topkara	2761	187	375	52.5	47.5
2011	Behr	1353	171	693	58.9	41.1
2012	Cantekin	1291	80	135	23.8	76.2
2012	Medina	607	25	40	55	45
Combined estimate, random effect (I^2=89.9)					**53.2 (49.3, 57.0)**	**46.8 (43.0, 50.7)**

Figures legends

Figure 1. Search results: MEDLINE, EMBASE, Google and Hand search

Figure 2. Prevalence of hypodontia in schoolchildren

Figure 3. Prevalence of hypodontia in dental patients

Figure 4. Prevalence of hypodontia in orthodontic patients

Figure 5. Relationship with gender (females compared to males)

Figure 6. Regression of publication year on Logit Event Rate

Figure 1: Search results: MEDLINE, EMBASE, Google and Hand search

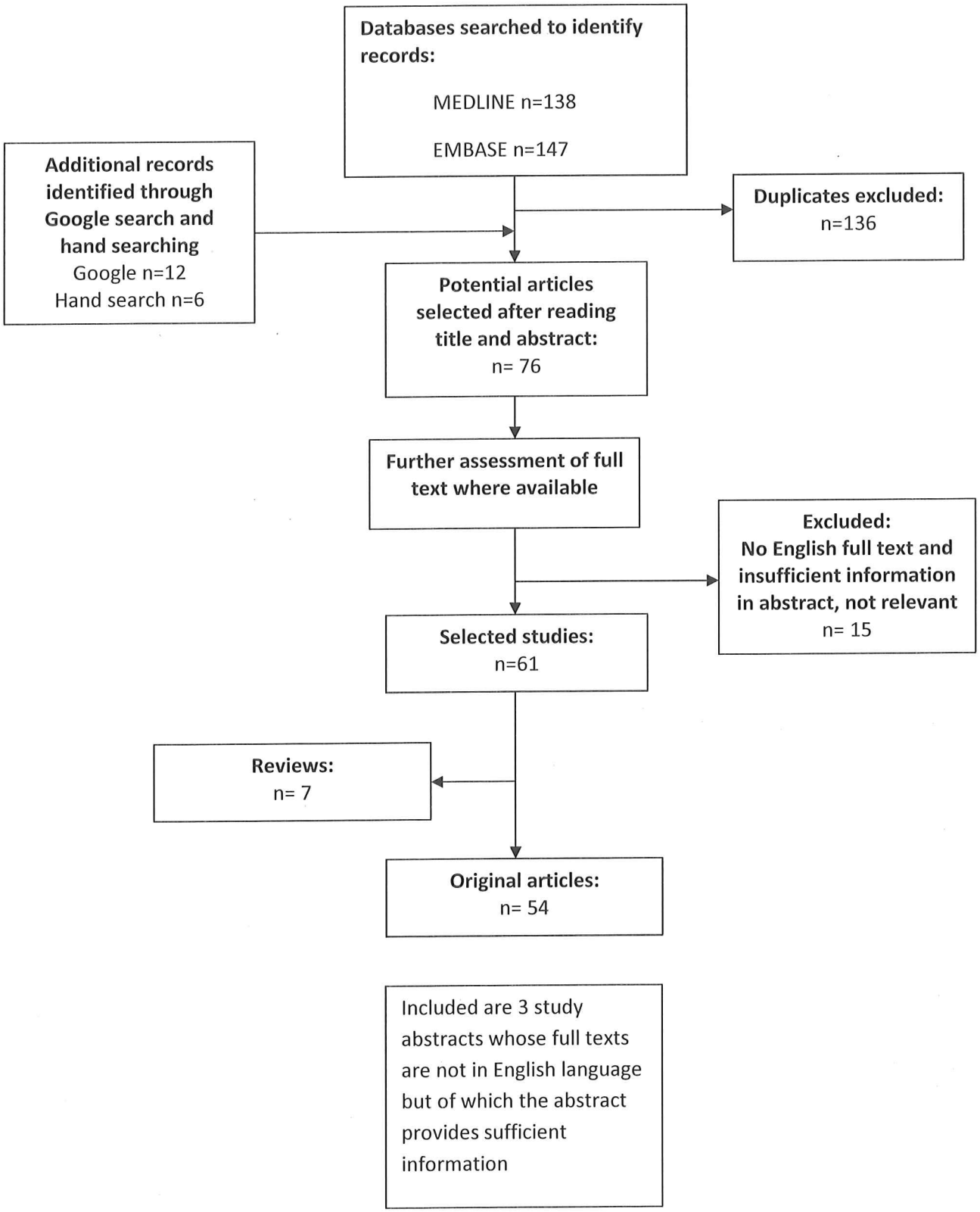
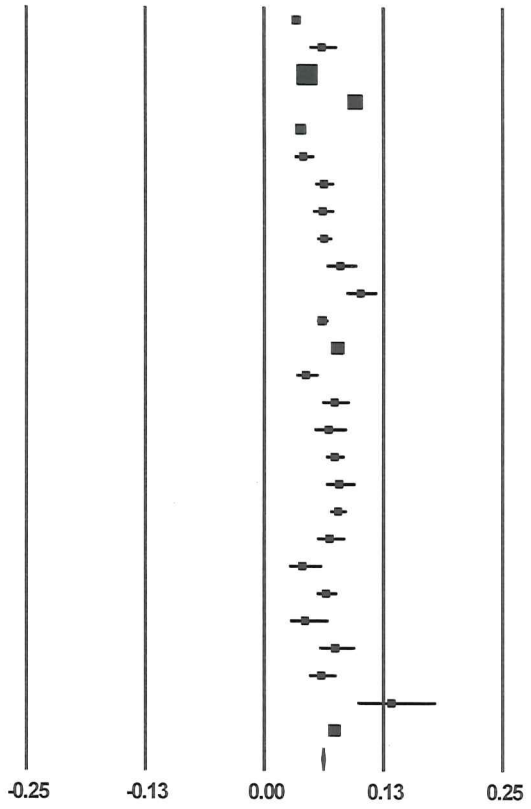


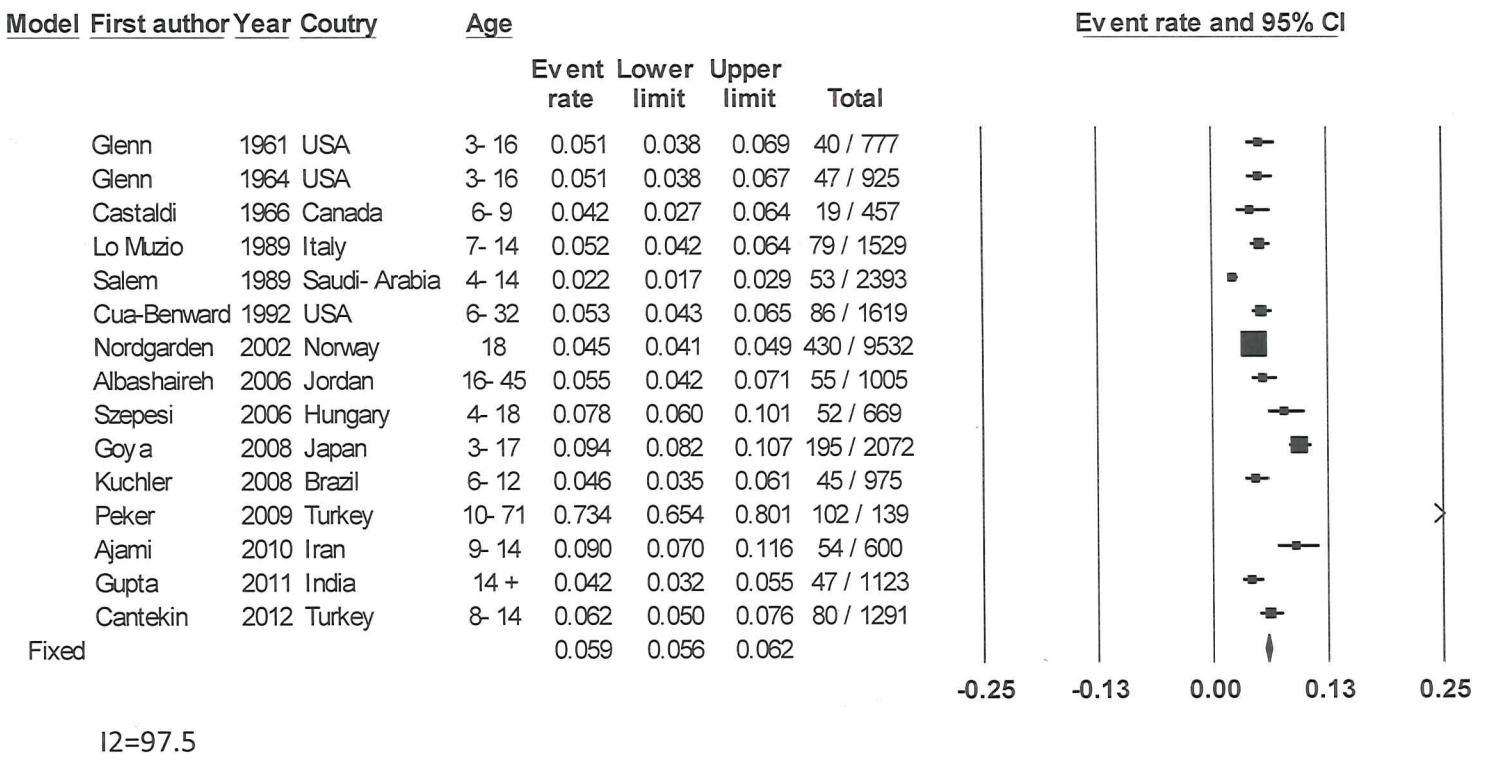
Figure 2. Prevalence of hypodontia in schoolchildren

Model	First author	Year	Country	Age	Event rate	Lower limit	Upper limit	Events/Total
	Dolder	1936	Switzerland	6-15	0.034	0.031	0.038	340 / 10000
	Grahnen	1956	Sweden	11-14	0.061	0.047	0.077	61 / 1006
	Gimnes	1963	Norway	6-15	0.045	0.043	0.047	1626 / 36000
	Volk	1963	Austria	9-15	0.096	0.090	0.102	911 / 9533
	Blayney_1	1967	USA	12-14	0.038	0.035	0.042	450 / 11713
	Blayney_2	1967	USA	12-14	0.041	0.031	0.053	54 / 1320
	Davies	1968	Australia	12-14	0.063	0.053	0.074	136 / 2170
	Helm	1968	Denmark	6-18	0.061	0.051	0.074	104 / 1700
	Egermark-Erikson	1971	Sweden	10-16	0.063	0.055	0.072	209 / 3327
	Haaviko	1971	Finland	5-13	0.080	0.065	0.098	83 / 1041
	Hunstadbraten	1973	Norway	7-14	0.101	0.086	0.119	131 / 1295
	Thilander	1973	Sweden	7-13	0.061	0.055	0.067	332 / 5459
	Bachmann	1974	Switzerland	9-10	0.077	0.072	0.083	670 / 8694
	Brook	1974	UK	11-14	0.044	0.033	0.058	49 / 1115
	Thompson	1974	Canada	6-12	0.074	0.060	0.090	88 / 1191
	Wisth	1974	Norway	9	0.068	0.052	0.087	55 / 813
	Bergstrom	1977	Sweden	8-9	0.074	0.065	0.085	192 / 2589
	Magnusson	1977	Iceland	8-16	0.079	0.064	0.096	88 / 1116
	Rolling	1980	Denmark	9-10	0.078	0.069	0.087	258 / 3325
	Davis	1987	Hong Kong	12	0.069	0.055	0.085	75 / 1093
	Al Emran	1990	Saudi Arabia	13-14	0.040	0.026	0.061	20 / 500
	Aasheim	1993	Norway	7-10	0.065	0.055	0.077	127 / 1953
	Johannsdottir	1997	Iceland	6-7	0.043	0.027	0.068	17 / 396
	Backmann	2001	Sweden	7	0.074	0.058	0.096	55 / 739
	Abu Alhaija	2005	Jordan	13-15	0.060	0.047	0.076	60 / 1003
	Maatouk	2008	Tunisia	12-18	0.134	0.097	0.180	35 / 262
	Rølling	2009	Denmark	9-12	0.074	0.068	0.080	601 / 8138
Fixed					0.061	0.060	0.062	



I2=96.6

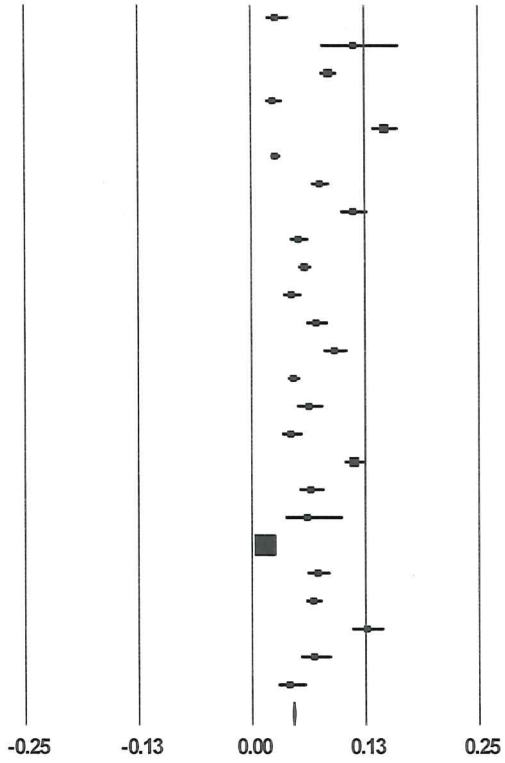
Figure 3. Prevalence of hypodontia in dental patients



Carvalho et al. (2011) reported prevalence of 6.5% but did not report the population size

Figure 4. Prevalence of hypodontia in orthodontic patients

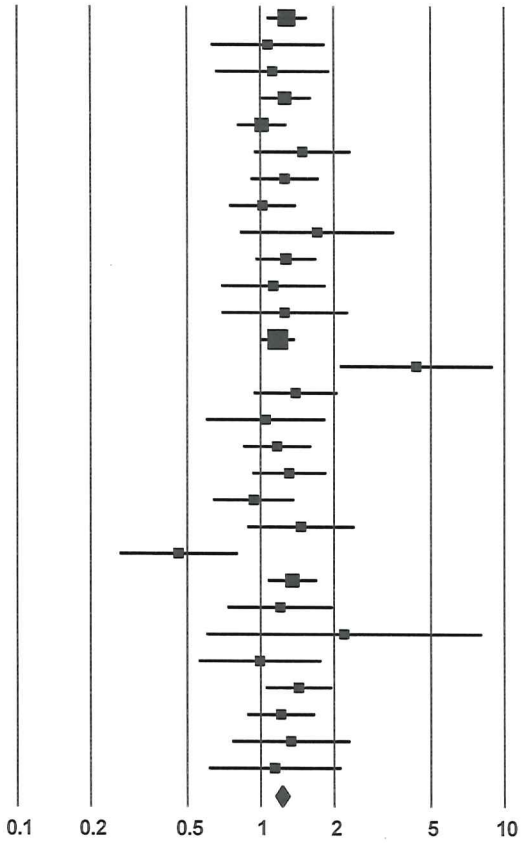
Model	First author	Year	Coutry	Age	Events/Total				Event rate and 95% CI
					Event rate	Lower limit	Upper limit	Total	
	Silva Meza	2003	Mexico	9- 20	0.027	0.017	0.042	18 / 668	
	Fekonja	2005	Slovenia	(mean 13)	0.113	0.077	0.163	24 / 212	
	Endo	2006	Japan	5- 15	0.085	0.076	0.095	286 / 3358	
	Rahardjo	2006	China	8- 38	0.024	0.016	0.035	24 / 1012	
	Gabris	2006	Hungary	6- 18	0.147	0.133	0.162	326 / 2219	
	Altug- Atac	2007	Turkey	8- 15	0.026	0.021	0.033	80 / 3043	
	Sisman	2007	Turkey	9- 36	0.075	0.066	0.087	182 / 2413	
	Chung	2008	South Korea	?	0.112	0.098	0.129	182 / 1622	
	Harris	2008	USA	12- 18	0.052	0.042	0.063	88 / 1700	
	Yamaguchi	2008	Japan	13- 42	0.058	0.051	0.066	215 / 3683	
	Shakra	2008	Jordan	8- 20	0.044	0.035	0.055	67 / 1524	
	Al-Moherat	2009	Jordan	12- 25	0.071	0.060	0.084	123 / 1726	
	Vahid-Dastjerdi	2010	Iran	9- 27	0.091	0.079	0.106	160 / 1751	
	Celikoglu	2010	Turkey	10- 25	0.046	0.039	0.054	154 / 3341	
	Gomes	2010	Brazil	10- 16	0.063	0.050	0.079	66 / 1049	
	Aslam	2010	Pakistan	11- 46	0.043	0.033	0.056	51 / 1185	
	Kim	2010	South Korea	9- 30	0.113	0.102	0.124	344 / 3055	
	Stefania	2010	Romania	7- 25	0.065	0.052	0.080	78 / 1206	
	Amin	2010	Pakistan	10- 32	0.061	0.036	0.100	14 / 230	
	Aktan	2010	Turkey	5- 37	0.015	0.014	0.015	1471 / 100577	
	Tallon-Walton	2010	Spain	6- 83	0.072	0.060	0.087	110 / 1518	
	Topkara	2011	Turkey	9- 46	0.068	0.059	0.078	187 / 2761	
	Behr	2011	Germany	5- 44	0.126	0.110	0.145	171 / 1353	
	Bud	2011	Romania	11- 21	0.068	0.053	0.088	55 / 804	
	Medina	2012	Venezuela	5- 11	0.041	0.028	0.060	25 / 607	
Fixed					0.045	0.043	0.046		



I2=99.3

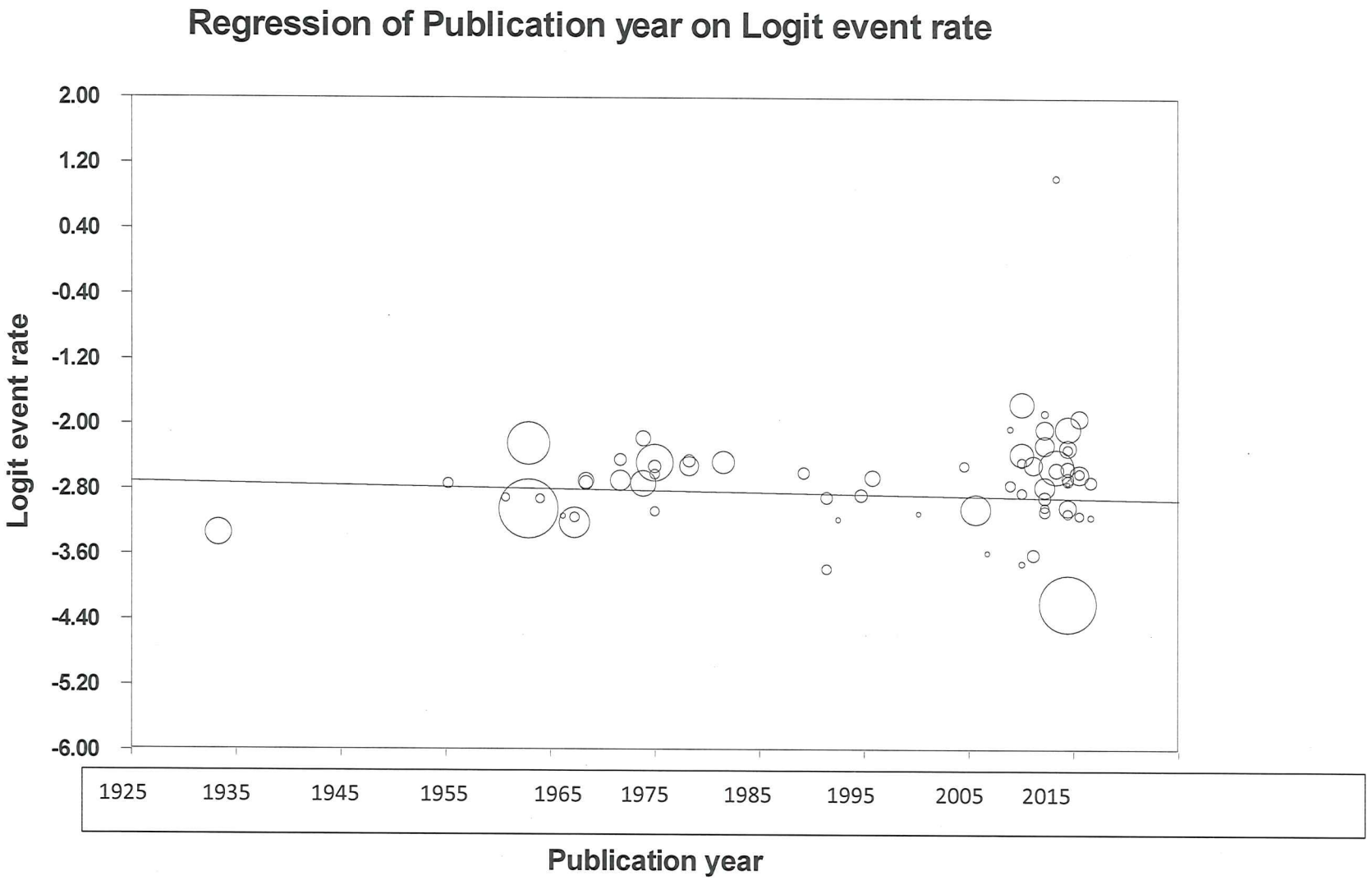
Figure 5. Relationship with gender (females compared to males)

Model	Study name	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Females	Events / Total Males
	Nordgarden	2002	1.290	1.063	1.566	2.574	0.010	237 / 4639	196 / 4893
	Abu Alhaija	2005	1.075	0.625	1.849	0.260	0.795	38 / 619	22 / 384
	Albashaireh	2006	1.122	0.652	1.932	0.417	0.677	28 / 484	27 / 521
	Endo	2006	1.265	0.986	1.622	1.848	0.065	177 / 1905	109 / 1453
	Gábris	2006	1.015	0.800	1.289	0.125	0.901	191 / 1293	135 / 926
	Altug-Atac	2007	1.489	0.938	2.362	1.689	0.091	51 / 1658	29 / 1385
	Sisman	2007	1.258	0.907	1.744	1.377	0.168	126 / 1557	56 / 856
	Chung	2008	1.020	0.742	1.403	0.124	0.902	114 / 1011	68 / 611
	Maatouk	2008	1.708	0.823	3.548	1.437	0.151	22 / 134	13 / 128
	Goya	2008	1.271	0.949	1.701	1.610	0.107	108 / 999	93 / 1073
	Shakra	2008	1.128	0.686	1.855	0.474	0.636	39 / 847	28 / 677
	Kuchler	2008	1.257	0.689	2.295	0.745	0.456	24 / 464	21 / 511
	Rølling	2009	1.176	0.995	1.389	1.900	0.057	321 / 4066	277 / 4072
	Peker	2009	4.353	2.105	9.001	3.969	0.000	57 / 84	18 / 55
	Al-Mbherat	2009	1.393	0.933	2.079	1.622	0.105	87 / 1101	36 / 625
	Ajami	2010	1.050	0.595	1.854	0.168	0.866	32 / 351	22 / 249
	Vahid-Dastjerdi	2010	1.170	0.845	1.620	0.943	0.346	85 / 870	75 / 881
	Celikoglu	2010	1.312	0.923	1.866	1.512	0.130	98 / 2040	48 / 1301
	Tallon-Walton	2010	0.937	0.635	1.382	-0.329	0.742	59 / 835	51 / 683
	Gomes	2010	1.465	0.879	2.443	1.465	0.143	40 / 542	26 / 507
	Aslam	2010	0.460	0.262	0.808	-2.701	0.007	26 / 810	25 / 375
	Kim	2010	1.348	1.064	1.709	2.471	0.013	230 / 1851	114 / 1204
	Stefania	2010	1.204	0.729	1.989	0.724	0.469	55 / 805	23 / 401
	Amin	2010	2.200	0.596	8.122	1.183	0.237	11 / 146	3 / 84
	Gupta	2011	0.993	0.553	1.780	-0.025	0.980	23 / 551	24 / 572
	Topkara	2011	1.436	1.044	1.974	2.227	0.026	128 / 1677	59 / 1084
	Behr	2011	1.211	0.876	1.675	1.160	0.246	98 / 718	73 / 635
	Bud	2011	1.331	0.758	2.337	0.997	0.319	34 / 445	21 / 359
	Cantekin	2012	1.143	0.608	2.147	0.414	0.679	20 / 613	20 / 678
Fixed			1.215	1.139	1.296	5.922	0.000		



I2=21.5

Figure 5.


Regression of Publication year on Logit event rate
2.00
1.20
0.40
-0.40
-1.20
-2.00
-2.80
-3.60
-4.40
-5.20
-6.00
Logit event rate
1925
1935
1945
1955
1965
1975
1985
1995
2005
2015
Publication year