Frequency of infraposition and missing contact points in implant-supported restorations within natural dentitions over time: A systematic review with meta-analysis

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Abstract: OBJECTIVES The aim of this systematic review was to assess clinical evidence on adverse effects of osseointegrated implants placed among natural teeth of a residual dentition. METHODS Seven databases were searched without restrictions up to January 2018 for clinical studies on implant infra-position (IIP) or proximal contact point (PCP) loss to the adjacent teeth. After duplicate selection, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of odds ratios (OR) or mean differences (MD) and their 95% confidence intervals (CI) were performed, followed by meta-regression and sensitivity analyses. RESULTS A total of 27 nonrandomized studies with 1,572 patients (mean age 42.2 years/51.2% female) followed up to 18.5 years after implant placement were included. The pooled %prevalence of IIP was 50.5% (nine studies; 95% CI = 26.3-74.5%), and the pooled IIP extent was 0.58 mm (six studies; 95% CI = 0.33-0.83 mm), while IIP > 1 mm was seen for 20.8% of placed implants (five studies; 95% CI = 8.3-37.1%), and male patients were less prone to IIP than female patients (three studies; OR = 0.30; 95% CI = 0.10-0.88; p = 0.03). The pooled %prevalence of PCP loss was 46.3% (nine studies; 95% CI = 32.3-60.6%), with increase through observation time (two studies; OR = 1.09; 95% CI = 1.03-1.16; p = 0.004) and predilection for mesial PCPs (five studies; OR = 2.25; 95% CI = 1.06-4.77; p = 0.03). However, the quality of evidence was very low due to bias. CONCLUSIONS Patients and doctors need to be aware that long-term adverse effects of dental implants among natural teeth can be observed in terms of IIP and PCP loss to the adjacent teeth.

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Title Page

Frequency of infraposition and missing contact points in implant supported restorations within natural dentitions over time: a systematic review with meta-analysis

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Running title
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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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Abstract

Objectives: Aim of this systematic review was to assess clinical evidence on adverse effects of osseointegrated implants placed among natural teeth of a residual dentition.

Methods: Seven databases were searched without restrictions up to January 2018 for clinical studies on Implant Infra-Position (IIP) or Proximal Contact Point (PCP) loss to the adjacent teeth. After duplicate selection, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of Odds Ratios (OR) and Mean Differences (MD) and their 95% confidence intervals (CIs) were performed, followed by meta-regression, and sensitivity analyses.

Results: A total of 27 non-randomized studies with 1572 patients (mean age 42.2 years/ 51.2% female) followed up to 18.5 years after implant placement were included. The pooled %prevalence of IIP was 50.5% (9 studies; 95% CI=26.3-74.5%) and the pooled IIP extent was 0.58 mm (6 studies; 95% CI=0.33-0.83 mm), while IIP>1 mm was seen for 20.8% of placed implants (5 studies; 95% CI=8.3-37.1%), and female patients were less prone to IIP than male patients (3 studies; OR=0.30; 95% CI=0.10-0.88; P=0.03). The pooled %prevalence of PCP loss was 46.3% (9 studies; 95% CI=32.3-60.6%), with increase through observation time (2 studies; OR=1.09; 95% CI=1.03-1.16; P=0.004) and predilection for mesial PCPs (5 studies; OR=2.25; 95% CI=1.06-4.77; P=0.03). However, the quality of evidence was very low due to bias.

Conclusions: Patients and doctors need to be aware that long-term adverse effects of dental implants among natural teeth can be observed in terms of IIP and PCP loss to the adjacent teeth.

KEYWORDS
dental implants, osseointegration, adverse effects, clinical research, systematic review, meta-analysis
1 | INTRODUCTION

1.1. | Rationale

Osseointegrated dental implants have become an integral part in contemporary dentistry as a popular treatment choice to replace one or more missing teeth. They have high survival rates after 5 to 10 years (Jung et al., 2012; Moraschini et al., 2015) or 15 or more years, even though research on their long-term performance focuses mostly on bone remodeling and clinical response parameters (Jemt 2008; Bergenblock et al., 2012; Dierens et al., 2012).

However, a wide variety of biological, technical, and aesthetic complications that are frequently seen has been reported (Albrektsson and Donos, 2012; Wittneben et al., 2014) with estimated cumulative complication rates around 7% after 5 years (Jung et al., 2012). Additionally, most complications described in the literature pertain to technical or biological failures of the osseointegrated fixture and its supraconstruction or on tissue destruction due to peri-implantitis. Aesthetic parameters, like soft tissue topography around the implant restoration and the position of its crown in relation to the adjacent teeth, are equally significant factors for the success of treatment success from an aesthetic point of view (Chang et al., 1999) and especially for implants placed in the anterior maxilla—yet, receive less attention.

Additionally, the absence of maxillary permanent anterior teeth due to trauma or congenital aplasia and the subsequent impact on the person’s quality of life means that sometimes the recipients of dental implants might be young patients with residual growth potential. The use of implants in growing patients has been studied both in humans (Thilander et al., 1994) and animals (Ödman et al. 1991), leading to the observation that dental implants behave like ankylosed teeth and are capable of following neither the growth of the jaws nor the continuous eruption of adjacent natural teeth (Thilander et al., 1994; Iseri and Solow, 1996). This most often results in a discrepancy in the occlusal plane, manifesting clinically in an Implant Infra-Position (IIP) compared to the crowns of the adjacent teeth. However, similar observations of IIP have also been done among mature adult patients (Thilander et al. 1999; Bernard et al., 2004) with little to no active growth potential, which could lead to aesthetic impairment and ultimately the need to replace the implant-supported restoration.
Another post-treatment complication that has been reported increasingly during the last decade is the loss of the Proximal Contact Point (PCP) between the restored implant’s crown and the adjacent natural teeth (Wei et al., 2008; Byun et al. 2015; Wong et al. 2015). It has been postulated that natural teeth move in vertical and sagittal directions both during active adolescent growth of the jaws, but also during the slow growth that can be seen in both young and mature adults (Oesterle and Croni, 2000). Additionally, the position of the teeth within the dental arch is not stable and a number of factors, including among others location, tooth type, gender, age, vitality of adjacent teeth, and the strength of occlusal forces, have been proposed as important in both PCP tightness and PCP loss (Pang et al., 2017). At the same time PCP loss has been associated with food impaction in the interdental area, with subsequent patient dissatisfaction (Jeong and Chang, 2015), and with periodontal disease (Jernberg et al., 1983).

1.2. | Aim

Current evidence on long-term complications of implants functioning among natural teeth that are related to their osseointegration and ankylotic nature is limited. Therefore, aim of the present systematic review was to assess in an evidence-based manner the existing data from longitudinal studies and try to answer the question: What are the adverse effects of osseointegrated dental implants functioning among natural teeth in residual dentitions of adolescent and adult patients and especially the rate and extent of IIP and PCP loss?

2 | MATERIAL AND METHODS

2.1. | Protocol and registration

The review’s protocol was made a priori following the PRISMA-P statement (Shamseer et al. 2015), registered in PROSPERO (CRD42018086404), and all post hoc changes were appropriately noted. This systematic review was conducted and reported according to Cochrane Handbook (Higgins and Green 2011) and PRISMA statement (Liberati et al. 2009), respectively.

2.2. | Eligibility criteria
According to the Participants-Intervention-Comparison-Outcome-Study design (PICOS) schema, we included randomized or non-randomized clinical studies on human patients of any age, sex, or ethnicity with at least one osseointegrated dental implant placed (including its restoration) among natural teeth. The primary outcome of this systematic review was the IIP of the osseointegrated implant (and its suprastructure) compared to adjacent teeth, while the secondary outcome pertained to loss of the PCP of the implant’s crown with the adjacent natural tooth. Excluded were non-clinical studies, case reports, animal studies, studies on patients with systemic diseases or syndromes, studies on implant-supported overdentures or tooth-and-implant restorations, studies on surgical or short-term (< 6 months) outcomes, and studies with non-relevant outcomes.

2.3. | Information sources and literature search

Seven electronic databases were systematically searched by one author (SNP) without any limitations from inception up to January 10th, 2018 (Appendix S1): MEDLINE (searched via PubMed), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Embase, Virtual Health Library, Scopus, and Web of Knowledge. Additionally, five sources (Google Scholar, International Standard Registered Clinical/ soCial sTudy Number Registry, Directory of Open Access Journals, Digital Dissertations, metaRegister of Controlled Trials, and ClinicalTrials.gov) and the reference/citation lists of included trials were manually searched for any additional trials. No limitations concerning publication language, publication year, or publication status were applied.

2.4. | Study selection

The eligibility of identified studies was checked sequentially from their title, abstract, and full-text against the eligibility criteria by one person (SNP) and were subsequently checked independently by a second one (TE), with any conflicts being resolved by a third person (CHFH).

2.5 | Data collection and data items

Study characteristics and numerical data were extracted from included studies independently by two authors (SNP, TE) using predefined and piloted extraction forms including: (i) study characteristics (design,
clinical setting, country), (ii) patient characteristics (age, sex, or smoking at implant placement and orthodontic treatment prior to implant placement), (iii) number and type of implants, (iv) type and localization of prosthetic restoration, (v) analyzed sample, and (vi) outcome details (type of adverse effect, nature, measurement method, timing, and any treatments for these adverse effects). Piloting of the forms was performed during the protocol stage until over 90 per cent agreement was reached. Missing or unclear information was calculated, whenever possible. Any individual patient data provided in an included study were extracted and re-analyzed firsthand (Appendix S2).

2.6. | Risk of bias in individual trials

The risk of bias of included randomized trials was to be assessed using Cochrane’s risk of bias tool (Higgins and Green 2011); the risk of bias of included non-randomized studies was assessed using a modified Newcastle-Ottawa scale for cohort studies (Wells et al. 2017) on outcome level as, as guided by the Cochrane Handbook (Higgins and Green 2011).

2.7. | Outcomes and data synthesis

The primary outcome of IIP was measured as binary yes/no variable (existence of IIP), as continuous variable (extent of IIP in mm), and as categorical variable according to magnitude, for which most authors took the 1 mm cut-off to denote considerable IIP. The secondary outcome of PCP loss was measured as binary yes/no variable (lack of PCP). These outcomes were reported either on patient level or on implant/tooth level and, as the latter was more often reported, this was adopted as main analysis unit.

Initially, the pooled % event rate of IIP or PCP loss and the pooled IIP extent in mm was calculated in an indirect explorative analysis across studies (1-group pooling). Subsequently, direct comparisons were made from within- and across-studies data regarding the influence of various patient-, implant-, or study-related characteristics using Relative Risks (RR) for binary/categorical or Mean Differences (MD) for continuous outcomes with the corresponding 95% Confidence Intervals (CI) (2-groups’ pooled comparisons). In case of identified studies reporting Odds Ratios (OR) adjusted for confounders, these were used instead of RRs to improve effect precision. Statistically significant ORs/RRs were translated clinically with the Number Needed to Treat (NNT).
As adverse effects of dental implants among natural teeth are bound to be affected by the person’s residual growth potential, the masticatory habits, issues pertaining to the implant or its prosthetic reconstruction, and the periodontal or functional status of adjacent teeth, a wide variation of true effects was expected to exist. Therefore, a random-effects model was judged a priori to be appropriate to calculate the average of the distributions of effects, based on biological, clinical, and statistical grounds (Papageorgiou 2014a). Novel random-effects model estimators were used instead of the more widely known DerSimonian and Laird (1986) estimator, based on contemporary guidelines and software availability, due to their improved performance. The bootstrapped-DerSimonian-Laird method (Petropoulou and Mavridis, 2017) was used for indirect pooling of IIP/PCP loss event rates and the Paule-Mandel method (Veroniki et al., 2016) was used for indirect pooling of IIP extent and direct meta-analyses of OR, RR, and MD.

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and calculating the tau^2 (absolute heterogeneity) and the I^2 (relative heterogeneity), respectively; I^2 defines the proportion of total variability in the result explained by heterogeneity, and not chance (Higgins et al. 2003). Heterogeneity was roughly categorized as low, moderate, and high according to I^2 values of 25, 50, and 75 per cent (Higgins et al. 2003), although the heterogeneity’s localization on the forest plot was also judged. Additionally, the 95 per cent CIs around tau^2 and I^2 were calculated (Ioannidis et al. 2007) to quantify our uncertainty around these estimates. Ninety-five per cent predictive intervals were calculated for meta-analyses of ≥3 trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting, which is crucial for the correct interpretation of random-effects meta-analyses (IntHout et al. 2016). All analyses were conducted in Stata SE version 14.2 (StataCorp LP, College Station, Texas, USA) by one author (SNP) with the data made freely available in Zenodo (Papageorgiou et al. 2018). A two side P < 0.05 was considered significant for hypothesis-testing, except for P < 0.10 used for tests of between-studies or between-subgroups heterogeneity (Ioannidis 2008).

2.8. | Additional analyses and quality of meta-evidence

Possible sources of heterogeneity were a priori planned to be sought through random-effects subgroup analyses and random-effects meta-regression for meta-analyses of ≥ five studies, including: mean patient
age, % male proportion of the patient sample, % of restorations in the maxilla, % of restoration in the anterior region (canine to canine), and the length of follow-up. Additional analyses for subgroups, meta-regressions, and reporting biases were planned, but were not conducted, due to lack of available studies (Appendix S2).

The overall quality of clinical recommendations for outcomes addressed by direct evidence (analyses with OR, RR, or MD) was rated using the GRADE approach, as very low, low, moderate, or high (Guyatt et al. 2011) and a Summary of Findings table was constructed using the improved format proposed by Carrasco-Labra et al. (2016) and recent guidance on incorporating non-randomized studies (Schünemann et al. 2018). The minimal clinical important (Norman et al. 2003), large, and very large effects were defined as half, one, and two standard deviations (using the average standard deviation for an outcome across included studies), respectively. Arbitrary cut-offs of 1.5, 2.0, and 5.0 (Schünemann et al. 2009) were adopted for OR and RR. The produced forest plots were augmented with contours denoting the magnitude of the observed effects (Papageorgiou 2014b) to visually gauge heterogeneity, clinical relevance, and imprecision.

Robustness of the results was planned a priori to be checked with sensitivity analyses based on (i) inclusion/exclusion of trials with methodological shortcomings, (ii) improvement of the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) classification, and (iii) inclusion/exclusion of large-scale studies.

3 | RESULTS

3.1. | Study selection

The literature search yielded a total of 579 hits (Figure 1), 161 of which proceeded to full text assessment after eliminating duplicates and ineligible studies by title or abstract (Appendix S3). Finally, a total of 34 papers were identified as eligible for inclusion in the present systematic review. After pooling multiple papers relating to the same study, a total of 27 unique clinical studies published in Dutch, English, Japanese, or Portuguese between 1994 and 2017 were included. Apart from data from published reports, a total of 4 authors of identified studies were contacted for raw data, from which however none responded up to now (Appendix S4).
3.2. | Study characteristics

The descriptive characteristics of the 27 included studies can be seen in Table 1a and Table 1b. From these, none was a randomized trial, 4 (15%) were prospective non-randomized studies, and the remaining 23 (85%) studies were non-randomized studies with retrospective or unclear design. Most studies were conducted in university clinics (n=16; 59%) or private practices (n=8; 30%) in at least 15 different countries (with Sweden contributing the greatest with 8 studies). Overall, at least 1,572 patients were included (from the 26 studies reporting patient sample) with a mean age of 42.2 years (from the 22 studies reporting age) and with 51.2% of the patients being female (from the 22 studies reporting sex). These patients had been treated with the placement of at least 7835 implants (from the 25 studies reporting implant number) and re-examined after a median of average follow-up periods 5.7 years afterward, ranging from 1 to 18 years (from the 22 studies reporting mean follow-up). The primary outcome of IIP was the most widely-used outcome (assessed in 16 studies), followed by the secondary outcome of PCP loss (assessed in 10 studies). Other outcomes (not analyzed here) included mesiodistal movement of adjacent tooth at crown or root (2 studies each), buccolingual movement of adjacent tooth at crown (1 study), PCP space (1 study), and PCP tightness (1 study).

3.3. | Risk of bias within studies

The methodological adequacy (with possible implications for the risk of bias) of identified studies according to the modified Newcastle-Ottawa tool is given in detail in Appendix S5a-5b and in summary in Figure 2. All included studies were found to have serious methodological issues, with the most problematic domains being the blinding of outcome assessment (completely absent in 93% of studies), the basic study design (being retrospective in 85% of studies), the use of reliable outcome measurement methods (issues existing in 81% of studies), and the use of inadequate samples (in 74% of studies), which could influence the studies' results and their precision.

3.4. | Results of individual studies and data synthesis

All analyses are based on data extracted from the published reports of identified studies, which apart from aggregate data also included raw data on three occasions (Thilander et al., 1994; Bernard et al., 2004;
Kuijpers et al., 2006) that were re-analyzed in Appendix S6a-6c. The results of the Thilander et al. (1994) study indicated that patient age, skeletal maturation stage, and residual height growth all had a significant effect on the amount of observed IIP, with older/more skeletally mature patients having less IIP. Additionally, maxillary implants were tangentially more likely to experience considerable IIP (>1 mm) than mandibular ones.

As far as data synthesis is concerned, initially the average event rates or the average amounts of the primary and secondary outcomes were calculated across all studies through indirect random-effects meta-analyses (1-group pooling; Table 2). The results indicated that about half of placed implants show after average periods of 4.0 to 18.5 year signs of IIP (9 studies; pooled average rate of 50.5%; Figure 3) and the extent of which is on average at 0.58 mm (6 studies; Figure 4). However, extreme heterogeneity existed across the identified studies, which led to a random-effects prediction of 10.4% to 90.0% for the prevalence of IIP and a prediction of up to 1.43 mm for the extent of IIP. The pooled prevalence for IIP of considerable magnitude (IIP > 1 mm), again after an average follow-up of 4.3 to 18.5 years, was 20.8% (5 studies; Figure 5), which meant that about every 5th implant placed will be in risk of considerable IIP at some time. For this analysis too, great heterogeneity was seen across studies, which led to a very imprecise future prediction for IPP > 1 mm prevalence of 4.3%-60.9%. Finally, as far as mesiodistal movements of the adjacent teeth are concerned, meta-analysis of 9 studies indicated that the risk of PCP loss after mean observations of 3.9 to 7.0 years was 46.3% (Figure 6), which translated roughly to every second implant loosing its PCP. Similarly to the previous analyses however, a wide random-effects prediction was calculated, which placed the PCP loss risk for a future implant somewhere between 20.0% and 74.8%, due to the extreme heterogeneity seen across the results of existing studies.

This heterogeneity observed across studies was attempted to be explained through various patient-, implant-, or study-related characteristics (Table 3). As such, implant placement jaw was significantly associated with IIP development, with IIP rate increasing parallel to an increasing proportion of implants placed in the maxilla (P=0.02). Additionally, the extent of observed IIP was significantly associated with patient age, patient sex, placement jaw, and follow-up duration. This indicated that smaller amounts of IIP were observed for older patients and for male patients. Additionally, the amount of IIP observed was significantly associated with observation period, which averaged a 0.05 mm increase in IIP per year.

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Interestingly, the amount of IIP seem to decrease as the proportion of implants placed in the maxilla increased, which is contrary to the effect seen for the prevalence of IIP. However, a post hoc meta-regression indicated an association of mean age with % of implants placed in the maxilla across studies (11.7% increase of maxillary-placed implants for every 10 patient years; \( P<0.001 \)), which could indicate a possible confounding effect. Finally, implantation area in terms of anterior jaw (up to the canine) or posterior jaw (from the premolar and posteriorly) was significantly associated with the risk of considerable IIP (>1 mm).

Insights into the effect of patient-, implant-, or study-related characteristics can be more robustly gleamed from the direct random-effects meta-analyses of these factors from within- and across-studies (2-groups’ comparison; Table 4). Patient sex was confirmed as a significant factor for IIP, where male patients had lower odds for IIP than female patients (3 studies; \( OR=0.3; 95\% \text{ CI}=0.1 \text{ to } 0.9 \)). This is translated clinically to an NNT of 6 (95% CI=3 to 77), which indicates that for every 6 implants placed in female patients, one more implant will have IIP than in male patients. A tendency for less IIP in the mandible compared to the maxilla was seen (MD=-0.21 mm), although this was marginally close to significance (\( P=0.07 \)). Apart from that, a significant influence was seen for follow-up duration and PCP side on the observed PCP loss, where the odds for PCP loss increased by about 10% each additional year the implant was in the mouth (2 studies; \( OR=1.1; 95\% \text{ CI}=1.0 \text{ to } 1.1 \)) and implants had higher odds of losing their mesial PCP than their distal one (5 studies; \( OR=2.3; 95\% \text{ CI}=1.1 \text{ to } 4.8 \)). This would be translated to an NNT of 6 (95% CI=3 to 91) and would indicate that for every 6th implant placed, one additional mesial PCP is lost over the loss rate of the distal PCP.

The GRADE approach was used to assess the quality of evidence originating from direct meta-analytical comparisons (Table 5). As analyses were done in an explorative fashion and multiple meta-analytical comparisons existed (Table 4), only comparisons with \( P < 0.05 \) were included in the GRADE approach (Table 5), where very low quality of evidence was found in all cases. This indicates that our confidence in these recommendations is limited and could be altered by future studies.

Finally, several patient-, implant-, or study-related characteristics were assessed within included studies, but as only one study contributed to each comparison, no meta-analysis could be performed (Appendix S7). Summarizing studies with results that were both statistically and clinically relevant, it was
seen that IIP was greater in the anterior region (compared to the posterior region), in orthodontically-treated patients (compared to not treated patients), and in skeletally young patients (compared to skeletally mature patients). As far as PCP is concerned, greater PCP loss was seen in patients over 60 years old (compared to patients between 20-39 years old), as well as for teeth with increased marginal bone loss (compared to no bone loss), with bone density D3-D4 according to Misch (compared to categories D1-D2), for single-rooted teeth (compared to multi-rooted teeth), for teeth with increased mobility (compared to teeth with normal mobility), and for teeth participating in lateral occlusal guidance (compared to non-participating teeth). However, only one study contributed to each factor and caution is warranted by the interpretation of these, until they are confirmed by future studies.

3.5. | Sensitivity analyses
Sensitivity analyses were attempted using the blinding of outcome assessment, but no identified study employed properly blinded assessors. Likewise, sensitivity analyses using only prospective studies were impossible, as 1-2 prospective studies were included at best in each meta-analysis, making comparisons unstable. A post hoc sensitivity analysis was conducted by including data on the patient level, instead of the implant-level that was included in the main analysis (Appendix S8a-b), which indicated no important influence on effect estimation, precision, or heterogeneity. The only exception was the direct meta-analysis of IIP among male and female patients, where the sensitivity analysis found a smaller effect (RR of 0.7 compared to OR of 0.3), which was attributed to the ORs used in the main analysis that were adjusted for confounders. A post hoc sensitivity analysis including only studies with patients over 20 years old (judging by their inclusion criteria and age range) indicated similar results to the main analysis (Appendix S9). Finally, an a priori sensitivity analysis was attempted by including only large-scale studies (set as including at least 100 implants), but could only partially be conducted, and no discrepancies were found (Appendix S10).

4 | DISCUSSION
4.1. | Summary of evidence
To our knowledge this is the first systematic review to summarize and assess in a systematic manner the late post-treatment complications of dental implants placed among natural teeth. The literature search yielded a total of 27 (mostly retrospective) non-randomized studies including at least 1572 patients (mean age 42.2 years; 51.2% female) and at least 7,835 dental implants followed for up to 18.5 years post-insertion. The pooled % prevalence of IIP on tooth level was 50.5% (9 studies; 95% CI=26.3-74.5%; Figure 3) and the pooled average IIP extent was 0.58 mm (6 studies; 95% CI=0.3-0.8 mm; Figure 4), while IIP>1 mm was seen for 20.8% of placed implants (5 studies; 95% CI=8.3-37.1%; Figure 5). This indicated that both IIP on general and considerable IIP (> 1 mm) are frequent complications of dental implants during their long-term function in the mouth. As stated before, this has been described by some authors as a response to sagittal or transversal growth of the jaws during adolescent and post-adolescent active growth (Thilander et al., 1994). Indeed, re-analysis of available raw data indicated that the amount of IIP was directly associated to the skeletal maturation phase as gauged by hand-wrist radiographs and to the amount of residual height a patient attained through growth (Appendix S6b). However, the results were the same in the sensitivity analysis with the inclusion criterion of only patients ≥ 20 years old (Appendix S9), with IIP prevalence being 43% (including patients 27-63 years old), IIP extent being 0.44 mm (including patients 20-56 years old), IIP > 1 mm prevalence being 42% (including patients 33-58 years old), and PCP loss prevalence being 46% (including patients 21-83 years old). This indicates that both IIP and PCP are not limited in the active growth period of adolescence and early adulthood. Other studies have described that IIP can also be seen among mature adults with practically no active growth potential, as a response to ‘slow growth’ and the continuous eruption of natural teeth (Oesterle and Croni, 2000). The available data from Bernard et al. (2004) corroborate this, as even patients older than 35 years showed definite signs of IIP (mean IIP of 0.67 mm and range of 0.12-1.86 mm for the 19 patients over 35 years).

As far as the extent of IIP is concerned, the results of existing studies were very heterogeneous, which was reflected in a random-effects prediction for IIP ranging from 0 to 1.43 mm (Table 2), and even IIPs of up to 1.86 or 2.00 mm have been reported (Appendix S6a-c). It seems that IIP is the result of a slow continuous process through time with an estimated mean increase of 0.05 mm per observation year (Table 3), which indicates that the combination of patient age and follow-up duration might explain some of the heterogeneity observed across studies. It seems therefore prudent that regular clinical examinations of...
placed implants take place to timely identify implant crowns with IIP, where action might be indicated (for example in terms of crown replacement).

Additionally, a significant influence of patient sex on IIP was found, which was supported by indirect (Table 3) and direct evidence (Table 4) and indicated that male patients were associated with milder IIP than female patients. This might be attributed to the more pronounced increase of anterior face height and posterior rotation of the mandible seen among female patients (Jemt et al., 2007). Especially in late growth periods of 25-45 years of age, female patients seem to have greater increases in both overbite and upper anterior face height than male patients (Bishara and Jakobsen 1998), which might explain at least in part this sex-specific difference in IIP.

Furthermore, no reliable evidence was found of a significant influence of pre-implant orthodontic treatment on increased risk of IIP or PCP loss (Brahem et al. 2017). Even though signs were seen for increased risk of orthodontically-treated patients for IIP (OR=3.42), IIP>1 mm (RR=2.83), or PCP loss (OR=2.97) were found (Appendix S7), these were not statistically significant (P>0.05). Additionally, a potentially large difference in the amount of IIP was found between orthodontically treated and untreated patients (IIPs of 0.97 and 0.21 mm, respectively) by one study (Gjelvold et al. 2017). However, caution is warranted since the risk of confounding by indication is high, due to the non-randomized design of included studies. To put it simply, patient receiving orthodontic treatment might present with more extreme craniofacial configurations in the vertical or sagittal plane and a potential for increased mandibular rotation than non-orthodontic patients, which might directly influence the observed IIP or PCP loss. Therefore, additional prospective studies are needed with either randomized design or statistical methods that minimize confounding in order to provide more conclusive evidence on the subject.

The influence of craniofacial morphology on the observed IIP has been previously suggested (Jemt et al. 2007), but remains currently unclear. This is based on the assumption that patients with slow continuous posterior rotation of the mandible, combined with slow increase of anterior face height, would present a more "long-face" appearance in combination with greater infraposition of single-implant restorations in relation to adjacent anterior teeth in the upper jaw. However, this was not formally confirmed from the single study on the matter (Bergenblock et al. 2012), even though long-face patients tended to have higher IIP odds than normal-face patients (OR=2.14; P=0.42). This needs to be assessed in the future.
with robust methodology (for example through cephalometric analysis), as only a subjective evaluation of face shape was performed in the currently existing study.

As far as the review’s secondary outcome of PCP loss is concerned, a likewise high prevalence of 46.3% was found (Table 2; Figure 6), which indicated that almost every second implant might be in risk. Open PCPs of implant-restorations have been associated with increased patient discomfort (Jeong et al., 2015; Ryu et al., 2016), which might be attributed to the increased food impaction between teeth (Jeong et al., 2015), reduced fill of the proximal spaces by the papilla (Jeong et al., 2015), and periodontal health (Jernberg et al., 1983). Also, similar to IIP, the process of PCP loss seemed to be a continuous procedure, with its prevalence increased with each follow-up year (Table 4; OR=1.09) and with the time of half occurrence being reported between 3.0 years (Pang et al., 2017) and 5.5 years post-insertion (Koori et al., 2010).

There was a clear predilection of PCP loss for the mesial PCP of implant-supported prostheses over the distal ones (Table 4), which remained after including only bounded cases of restorations (i.e. having both mesial and distal PCPs with natural teeth) (Pang et al., 2017). This has been attributed to mesial drifting of the teeth mesially to the implant restoration mesial components of the occlusal forces (Heij et al. 2006; Koori et al., 2010; Wat et al. 2011). Finally, marginal bone loss of the adjacent tooth was significantly associated with PCP loss (Pang et al., 2017), which could be explained by an increased mesial dislocation of the tooth under occlusal forces (Wei et al., 2008). All these indicate that the physiological or increased mobility of the natural adjacent teeth in combination with the anterior or lateral force components of mastication might play an important role in PCP loss of the implant-supported reconstruction.

4.2. | Strengths and limitations

The strengths of this systematic review consist of the registration of its a priori protocol in PROSPERO (Sideri et al., 2018), its exhaustive literature search, its improved analytical methods (Veroniki et al., 2016; Petropoulou et al., 2017), the use of the GRADE approach (Guyatt et al. 2011) to assess the quality of the meta-evidence, and the transparent provision of the study’s data (Papageorgiou et al. 2018). However, certain limitations also exist. First and foremost, this systematic review included only non-randomized trials that are at higher risk of bias than randomized ones (Papageorgiou et al., 2015b). As the scope of the
review pertained more to adverse effects and diagnosis, non-randomized designs might be applicable, but the vast majority of included studies (85%) were retrospective and therefore at higher risk of bias than prospective studies (Papageorgiou et al., 2015c). Additionally, methodological issues existed for all included studies, as has been often reported for clinical trials in prosthodontics and implant dentistry (Papageorgiou et al., 2015a), and these might have influenced the review’s results. Furthermore, the identified studies were predominantly small and this might introduce small-study effects (Cappelleri et al. 1996). Finally, the limited number of included studies and their suboptimal reporting did not enable robust assessments of heterogeneity, as well as the conduct of several analyses for subgroup, small-study effects, and reporting biases that were planned.

5 | CONCLUSIONS

Based on a limited number of mostly small to medium non-randomized studies on the long-term performance of implant supported restorations among natural teeth, it seems that about every second implant is affected by IIP and PCP loss during its first 5 to 15 years of life. However, high heterogeneity exists among the results of existing studies, which make accurate predictions about the risk and extent of these adverse effects difficult. There is some scant evidence about increased risk of IIP for female patients and increased risk of PCP loss for the mesial side of the implant, but the quality of evidence is very low. Given the high prevalence of both IIP and PCP loss and their potential influence on patient satisfaction, further research on the minimization and treatment of IIP and PCP loss is advised, which should however be utilized using well-controlled prospective blinded study designs with higher internal validity than existing studies.
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FIGURE 1 PRISMA flow diagram for the identification and selection of eligible studies

561 records identified electronically

18 records identified manually

152 duplicates were removed

391 records were screened

225 were excluded by title/abstract

161 Full texts were checked for eligibility against the criteria

127 were not eligible
6 had missing full texts
5 was no clinical study
1 with systematic health problems
5 had no implants among natural teeth
21 were on tooth-implant restorations
1 were on surgical aspects
1 assessed implants in the short-term
70 included no relevant outcomes
3 assessed caries/loss of adjacent teeth
8 were review articles
5 were case series/reports
1 was study protocol
5 had data handling issues

34 papers (27 unique studies) were included
FIGURE 2  Summary of the methodological adequacy (including potential bias) of identified studies using a modified Newcastle-Ottawa tool

1. Selection
   - Representative of cohort
   - Ascertainment of exposure
   - Outcome was absent at start

2. Outcome
   - Blind assessment
   - Method valid and reliable
   - Free from contact artifacts
   - Method reliability assessed
   - Follow-up adequate for outcome
   - Follow-up of the whole cohort

3. Reporting
   - Was the study’s main scope
   - Patient characteristics given
   - Treatment characteristics given

4. Bias
   - Prospective planning/conduct
   - Adjust for variable follow-ups
   - Clustering adequately assessed
   - Adjusted for confounders
   - Sufficient sample size

Legend:
- Not applicable
- Unclear
- Criterion met
- Criterion half-met
- Criterion unmet
FIGURE 3   Contour enhanced forest plot of the pooled % event rate of implant infraocclusion at implant level. CI, confidence interval; mAge, mean age at implant placement in year; mFU, mean follow-up in years after implant placement; R, range

| Study            | mAge (R)       | mFU (R)       | Implant infraposition (% event rate) | % Rate (95% CI) | Weight |
|------------------|----------------|---------------|--------------------------------------|-----------------|--------|
| Avivi-Arber 1996| 33.5 (14.5-63.9)| 4.0 (1.0-8.0) | 33.5 (14.5-63.9)                      | 3.39 (0.13, 10.79) | 11     |
| Bonde 2013       | NR (NR)        | 10.0 (8.0-12.0)| 10.0 (8.0-12.0)                       | 18.07 (8.52, 30.22) | 11     |
| Ekfeldt 2011     | 30.0 (27.0-63.0)| 10.5 (10.0-11.0)| 30.0 (27.0-63.0)                      | 17.71 (6.53, 32.86) | 11     |
| Jemt 2007        | 26.9 (NR)      | 15.9 (NR)     | 26.9 (NR)                             | 39.65 (22.91, 57.74) | 11     |
| Chang 2012       | 40.0 (19.0-71.0)| 8.0 (-)       | 40.0 (19.0-71.0)                      | 57.82 (40.58, 74.12) | 11     |
| Dierens 2013     | 23.0 (33.0-68.0)| 18.0 (16.0-22.0)| 23.0 (33.0-68.0)                      | 70.02 (51.00, 86.00) | 11     |
| Bergenblock 2012 | 31.4 (18.0-56.0)| 18.5 (17.0-19.0)| 31.4 (18.0-56.0)                      | 70.01 (54.02, 83.63) | 11     |
| Brahem 2017      | 29.7 (NR)      | 7.0 (NR)      | 29.7 (NR)                             | 81.59 (70.58, 90.48) | 11     |
| Jamilian 2015    | 20.0 (NR)      | 5.6 (NR)      | 20.0 (NR)                             | 98.30 (85.99, 98.51) | 11     |
| Overall (I²=95%) |                |               | Overall (I²=95%)                      | 50.46 (26.28, 74.53) | 100    |

with 95% prediction
FIGURE 4  Contour enhanced forest plot of the pooled amount of implant infraocclusion in mm at implant level. CI, confidence interval; mAge, mean age at implant placement in year; mFU, mean follow-up in years after implant placement; R, range

| Study          | mAge (R)       | mFU (R)     | Implant infraposition (extent in mm) | Effect (95% CI) | Weight |
|----------------|----------------|-------------|--------------------------------------|-----------------|--------|
| Gjelvold 2017  | NR (NR)        | 7.5 (3.6-11.1) |                                      | 0.13 (0.01, 0.25) | 20     |
| Chang 2012     | 40.0 (19.0-71.0) | 8.0 (-)    |                                      | 0.38 (0.16, 0.60) | 18     |
| Vilhjalmsson 2013 | 34.8 (20.0-56.0) | 3.0 (-)     |                                      | 0.66 (0.15, 1.17) | 11     |
| Bernard 2004   | 31.0 (15.4-56.7) | 4.3 (1.1-9.1) |                                      | 0.69 (0.55, 0.83) | 20     |
| Kuijpers 2006  | 16.7 (12.9-18.8) | 11.0 (9.9-12.0) |                                      | 0.77 (0.42, 1.12) | 15     |
| Thilander 1994c| 15.3 (13.2-19.3) | 10.0 (-)    |                                      | 0.98 (0.69, 1.27) | 16     |
| Overall (I²=88%) |               |              |                                      | 0.58 (0.33, 0.83) | 100    |
| with 95% prediction |              |              |                                      | (0, 1.43)       |        |
FIGURE 5  Contour enhanced forest plot of the pooled % event rate of considerable implant infraocclusion (>1 mm) at implant level. CI, confidence interval; mAge, mean age at implant placement in year; mFU, mean follow-up in years after implant placement; R, range

| Study          | mAge (R)       | mFU (R)    | Implant infraposition >1 mm (% event rate) | % Rate (95% CI) | Weight |
|----------------|----------------|------------|------------------------------------------|-----------------|--------|
| Brahem 2017    | 29.7 (NR)      | 7.0 (NR)   |                                          | 4.34 (0.64, 11.11) | 21     |
| Jemt 2007      | 26.9 (NR)      | 15.9 (NR)  |                                          | 15.48 (4.86, 30.61) | 19     |
| Bernard 2004   | 31.0 (15.4-56.7) | 4.3 (1.1-9.1) |                                    | 18.28 (8.11, 31.40) | 21     |
| Bergenblock 2012 | 31.4 (18.0-56.0) | 18.5 (17.0-19.0) |                          | 35.71 (20.90, 52.07) | 20     |
| Dierens 2013   | 23.0 (33.0-58.0) | 18.0 (16.0-22.0) |                                     | 41.99 (23.75, 61.46) | 19     |
| Overall (I²=84%) |               |            |                                          | 20.84 (8.35, 37.09) | 100   |
| with 95% prediction |          |            |                                          | (4.30, 60.90)     |        |
FIGURE 6  Contour enhanced forest plot of the pooled % event rate of proximal contact point loss at implant level. CI, confidence interval; mAge, mean age at implant placement in year; mFU, mean follow-up in years after implant placement; PCP, proximal contact point; R, range

| Study      | mAge (R)         | mFU (R)    | Contact point loss to implant (% event rate) | % Rate (95% CI) | Weight |
|------------|------------------|------------|---------------------------------------------|-----------------|--------|
| Son 2009   | NR (NR)          | 6.0 (NR)   |                                             | 13.38 (10.11, 17.03) | 11     |
| Ryu 2016   | 60.0 (21.0-78.0) | 5.8 (0-14.9)|                                             | 28.31 (19.19, 38.43) | 11     |
| Byun 2015  | 56.0 (27.0-83.0) | 4.8 (0.3-13.0)|                                             | 34.11 (27.59, 40.96) | 11     |
| Koori 2010 | 58.4 (21.0-79.0) | NR (0.1-10.3)|                                             | 43.05 (36.05, 50.19) | 11     |
| Varthis 2016 | NR (19.0-91.0)    | NR (0.3-11.0)|                                             | 52.86 (45.46, 60.19) | 11     |
| Fukunishi 2016 | 61.6 (NR)    | 5.0 (NR)   |                                             | 57.26 (50.10, 64.27) | 11     |
| Pang 2017  | 58.4 (21.0-79.0) | 7.0 (-)    |                                             | 59.83 (54.23, 65.31) | 11     |
| Wong 2015  | 45.0 (27.0-74.0) | 3.9 (0.5-12.0)|                                             | 64.93 (53.18, 75.82) | 11     |
| Brahem 2017 | 29.7 (NR)        | 7.0 (NR)   |                                             | 69.83 (57.50, 80.86) | 11     |
| Overall (I²=97%) |             |            |                                             | 46.31 (32.52, 60.40) | 100    |
| with 95% prediction          |            |            |                                             | (20.00, 74.8)    |        |
### TABLE 1a  
Patient and implant characteristics of included studies

| Nr | Study ID       | Design; Setting; Country (ISO Alpha 3) | Patients (F/M); mAge (R) in years | Smok\% | Ortho\% | Imps | Restoration | Max\% | ANT\% |
|----|----------------|--------------------------------------|-----------------------------------|-------|---------|------|-------------|-------|-------|
| 1  | Avivi-Abber 1996 | uNRS; Uni; CAN                       | 41 (19/22); 33.5 (14.5-63.9)      | NR    | NR      | 49 Imps (NB) | SC    | 71\% | 63\% |
| 2  | Bergenblock 2012; Andersson 2013\a | rNRS; Clinic; SWE                    | 57 (25/32); 31.9 (15.0-57.0)      | 8/27  | 9\%     | 65 Imps (NB) | SC    | >50\% | 77\% |
| 3  | Bernard 2004    | rNRS; Uni; CHE                       | G1: 14 (9/5); 18.4 (15.5-21.0) G2: 14 (9/5); 43.6 (40.0-55.0) | NR    | NR      | G1-2: 40 Imps (ST) | SC    | 100\% | 100\% |
| 4  | Bonde 2013\b   | rNRS; Uni; DNK                       | 51 (NR); NR                        | NR    | NR      | 55 Imps (NB) | SC    | NR    | NR   |
| 5  | Brahem 2017     | uNRS; Uni; DNK                       | G1: 20 (13/7); 33.8 (G1-2 18.0-61.0) G2: 37 (24/13); 27.5 (G1-2 18.0-61.0) | NR    | in G2 (43\% Ret) | G1-2: 89 Imps (NR) | SC    | 100\% | 100\% |
| 6  | Byun 2015\c; Jeong 2015 | rNRS; Uni; KOR                    | 94 (44/50); 56.0 (27.0-83.0)      | NR    | NR      | 188 Imps (NR) | SC/FIP | 48\% | 6\%  |
| 7  | Chang 2012      | rNRS; Uni; SWE                       | 31 (13/18); 40.0 (19.0-71.0)      | NR    | NR      | 33 Imps (AT) | SC    | 100\% | 58\% |
| 8  | Cosyn 2012      | rNRS; Uni/practice; BEL             | 97 (37/60); 51.0 (23.0-80.0)      | NR    | NR      | 97 Imps (NB) | SC    | 100\% | 66\% |
| 9  | Dieren 2013\d; Dieren 2016 | rNRS; clinic; SWE                | 21 (9/12); 23.0 (33.0-58.0)      | 4\%   | NR      | 24 Imps (NB) | SC    | 100\% | 83\% |
| 10 | Ekfeldt 2011; 2017 | rNRS; clinic; SWE              | 30 (NR); 23.0 (17.0-72.0)        | 3\%   | NR      | 30 Imps (NB) | SC    | 84\% | 6\%  |
| 11 | Fukunishi 2016  | uNRS; clinic; JAP                  | 135 (83/52); 61.6 (NR)            | NR    | NR      | 185 Imps (BM) | SC    | 0\%  | 0\%  |
| 12 | Gjevold 2017    | rNRS; clinic; SWE                  | 87 (36/51); 21.4 (17.0-68.0)     | 17\%  | 67\%    | 126 Imps (DE) | SC    | 81\% | 83\% |
| 13 | Jamilian 2015   | rNRS; Uni; IRN                      | 10 (5/5); 20.0 (NR)               | NR    | Prb. (100\%) | 14 Imps (NR) | SC    | 100\% | 100\% |
| 14 | Jemt 2007\e; Jemt 2008 | rNRS; clinic; SWE               | 25 (7/18); 26.9 (NR)              | NR    | NR      | 56 Imps (NB) | SC    | 100\% | 100\% |
| 15 | Koori 2010      | rNRS; practice; JAP                | 105 (67/38); NR (20.0-78.0)       | NR    | NR      | 353 Imps (misc) | SC/FIP | 26\% | NR   |
| 16 | Kuipers 2006    | rNRS; clinic; NLD                  | 8 (3/5); 16.6 (12.1-18.9)        | NR    | 86\%    | 11 Imps (NR) | SC    | 100\% | 100\% |
| 17 | Nilsson 2017    | pNRS; hosp; SWE                    | 52 (29/23); 22.0 (17.0-52.0)     | 15\%  | Few     | 69 Imps (ST) | SC    | 93\% | 100\% |
| 18 | Pang 2017       | pNRS; Uni; KOR                     | 150 (83/67); 58.4 (21.0-79.0)    | NR    | NR      | 384 (misc) | SC/FIP | 42\% | 0\%  |
| 19 | Ren 2016        | pNRS; Uni; CHN                     | 20 (10/10); 40.0 (NR)             | NR    | NR      | 20 Imps (NB) | SC    | 0\%  | 0\%  |
| 20 | Ryu 2016        | uNRS; Uni; KOR                     | 28 (14/14); 60.0 (21.0-78.0)     | NR    | NR      | 62 Imps (NR) | SC/FIP | NR    | NR   |
| 21 | Schwartz-Arad 2015 | rNRS; clinic; ISR                 | 35 (14/21); 29.2 (NR)             | NR    | NR      | 35 (NR) | SC    | 100\% | 100\% |
| 22 | Son 2009        | uNRS; Uni; KOR                     | 196 (NR); NR                      | NR    | NR      | NR; NR | NR    | NR    | 0\%  |
| 23 | Thilander 1994\f; Thilander 1999; Thilander 2001 | rNRS; Uni; SWE                  | 15 (7/8); 15.3 (13.2-19.3)       | NR    | 100\%   | 27 Imps (NB) | SC    | 70\% | 67\% |
| 24 | Varthis 2016    | rNRS; Uni/practice; USA            | 128 (NR); NR (19.0-91.0)          | NR    | NR      | 174 Imps (misc) | SC    | NR    | NR   |
| 25 | Vilhjalmsson 2013 | pNRS; Uni; NOR                   | 26 (11/15); 34.8 (20.0-56.0)     | 35\%  | NR      | 28 Imps (NB/AT) | SC    | 100\% | 100\% |
| 26 | Wang 2016\g     | rNRS; practice; AUS                | NR; NR                            | NR    | NR      | 5621 Imps (NR) | SC/FIP | NR    | NR   |
| 27 | Wong 2015\h     | rNRS; Uni; HKG                     | 45 (27/18); 45.0 (27.0-74.0)     | NR    | None    | (NB) | SC/FIP | NR    | 0\%  |

ANT, in anterior region (canine to canine); AT, Astra Tech; BM, Biomet; DE, Dentsply; F/M, female/male; FIP, fixed implant prosthesis; FR, Friatec; G, group; Hosp, hospital; Imp, implant; mAge, mean age; Max, in the maxilla; Misc, miscellaneous; NB, Nobel Biocare; NR, not reported; Ortho, had orthodontic treatment prior to implant treatment; pNRS, prospective non-randomized study; Prb., probably; R, range of included ages; Ret, retention regimen; rNRS, retrospective non-randomized study; SC, single crown; Smok, smokers at baseline; ST, Straumann; Uni, university; uNRS, unclear design of non-randomized study (probably retrospective); WA, Warentec.

\a follow-up publication of previous studies (Andersson B. Implants for single-tooth replacement. A clinical and experimental study on the Brånemark Cera-One system. Swed Dent J 1995; Suppl. 108;7–41 / Andersson B, Ödman P, Lindvall A-M, Brånemark P-I. Cemented single crowns on osseointegrated implants after 5 years: results from a prospective study on CeraOne abutments. Int J Prosthodont 1998; 11:212–218).

\b follow-up publication of previous study (Bonde MJ, Stokholm R, Isidor F, Schou S. Outcome of implant-supported single-tooth replacements performed by dental students. A 10-year clinical and radiographic retrospective study. Eur J Oral Implantol 2010;3:37-46).

\c the subsequent identified study Jeong 2015 was judged to have the same cohort according to the patient/methods description given; results regarding mesiodistal tooth-to-implant distance and contact point height are given only at the follow-up appointment and not at baseline and therefore are not reported here.
follow-up publication of previous study (Dierens M, Vandeweghe S, Kisch J, Nilner K, De Bruyn H. Long-term follow-up of turned single implants placed in periodontally healthy patients after 16-22 years: radiographic and peri-implant outcome. Clin Oral Implants Res 2012;23(2):197-204). The subsequent identified study Dierens 2016 also used the same patient cohort, but reported only infrapositions that were severe enough to lead to crown replacement and therefore the Dierens 2013 publication is primarily used here.

follow-up publication of previous report (Jemt T, Ahlberg G, Henriksson K, Bondevik O. Changes of anterior clinical crown height in patients provided with single-implant restorations after more than 15 years of follow-up. Int J Prosthodont 2006;19:455–461) The subsequent identified study Jemt 2008 also used the same patient cohort, but reported infrapositions in terms of crown replacement need and therefore the Jemt 2007 study is primarily used here.
two subsequent identified studies Thilander 1999 and Thilander 2001 reported results from the same cohort of patients, but with different follow-up.

various types of fixed restorations were included that were supported by implants, teeth, or both. Only single implant crowns, single-implant cantilever crowns, and three-unit implant-supported fixed restorations are included here.
TABLE 1b Outcome details of the included studies

| Nr | Study ID | Analyzed sample | Outcome | Outcome details | mFU (R) in years \( ^{1} \) | Treatment |
|----|----------|-----------------|---------|-----------------|-----------------|-----------|
| 1  | Avivi-Arber 1996 | 35/41 Pats; 42/49 Imps | IIP | bin; clin; Pat/Imp-L | 4.0 (1.0-8.0) | Replacement |
| 2  | Bernard 2004 | All | IIP | cont; Rx; Pat/Imp-L | 4.3 (1.1-9.1) | NR |
| 3  | Bergenblock 2012; Andersson 2013 | Prb all | IIP | cat (Jemt 2007); photo.; Pat/Imp-L; 4 obs | NR (17-19) | Replacement |
| 4  | Bonde 2013 | 42/51 Pats; 46/55 Imps | IIP | bin; clin; Imp-L | 10.0 (8.0-12.0) | NR |
| 5  | Brahem 2017 | Prb all | IIP | MD displacement at crown | cat (Jemt 2007); 3D superimposition.;Imp-L; cat; clin | 7.0 (NR) | NR |
| 6  | Byun 2015; Jeong 2015 | Prb all | PCP loss | cat (O’Leary et al., 1975); clin | 4.8 (0.3-13.0) | Tx |
| 7  | Chang 2012 | 31/33 Imps | IIP | MD displacement at root | Rx; Imp-L; Rx; Imp-L | 1.0/ 5.0/ 8.0 (-) | NR |
| 8  | Cosyn 2012 | Prb all | PCP loss | MD displacement at root | bin; bin; clin | 2.6 (1.4-3.5) | NR |
| 9  | Dierens 2013; Dierens 2016 | Prb all | IIP | cat; clin/phot | 18.0 (16.0-22.0) | NR |
| 10 | Eksfeldt 2011; 2017 | 30/31 Pats/Imps | IIP | bin; NR | NR (10.0-11.0) | NR |
| 11 | Fukunishi 2016 | Prb all | PCP loss | bin; clin | 5.0 (NR) | NR |
| 12 | Gjelvold 2017 | 59/87 Pats; 85/126 Imps | IIP | MD displacement at crown | cont; Rx; Pat/Imp-L | 7.5 (3.6-11.1) | NR |
| 13 | Jamilian 2015 | All | IIP | BP displacement at crown | cont; Rx; Pat/Imp-L | 5.6 (NR) | NR |
| 14 | Jemt 2007; Jemt 2008 | All | IIP | BP displacement at crown | cat (Jemt 2007); photo.; Imp-L; 3 obs | 15.9 (NR) | NR |
| 15 | Koon 2010 | All | PCP loss | bin; clin; Imp-L | (0.1-10.3) | NR |
| 16 | Kuijpers 2006 | All | IIP | cont; clin/Rx; Imp-L | 11.0 (9.9-12.0) | NR |
| 17 | Nilsson 2017 | All | IIP | cont; clin; Imp-L | 4.5 (3.3-6.6) | Replacement |
| 18 | Pang 2017 | Prb all | PCP loss | bin; clin; Imp-L | 7.0 (-) | NR |
| 19 | Ren 2016 | 18/20 Pats/Imps | PCP tightness | cont; clin-app; Imp-L | 1.0 (-) | NR |
| 20 | Ryu 2016 | All | PCP loss | cat (O’Leary et al., 1975); clin | 5.8 (0-14.9) | NR |
| 21 | Schwartz-Arad 2015 | All | IIP | cont; clin; Imp-L | 7.5 (NR) | NR |
| 22 | Son 2009 | NR | PCP loss | bin; clin | NR (0-6.0) | Composite filling; Replacement |
| 23 | Thilander 1994; Thilander 1999; Thilander 2001 | 14/15 Pats; 26/27 Imps | IIP | cont; clin/Rx; Pat/Imp-L | 3.0/ 8.0/ 10.0 (-) | NR |
| 24 | Varthis 2016 | Prb all | PCP loss | bin; clin/floss & Rx | (0.3-11.0) | NR |
| 25 | Vilhjalmssson 2013 | 23/26 Pats | IIP | cont; Rx; Pat/Imp-L | 3.0 (-) | NR |
| 26 | Wang 2016 | Prb all | PCP loss | bin; clin; Imp-L | 3.1 (NR) | NR |
| 27 | Wong 2015 | Prb all | PCP loss | PCP space | bin; clin-matrix; Imp-L | 3.9 (0.5-12.0) | NR |

app, appliance specific for contact area/point/tightness/thickness measurement; bin, binary; BP, buccopalatal (or -lingual); cat, categorical; clin, clinical examination; cont, continuous; Imp, implant; IIP, infraposition of the implant restoration compared to the adjacent teeth; L, level; MD, mesiodistal; NR, not reported; obs, observers; Pat, patient; PCP, proximal contact point; photo, photographic examination; Prb, probably; Rx, radiology.

\( ^{1} \) Follow-up ranges given as (-) indicate that exact follow-up periods were followed in the study.
TABLE 2  Indirect random-effects meta-analysis across studies on the pooled event rate or values of the primary and secondary outcomes at implant/tooth/contact point level. All datasets (pertaining to different follow-ups) are extracted from each study, but only the one with the longest follow-up is included in the analysis.

| Outcome                        | Studies | Effect   | 95% CI          | $\text{tau}^2$ (95% CI) | $I^2$ (95% CI) | 95% prediction       |
|--------------------------------|---------|----------|-----------------|-------------------------|----------------|----------------------|
| IIP, infraposition of the implant restoration relative to adjacent teeth |         |          |                 |                         |                |                      |
| binary % event rate            | 9       | 50.5%    | 26.3% to 74.5%  | 0.56 (NC)               | 95% (92 to 97%) | 10.4 to 90.0%        |
| continuous extent in mm        | 6       | 0.58 mm  | 0.33 to 0.83 mm | 0.08 (0.02 to 0.53)     | 88% (69 to 98%) | 0* to 1.43 mm        |
| IIP > 1 mm, binary % event rate| 5       | 20.8%    | 8.3 to 37.1%    | 0.14 (NC)               | 84% (63 to 93%) | 4.3 to 60.9%         |
| PCP, proximal contact point    | 9       | 46.3%    | 32.3 to 60.6%   | 0.19 (NC)               | 97% (96 to 98%) | 20.0 to 74.8%        |

CI, confidence interval; IIP, infraposition of the implant restoration relative to adjacent teeth; NC, non-calculable; PCP, proximal contact point. *truncated at zero.
TABLE 3 Random-effects meta-regression on the event rates or average values of the primary and secondary outcomes (indirect data) at implant/tooth/contact point level. All datasets (pertaining to different follow-ups) are extracted from each study and all are included in the analyses.

| Outcome                  | Factor     | Category                  | n  | b       | 95% CI         | P     |
|--------------------------|------------|---------------------------|----|---------|----------------|-------|
| IIP binary % event rate  | Age        | Per year                  | 9  | -0.90%  | -4.8 to 3.0%   | 0.60  |
|                          | Sex        | % male (per 10%)          | 8  | -11.20% | -35.1 to 12.7% | 0.29  |
|                          | Follow-up  | Per year                  | 10 | 1.90%   | -1.6 to 5.3%   | 0.25  |
|                          | Jaw*       | % in maxilla (per 10%)    | 8  | 19.70%  | 5.1 to 34.3%   | 0.02† |
|                          | Region     | % anterior (per 10%)       | 9  | 5.50%   | -1.6 to 12.6%  | 0.11  |
| IIP continuous extent in mm | Age        | Per year                  | 13 | -0.02 mm| -0.03 to -0.01 mm | 0.001† |
|                          | Sex        | % male (per 10%)          | 12 | -0.48 mm| -1.06 to 0.11 mm | 0.10† |
|                          | Follow-up  | Per year                  | 14 | 0.05 mm | -0.01 to 0.10 mm | 0.08† |
|                          | Jaw        | % in maxilla (per 10%)    | 14 | -0.11 mm| -0.22 to -0.01 mm | 0.04† |
|                          | Region     | % anterior (per 10%)       | 13 | 0.04 mm | -0.06 to 0.15 mm | 0.41  |
| IIP > 1 mm binary % event rate | Age        | Per year                  | 5  | -1.80%  | -9.7 to 6.1%   | 0.52  |
|                          | Sex        | % male (per 10%)          | 4  | NC      |                |       |
|                          | Follow-up  | Per year                  | 5  | 1.60%   | -1.4 to 4.7%   | 0.19  |
|                          | Jaw        | % in maxilla (per 10%)    | 4  | NC      |                |       |
|                          | Region     | % anterior (per 10%)       | 5  | -12.90% | -26.3 to 0.4%  | 0.05† |
| PCP loss binary % event rate | Age        | Per year                  | 8  | -0.40%  | -1.5 to 0.6%   | 0.34  |
|                          | Sex        | % male (per 10%)          | 8  | -12.70% | -29.8 to 4.5%  | 0.12  |
|                          | Follow-up  | Per year                  | 8  | 0.50%   | -16.8 to 17.7% | 0.95  |
|                          | Jaw        | % in maxilla (per 10%)    | 6  | 0.40%   | -4.4 to 5.2%   | 0.84  |
|                          | Region     | % anterior (per 10%)       | 8  | 1.20%   | -2.8 to 5.2%   | 0.50  |

b, unstandardized meta-regression coefficient; CI, confidence interval; IIP, infraposition of the implant restoration relative to adjacent teeth; NC, non-calculable; PCP, proximal contact point.
† Statistically significant meta-regression findings with P<0.10
| Outcome | Reference | Experimental | n | Effect | 95% CI | P  | I² (95% CI) | tau² (95% CI) | 95% prediction |
|---------|-----------|--------------|---|--------|--------|----|------------|----------------|---------------|
| IIP_binary | Female | Male | 3 | OR=0.29 | 0.10,0.88 | 0.03 | 0% (0%,98%) | 0 (0.55.68) | 0.390.39 |
| IIP_continuous | Central incisor | Lateral incisor | 2 | MD=0.12 | -0.21,0.44 | 0.48 | 0% (0%,97%) | 0 (0.3.16) | NA |
| IIP_continuous | Female | Male | 3 | MD=0.00 | -0.43,0.44 | 1.00 | 70% (16%,99%) | 0.10 (0.01,4.80) | NA |
| IIP_continuous | Posterior region | Anterior region | 2 | MD=0.19 | -0.14,0.52 | 0.25 | 34% (0%,100%) | 0.02 (0.58,82) | NA |
| IIP_continuous | Maxilla | Mandibula | 2 | MD=0.21 | -0.44,0.02 | 0.07 | 0% (0%,99%) | 0 (0.3,23) | NA |
| IIP > 1 mm_binary | Age over 20 years | Age under 20 years | 2 | RR=2.13 | 0.98,4.61 | 0.06 | 0% (0%,99%) | 0 (0.65,58) | NA |
| IIP > 1 mm_binary | Age over 25 years | Age under 25 years | 2 | RR=1.77 | 0.82,3.83 | 0.15 | 0% (0%,99%) | 0 (0.58,45) | NA |
| IIP > 1 mm_binary | Age over 30 years | Age under 30 years | 2 | RR=2.33 | 0.95,5.70 | 0.07 | 0% (0%,44%) | 0 (0.0,36) | NA |
| IIP > 1 mm_binary | Age over 30 years | Age between 25 and 30 years | 2 | RR=1.32 | 0.47,3.72 | 0.61 | 0% (0%,0%) | 0 (0.0) | NA |
| IIP > 1 mm_binary | Female | Male | 2 | RR=0.62 | 0.28,1.39 | 0.25 | 0% (0%,100%) | 0 (0.15,9.14) | NA |
| PCP loss_binary | Adjacent tooth not splinted | Adjacent tooth splinted | 2 | OR=0.6 | 0.19,2.49 | 0.58 | 76% (0%,100%) | 0.65 (0.87,3.51) | NA |
| PCP loss_binary | Adjacent tooth vital | Adjacent tooth non-vital | 2 | OR=1.19 | 0.66,2.17 | 0.56 | 29% (0%,100%) | 0.06 (0.2,0.93) | NA |
| PCP loss_binary | Patient age in years | | 2 | OR=1.02 | 0.99,1.05 | 0.16 | 0% (0%,100%) | 0 (0.0,20) | NA |
| PCP loss_binary | Distal PCP | Mesial PCP | 5 | OR=2.25 | 1.06,4.77 | 0.03 | 78% (25%,98%) | 0.56 (0.05,6.30) | 0.16,32.53 |
| PCP loss_binary | Female | Male | 4 | OR=0.83 | 0.33,1.10 | 0.19 | 0% (0%,89%) | 0 (0.0,68) | 0.44,1.54 |
| PCP loss_binary | Follow-up in years | | 2 | OR=1.09 | 1.03,1.16 | 0.004 | 0% (0%,0%) | 0 (0,0) | NA |
| PCP loss_binary | Maxilla | Mandibula | 5 | OR=1.32 | 0.84,2.08 | 0.23 | 59% (7%,95%) | 0.15 (0.01,1.82) | 0.31,5.62 |
| PCP loss_binary | Molar | Premolar | 2 | OR=0.84 | 0.40,1.77 | 0.64 | 66% (0%,100%) | 0.19 (0.29,3.97) | NA |

CI, confidence interval; IIP, infraposition of the implant restoration relative to adjacent teeth; MD, mean difference; NC, not calculable; OR, odds ratio; PCP, proximal contact point; RR, relative risk.
TABLE 5  Summary of findings table according to the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach

| Outcome | Trials (patients) | Relative effects (95% CI) | Anticipated absolute effects\(^a\) (95% CI) | Quality of the evidence (GRADE)\(^c\) | What happens |
|---------|-------------------|---------------------------|---------------------------------------------|-----------------------------------|--------------|
|         |                   |                           | CTR | EXP | Difference |                                             |              |
| IIP     | 3 studies (88 patients) | OR 0.3 (0.10 to 0.88) | 89.3\(^b\) | 70.8% (45.5 to 88.0) | 18.5% fewer implants (1.3 to 43.8 fewer) | ☐☐☐☐ very low\(^d\) due to bias | Lower IIP incidence among male patients |
|         |                   |                           | Female | Male |           |                                             |              |
| PCP loss| 5 studies (573 patients) | OR 2.3 (1.06 to 4.77) | 24.1\(^b\) | 41.7% (25.2 to 60.2) | 17.6% more PCPs (1.1 to 36.1 more) | ☐☐☐☐ very low\(^d\) due to bias | Greater incidence of PCP loss on the mesial side of the implant |
|         |                   |                           | Distal PCP | Mesial PCP |            |                                             |              |
| PCP loss| 2 studies (229 patients) | OR 1.1 (1.03 to 1.16) | 45.7\(^b\) | 47.8% (46.4 to 49.4) | 2.1% more PCPs (0.7 to 3.7 more) | ☐☐☐☐ very low\(^d\) due to bias | Incidence of PCP loss increases each year |
|         |                   |                           | Baseline year | Per extra year |          |                                             |              |

Factors associated with implant infra-position or proximal contact point loss.

Population & intervention: adolescent / adult patients receiving dental implant treatment.

Settings: university clinics, private practices, and clinics (Japan, South Korea, Sweden).

\(^a\) The basis for the risk in the control group (e.g., the median control group risk across studies) is provided in footnotes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

\(^b\) Response in the control group is based on average event rate of included studies in each case.

\(^c\) GRADE for both randomized and non-randomized studies starts from “high”.

\(^d\) Downgraded initially to ‘low’ due to the lack of randomization; further downgraded to very low for lack of blinding serious limitations (high risk of bias).

CI, confidence interval; CTR, control category; EXP, experimental category; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IIP, implant infra-position; PCP, proximal contact point.
## APPENDIX

### Appendix S1  List of databases searched with search strategies, limitations, and hits (all searched on January 10, 2018)

| Database                                                                 | Search strategy                                                                                                                                                                                                 | Limits     | Hits     |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|----------|
| MEDLINE (via PubMed)                                                     | (dent* OR tooth OR teeth OR osseointegrated) AND implant* AND ("natural dentition" OR "natural teeth" OR "adjacent teeth") AND ("adverse effects" OR "negative effects" OR "undesirable effects" OR "adverse reaction" OR "negative reaction" OR "undesirable reaction" OR complication$ OR tolerability OR toxicity) | Human      | 126      |
| https://www.ncbi.nlm.nih.gov/pubmed                                      |                                                                                                                                                                                                             | Human      | 63       |
| Embase                                                                  | Same as MEDLINE’s search 1                                                                                                                                                                                   |            | 34       |
| https://www.embase.com/login                                             | Same as MEDLINE’s search 2                                                                                                                                                                                   |            | 5        |
| Cochrane Database of Systematic Reviews                                 | Same as MEDLINE’s search 1                                                                                                                                                                                   |            | 2        |
| http://www.cochranelibrary.com/                                          | Same as MEDLINE’s search 2                                                                                                                                                                                   |            | 4        |
| Cochrane Central Register of Controlled Trials                          | Same as MEDLINE’s search 1                                                                                                                                                                                   |            | 4        |
| http://www.cochranelibrary.com/                                          | Same as MEDLINE’s search 2                                                                                                                                                                                   |            | 1        |
| Scopus                                                                   | Same as MEDLINE’s search 1                                                                                                                                                                                   | Dentistry  | 104      |
| https://www.scopus.com/                                                  | Same as MEDLINE’s search 2                                                                                                                                                                                   | Human(s)   | 36       |
| Web of Science                                                          | Same as MEDLINE’s search 1                                                                                                                                                                                   | Dentistry  | 128      |
| https://apps.webofknowledge.com/                                         | Same as MEDLINE’s search 2                                                                                                                                                                                   | Dentistry  | 42       |
| Virtual Health Library*                                                   | Same as MEDLINE’s search 1                                                                                                                                                                                   |            | 14       |
| http://bvsalud.org/en/                                                    | Same as MEDLINE’s search 2                                                                                                                                                                                   |            | 2        |

**Hits (with overlap)**

561

**Hits (without overlap)**

373

* covering among other the databases LILACS (Literatura Latino Americana em Ciências da Saúde), BBO (Brazilian Bibliography of Dentistry), WHOLIS (WHO Library Database), IBECS (Índice Bibliográfico Español en Ciencias de la Salud), CUMED (Cuba Medicina), PAHO (Pan American Health Organization), and MedCarib (Caribbean Health Sciences Literature).
APPENDIX S2 Additional details of review procedures

Notes on data extraction

For outcome measurement infraposition of the implant or vertical movement of the adjacent tooth are reported interchangeably. Additionally, only outcomes relevant to the present review as per its protocol are listed here.

When identified studies provided raw study results in tabular form in their paper, these were extracted and re-analyzed statistically. If this was allowed, descriptive statistics were calculated in both implant/tooth and patient level separately, to fuel both analyses. Generalized linear regression models for continuous or binary outcomes were fitted accounting for within-patient clustering with robust standard errors. Either the unstandardized regression coefficients or the relative risks with their 95% confidence intervals were calculated, according to outcome nature.

Notes on risk of bias assessment

- When judging the methodological adequacy of individual studies, and subjective visual/photographic assessments of IIP were conducted, multiple evaluators were deemed appropriate to remove some of this subjectivity.
- When raw data (including follow-up and confounders) were given in a study, these were re-analyzed firthisand for this review. Therefore, this was taken to be equivalent to the identified study accounting for different follow-ups or confounders in its analysis
- When a study included follow-up ranges of more than 2 years, this was taken to mean that sufficiently different follow-up periods existed, which the analysis should have taken account of.

Notes on data analysis

- Reports of horizontal crown movement (diagnostic limits were 0.50 or 0.25) were also taken to mean that a contact point loss existed.
Cosyn 2012 reported that 11 contact points were missing, but didn’t say how many were examined, so this was excluded; the same for the number of analyzed implants/teeth for the horizontal teeth (that was also excluded).

Eckfeldt 2011 gave a follow-up range of 10-11 years, but not a mean follow-up. For the analyses, a mean follow-up of 10.5 years was inputed, as the range was pretty narrow.

Koori 2010 gave multivariate regression with RR of only mesial contact losses. These were excluded from the analyses and raw data requested from the authors (simple cross-tabulation provided was included).

Nilsson 2017: “At the clinical follow-up, in mean 54 months after placement of the implant-supported restoration, several crowns in infraposition were registered and this will be discussed in an additional publication.”; otherwise the authors reported in the present publication only one infraposition, which was probably the most severe that was identified from patient/doctor. Data were excluded and the authors contacted for raw data or results.

Pang 2016 gave multivariate regression with HR of proximal contact losses. These were excluded from the analyses and raw data requested from the authors (simple cross-tabulation provided was included)

Schwartz-Arad 2015 gave % submersion rate per year and was therefore not compatible with the rest of the studies.

Varthis 2016 gave % of CP loss according to factors but not the eligible denumerators; this was not included and data were requested from the author (only the main overall CP loss rate is included).

Wang 2016 reported vaguely on “Food impaction and contact point complications included problems with the contours of implant prostheses, such as an open contact that led to food packing between the prosthesis and an adjacent tooth. In splinted crowns and FPDs, this also includes fitting surface issues.”. As this did not pertain solely to contact point problematic and no description of any assessment for contact point was given, this was though not to be precise enough to be included in the analyses.

Asked the authors of both Koori 2010 and Pang 2017 if there is any overlap between the two studies.
Notes on additional analyses

- Additional subgroup/meta-regression analyses were planned in the review protocol to assess the impact of among others skeletal age, ethnicity, craniofacial configuration, masticatory activity, replaced tooth's category, implant characteristics, surgical technique, type of fixed prosthesis, occlusal contact scheme installed, loading timing, nature of the opposing/adjacent tooth, prosthesis materials, orthodontic treatment, attachment loss, attrition, vitality, number of existing roots, etc. However, some of these characteristics were assessed in either the re-analysis of available raw data or the direct comparisons with OR, RR, and MD.

- Sensitivity analyses planned a priori included forming subsets of studies according to methodological inadequacies. As no randomized trials were identified, a sensitivity analysis was attempted using blinding of outcome measurement, as this is the single item from the Newcastle-Ottawa scale that has robustly been linked to bias empirically.

- Indications of reporting biases (including small-study effects and publication bias) were planned to be conducted for meta-analyses of ≥ 10 studies (Sterne et al., 2011) using contour-enhanced funnel plots and Egger’s test (Egger et al., 1997). However, all meta-analyses included less than 10 studies and such analyses were not possible.

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APPENDIX S4 Communication attempts with authors of identified studies.

| Author                        | Study                                                                 | Reason                                                                                     | Status                  |
|-------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------|
| Yoshihiro Tsukiyama           | Koori, H., Morimoto, K., Tsukiyama, Y., & Koyano, K. (2010)          | Asked for raw data; also asked if Pang 2017 study has any overlap/                         | Response pending        |
|                               | Statistical analysis of the diachronic loss of interproximal contact  |                                                                                           |                         |
|                               | between fixed implant prostheses and adjacent teeth. *International  |                                                                                           |                         |
|                               | Journal of Prosthodontics*, 23, 535–540                              |                                                                                           |                         |
| Lars-Åke Johansson            | Nilsson A, Johansson LA, Lindh C, Ekfeldt A. One-piece internal      | Asked if subsequent study on IIP has been accepted/ published or they are willing to share | Response pending        |
|                               | zirconia abutments for single-tooth restorations on narrow and regular| the raw data or the results                                                              |                         |
|                               | diameter implants: A 5-year prospective follow-up study. Clin Implant|                                                                                           |                         |
|                               | Dent Relat Res. 2017;19(5):916-925                                   |                                                                                           |                         |
| Bock-Young Jung               | Pang NS, Suh CS, Kim KD, Park W, Jung BY. Prevalence of proximal      | Asked for raw data or results with adjusted OR or RR (HRs are not compatible with the     | Response pending        |
|                               | contact loss between implant-supported fixed prostheses and adjacent  | others); also asked if Koori 2010 study has any overlap/                                 |                         |
|                               | natural teeth and its associated factors: a 7-year prospective        |                                                                                           |                         |
|                               | study. Clin Oral Implants Res 2017;28(12):1501-8.                    |                                                                                           |                         |
| Spyridon Varthis              | Varthis S, Randi A, Tarnow DP. Prevalence of Interproximal Open       | Asked for raw data or complete descriptives.                                              | Response pending        |
|                               | Contacts Between Single-Implant Restorations and Adjacent Teeth.     |                                                                                           |                         |
|                               | *Int J Oral Maxillofac Implants 2016;31(5):1089-92.                  |                                                                                           |                         |
### APPENDIX S5a  Assessment of the methodological adequacy (potentially associated with risk of bias) of included studies with a modified Newcastle-Ottawa tool for cohort studies (1st part)

| Issue† | Avivi-Arber 1996 | Bernard 2004 | Bergenblock 2012 | Bonde 2013 | Brahem 2015 | Byun 2015 | Chang 2012 | Cosyn 2012 | Dierens 2013 | Ekfeldt 2011 | Fukunishi 2016 | Gjelvold 2017 | Jamilian 2015 |
|--------|-----------------|--------------|-----------------|------------|-------------|-----------|------------|------------|-------------|-------------|--------------|-------------|-------------|
| **Selection** | | | | | | | | | | | | | |
| Representativeness of the exposed cohort | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes |
| Ascertainment of exposure? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Demonstration that IIP/PCPL was not present at delivery of restoration? | Yes | Yes | Yes | No | Yes | Yes | Yes | No | Yes | No | No | Yes | Yes |
| **Outcome** | | | | | | | | | | | | | |
| Assessment of outcome blindly? | No | No | No | No | No | No | No | No | No | No | No | Partially | No |
| Was the IIP/PCPL measurement method accurate (valid and reliable)?* | Unclear | Yes | Unclear | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes | Partially | Yes | |
| Were CP to be measured free from artifacts (restorations/mobility of adjacent teeth)?* | N/A | N/A | N/A | N/A | Yes | No | N/A | No | N/A | N/A | Partially | N/A | N/A |
| Was error/reliability of the method assessed?* | No | Yes | No | No | Yes | No | Yes | No | No | No | No | No | No |
| Was follow-up of all Imps long enough for IIP/PCPL to occur (>6 months) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes |
| Adequacy of follow-up of cohorts? | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| **Reporting** | | | | | | | | | | | | | |
| Was assessment of IIP/PCPL in the study's primary scope?* | No | Yes | No | No | Yes | Yes | Partially | No | No | No | Yes | No | Yes |
| Are characteristics of the patients (age/sex) included clearly described?* | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Partially | Yes | Partially |
| Are the interventions of interest clearly described (sites & implants)?* | Yes | Yes | Yes | No | Partially | Yes | Yes | Yes | Yes | Yes | Partially | Yes | Yes |
| **Bias** | | | | | | | | | | | | | |
| Is the study prospectively planned?* | No | No | No | No | No | No | No | No | No | No | No | No | No |
| Do the analyses adjust for different lengths of follow-up of patients?* | No | Yes | N/A | No | Yes | Yes | N/A | No | No | N/A | Unclear | No | Unclear |
| Is clustering adequately assessed in the statistical analysis? (if existing)?* | N/A | Yes | N/A | No | Partially | Yes | N/A | N/A | No | No | No | No | No |
| Were possible confounders adjusted for in the analyses (age, sex, jaw, site)?* | No | Yes | Partially | No | No | Yes | Yes | No | No | No | Yes | Partially | No |
| Did the study have sufficient sample to detect a clinically important effect (arbitrarily set as 100 implants)?* | No | No | No | No | No | No | Yes | No | No | No | No | Yes | No |

IIP, infraposition of the implant restoration; PCPL, proximal contact point loss.
* Question added manually to the Newcastle-Ottawa tool by the review authors during the protocol stage.
† The questions “Selection of the non-exposed cohort” & “Comparability of cohorts on the basis of the design or analysis” were omitted, as no non-exposed group was planned in the protocol of this review.
c multiple published reports were collacted as they pertained to the same patient cohort.
APPENDIX S5b  Assessment of the methodological adequacy (potentially associated with risk of bias) of included studies with a modified Newcastle-Ottawa tool for cohort studies (2nd part)

| Issue                                      | Jemt 2007c | Koori 2010 | Kuipers 2006 | Nilsson 2017 | Pang 2017 | Ren 2016 | Ryu 2016 | Schwartz-Arad 2015 | Son 2009 | Thilander 1994c | Vartio 2016 | Vilhjálmsson 2013 | Wang 2016 | Wong 2015 |
|--------------------------------------------|------------|------------|--------------|--------------|-----------|-----------|-----------|------------------|-----------|----------------|-------------|-------------------|-----------|-----------|
| Selection                                  |            |            |              |              |           |           |           |                  |           |                |              |                   |           |           |
| Representativeness of the exposed cohort   | Yes        | Yes        | Yes          | Yes          | Yes       | Yes       | Yes       | Yes              | Yes       | Yes            | Yes         | Partially        | Yes       | Yes       |
| Ascertainment of exposure?                | Yes        | Yes        | Yes          | Yes          | Yes       | Yes       | Yes       | Yes              | Yes       | Yes            | Yes         | Yes               | Yes       | Yes       |
| Demonstration that IIP/PCP LOSS was not present at delivery of restoration? | Yes        | Yes        | No           | Yes          | No        | Yes       | No        | Yes              | Yes       | Yes            | Yes         | No                | No        | No        |
| Outcome                                    |            |            |              |              |           |           |           |                  |           |                |             |                   |           |           |
| Assessment of outcome blindly?            | No         | No         | No           | No           | No        | No        | No        | No               | No        | No             | No          | Partially        | No        | No        |
| Was the IIP/PCP LOSS measurement method accurate (valid and reliable)?* | Yes        | Yes        | Unclear      | Unclear      | Yes       | Yes       | Yes       | Partially        | Yes       | Yes            | Yes         | Yes               | Yes       | No        |
| Were CP to be measured free from artifacts (restorations/mobility of adjacent teeth)?* | N/A        | Yes        | N/A          | N/A          | Yes       | No        | N/A       | No               | N/A       | No             | N/A         | Yes               | No        | No        |
| Was error/reliability of the method assessed?* | No         | No         | No           | No           | No        | No        | No        | No               | Yes       | No             | No          | Yes               | No        | No        |
| Was follow-up of all Imps long enough for IIP/PCP LOSS to occur (>6 months) | Unclear    | No         | Yes          | Yes          | Yes       | No        | Unclear   | Unclear          | Yes       | No             | Yes         | Unclear          | No        | No        |
| Adequacy of follow up of cohorts?         | Unclear    | Unclear    | Unclear      | No           | Yes       | Unclear   | Unclear   | Unclear          | Yes       | Unclear        | Unclear     | Unclear          | Yes       | Unclear |
| Reporting                                  |            |            |              |              |           |           |           |                  |           |                |             |                   |           |           |
| Was assessment of IIP/PCP LOSS in the study’s primary scope?* | Yes        | Yes        | Yes          | Yes          | Yes       | Yes       | Yes       | Yes              | Yes       | Yes            | Yes         | Yes               | Yes       | Yes       |
| Are characteristics of the patients (age/sex) included clearly described?* | Partially  | Yes        | Yes          | Yes          | Partially | Yes       | Partially | No               | Yes       | Partially      | Yes         | No                | Yes       | No        |
| Are the interventions of interest clearly described (sites & implants)?* | Yes        | Partially  | Yes          | Yes          | Yes       | No        | Yes       | No               | Yes       | Partially      | Yes         | Yes               | Yes       | Yes       |
| Bias                                       |            |            |              |              |           |           |           |                  |           |                |             |                   |           |           |
| Is the study prospectively planned?*       | No         | No         | No           | Yes          | Yes       | No        | No        | No               | No        | No            | Yes         | No                | No        | No        |
| Do the analyses adjust for different lengths of follow-up of patients?* | Unclear    | Yes        | Yes          | No           | Yes       | N/A       | No        | Unclear          | No        | N/A            | No          | Unclear          | No        | No        |
| Is clustering adequately assessed in the statistical analysis? (if existing)?* | No         | No         | Yes          | No           | No        | N/A       | No        | N/A              | Yes       | No            | N/A         | Unclear          | No        | No        |
| Were possible confounders adjusted for in the analyses (age, sex, jaw, site)?* | No         | Yes        | Yes          | No           | No        | No        | Partially | Yes              | No        | Partially      | Yes         | Yes               | Yes       | Yes       |
| Did the study have sufficient sample to detect a clinically important effect (arbitrarily set as 100 implants)?* | No         | Yes        | No           | No           | Yes       | No        | No        | Yes              | No        | Yes            | No          | Yes               | No        | No        |

IIP, infraposition of the implant restoration; PCP, proximal contact point.
* Question added manually to the Newcastle-Ottawa tool by the review authors during the protocol stage.
† The questions “Selection of the non-exposed cohort” & “Comparability of cohorts on the basis of the design or analysis” were omitted, as no non-exposed group was planned in the protocol of this review.
‡ multiple published reports were collacted as they pertained to the same patient cohort.
**APPENDIX S6a** Re-analysis of data provided in the study by Bernard et al., 2004.

| Descriptives | Regression on IIP | Regression on IIP>1 |
|--------------|-------------------|---------------------|
| Na           | n (%)             | Mean (SD)           | Range | Univariable | RR      | 95% CI | P | Univariable | RR      | 95% CI | P |
| **Patient level** |                   |                     |       |             | b        | 95% CI | P |             | b        | 95% CI | P |
| Age (years)  | 28                | 31.4 (13.8)         | 15.4-56.7 | Age | Per year | 0 | -0.01, 0.01 | 0.50 | 0.96 | 0.91, 1.02 | 0.20 |
| Follow-up (years) | 28            | 4.3 (2.4)           | 1.1-9.1   | Tooth | C. incisor | Ref |                     |       |       |       |       |
| **Implant level** |                   |                     |       |             | b        | 95% CI | P |             | b        | 95% CI | P |
| Central incisor | 40              | 16 (40%)            |         | L. incisor | 0.06     | -0.11, 0.24 | 0.49 | 0.94 | 0.41, 2.13 | 0.88 |
| Lateral incisor | 40              | 12 (30%)            |         | Follow-up | Per year | 0.03 | -0.04, 0.10 | 0.45 | 1.02 | 0.78, 1.32 | 0.90 |
| Canine       | 40                | 12 (30%)            |         |         |         |       |       |       |       |       |       |
| IIP          | 40                | 0.69 (0.43)         | 0.10-1.86 |       |         |       |       |       |       |       |       |
| IIP>1 mm     | 40                | 7 (18%)             |         |       |         |       |       |       |       |       |       |

CI, confidence interval; IIP, implant infraposition; Na, eligible sample; RR, relative risk; SD, standard deviation.
# APPENDIX S6b

Re-analysis of data provided in the study by Thilander et al., 1994

| Descriptives          | Regression on mean IIP | Regression on IIP>1 mm |
|-----------------------|------------------------|------------------------|
|                       | Na | n (%) | Mean (SD) | Range | Factor | b   | 95% CI | P    | RR  | 95% CI | P    |
| Patient level         | 15 | 15     | 15.3 (1.7) | 13.2-19.3 | Age | Per year | -0.16 | -0.25, -0.07 | <0.001 | 0.45 | 0.19, 1.08 | 0.08 |
| Age                   | 15 | 8 (53%) | 15.3 (1.7) | 13.2-19.3 | Sex | Female | Ref   |       |       |       |       |
| Male                  | 15 | 8 (53%) | 15.3 (1.7) | 13.2-19.3 | Male | 0.34 | -0.16, 0.84 | 0.18 | 5.00 | 0.93, 26.78 | 0.06 |
| Growth ended (HR)     | 15 | 9 (60%) | 15.3 (1.7) | 13.2-19.3 | Jaw | Mandible | Ref  |       |       |       |       |
| Height growth         | 15 | 4.57 (5.22) | 0-18.00 |       |       |       |       |       |       |       |       |
| Implant level         | 27 | 19 (70%) |       |       |       |       |       |       |       |       |       |
| Maxilla               | 27 | 19 (70%) |       |       |       |       |       |       |       |       |       |
| Anterior region       | 27 | 18 (67%) |       |       |       |       |       |       |       |       |       |
| IIP (Rx)              | 26 | 0.52 (0.50) | 0-1.70 |       |       |       |       |       |       |       |       |
| IIP (model)           | 22 | 0.50 (0.41) | 0-1.60 |       |       |       |       |       |       |       |       |
| IIP difference Rx-model | 21 | 0.09 (0.22) | -0.30, 0.50 | Growth end | No | Ref |       |       |       |       |       |
| IIP>1 mm              | 26 | 6 (23%) |       |       |       |       |       |       |       |       |       |

CI, confidence interval; HR, hand radiograph; IIP, implant infraposition; Na, eligible sample; RR, relative risk; Rx, radiology; SD, standard deviation.
**APPENDIX S6c**  Re-analysis of data provided in the study by Kuijpers et al., 2006. Data are given only on implant-level and only descriptive statistics were calculated due to the limited sample.

| Na | n (%) | Mean (SD) | Range |
|----|-------|-----------|-------|
| Implant-level                      |       |           |       |
| Age                                    | 11    | 16.7 (1.8)| 12.9-18.8 |
| Male                                   | 8 (73%) |
| Central incisor                        | 6 (55%) |
| Lateral incisor                       | 5 (45%) |
| Trauma                                | 8 (73%) |
| Graft                                 | 3 (27%) |
| Follow-up                              | 11    | 11.0 (0.8)| 9.9-12.0 |
| IIP                                   |       | 0.77 (0.61)| 0-2.00 |
| IIP>1mm                                | 1 (9%) |

IIP, implant infraposition; Na, eligible sample; SD, standard deviation.
### APPENDIX S7

Results of the included studies for factors assessed by a single study

| Outcome | Control                  | Experimental                  | Effect | 95% CI       | P   | SS | CS | What happens                                                                 |
|---------|--------------------------|-------------------------------|--------|--------------|-----|----|----|------------------------------------------------------------------------------|
| IIP risk | Age (per year)           | OR: 0.98                     | 0.91,1.06 | 0.62         | -   | -  | -  | Higher IIP odds in the posterior area                                         |
| IIP risk | Age over 20 yrs          | OR: 0.57                     | 0.08,4.06 | 0.58         | -   | -  | -  |                                                                             |
| IIP risk | Age over 25 yrs          | OR: 0.50                     | 0.11,2.27 | 0.37         | -   | -  | -  |                                                                             |
| IIP risk | Age over 30 yrs          | OR: 0.43                     | 0.09,2.05 | 0.29         | -   | -  | -  |                                                                             |
| IIP risk | No Ortho Tx              | OR: 3.42                     | 0.83,14.03 | 0.09         | -   | -  | -  |                                                                             |
| IIP risk | Normal face              | OR: 2.14                     | 0.33,13.76 | 0.42         | -   | -  | -  |                                                                             |
| IIP risk | Normal face              | OR: 0.91                     | 0.17,4.84 | 0.92         | -   | -  | -  |                                                                             |
| IIP risk | Posterior area           | OR: 8.67                     | 1.30,58.04 | 0.03         | Yes | Yes| Higher IIP odds in the anterior region                                         |
| IIP ext>1mm risk | Age over 18 yrs   | OR: 1.88                     | 1.06,3.36 | 0.03         | Yes | Yes| Greater IIP after ortho Tx                                                  |
| IIP ext>1mm risk | Central incisor     | OR: 3.86                     | 1.86,8.05 | 0.009        | Yes | Yes| Greater IIP in skeletally young patients                                    |
| IIP ext>1mm risk | Lateral incisor   | OR: 2.66                     | 1.15,6.19 | 0.02         | Yes | Yes|                                                                             |
| IIP ext>1mm risk | Canine incisor      | OR: 4.87                     | 2.03,12.29 | 0.002        | Yes | Yes|                                                                             |
| IIP ext>1mm risk | Follow-up under 3 yrs  | OR: 0.78                     | 0.41,1.47 | 0.22         | Yes | Yes|                                                                             |
| IIP ext>1mm risk | Follow-up under 5 yrs  | OR: 0.30                     | 0.16,0.61 | 0.003        | Yes | Yes|                                                                             |
| IIP ext>1mm risk | No Ortho Tx            | OR: 0.43                     | 0.25,0.72 | 0.0004       | Yes | Yes|                                                                             |
| IIP ext>1mm risk | Skeletally mature      | OR: 0.51                     | 0.30,0.91 | 0.003        | Yes | Yes|                                                                             |
| IIP ext>1mm risk | Bilateral agenesis     | OR: 0.42                     | 0.23,0.79 | 0.0006       | Yes | Yes|                                                                             |
| PCP loss | Age between 20 to 39 yrs | OR: 2.08                     | 0.76,5.64 | 0.15         | -   | -  | -  | Higher PCP odds in patients over 60 yrs                                      |
| PCP loss | Age over 60 yrs          | OR: 0.92                     | 1.07,7.92 | 0.04         | Yes | Yes|                                                                             |
| PCP loss | FD as antagonist         | OR: 1.42                     | 0.84,2.41 | 0.20         | -   | -  | -  |                                                                             |
| PCP loss | RD antagonist            | OR: 1.73                     | 0.43,6.97 | 0.44         | -   | -  | -  |                                                                             |
| PCP loss | Implant antagonist       | OR: 0.84                     | 0.44,1.60 | 0.59         | -   | -  | -  |                                                                             |
| PCP loss | No antagonist            | OR: 2.23                     | 0.09,55.39 | 0.63         | -   | -  | -  |                                                                             |
| PCP loss | Gold restoration         | OR: 0.34                     | 0.04,2.96 | 0.33         | -   | -  | -  |                                                                             |
| PCP loss | Crown to implant ratio   | OR: 1.21                     | 1.05,1.39 | 0.0007       | Yes | Maybe|                                                                             |
| PCP loss | Implant splinted         | OR: 1.75                     | 0.88,3.48 | 0.11         | -   | -  | -  | Higher PCP odds with increased MBL                                            |
| PCP loss | MBL<13%                  | OR: 2.12                     | 0.99,4.55 | 0.05         | Yes | Yes|                                                                             |
| PCP loss | MBL 13 to 25%            | OR: 2.66                     | 1.15,6.19 | 0.02         | Yes | Yes|                                                                             |
| PCP loss | MBL 25 to 50%            | OR: 5.87                     | 1.61,21.40 | 0.007        | Yes | Yes|                                                                             |
| PCP loss | MBL 50 to 75%            | OR: 1.46                     | 0.08,25.57 | 0.80         | -   | -  | -  |                                                                             |
| PCP loss | MBL 75%                  | OR: 0.45                     | 0.23,0.88 | 0.02         | Yes | Yes| Lower PCP odds with Misch category D3-D4                                     |
| PCP loss | Single-rooted tooth      | OR: 2.64                     | 1.65,4.22 | <0.001       | Yes | Yes| Higher PCP odds for single-rooted teeth                                      |
| PCP loss | Attrition                | OR: 0.78                     | 0.48,1.27 | 0.32         | -   | -  | -  |                                                                             |
| PCP loss | Lateral contact          | OR: 2.83                     | 1.40,5.73 | 0.004        | Yes | Yes| Higher PCP odds for teeth with contact on lateral excursion                  |
| PCP loss | Mobility                 | OR: 3.86                     | 1.39,10.69 | 0.009        | Yes | Yes| Higher PCP odds for teeth with mobility                                      |
| PCP loss | Molar                    | OR: 1.88                     | 0.96,3.66 | 0.06         | -   | -  | -  |                                                                             |
| PCP loss | No Ortho Tx              | OR: 2.97                     | 0.92,9.64 | 0.07         | -   | -  | -  |                                                                             |
| PCP loss | Digital measurement      | OR: 0.88                     | 0.48,1.61 | 0.68         | -   | -  | -  |                                                                             |

CI, confidence interval; CS, clinically significant (judged as MD greater than ½ SD of the control group or as OR/RR greater than 2); FD, fixed denture; IIP, implant infra-position; MBL, marginal bone loss; MD, mean difference; OR, odds ratio; Ortho, orthodontic; PCP, proximal contact point; RD, removable denture; RR, relative risk; SS, statistically significant at 5%; Tx, treatment; yr, year
**APPENDIX S8a** Indirect random-effects meta-analysis across studies on the pooled event rate or values of the primary and secondary outcomes at implant/tooth/contact point level and patient level. All datasets (pertaining to different follow-ups) are extracted from each study, but only the one with the longest follow-up is included in the analysis. Comparison of results at the implant/site level (main analysis) and at the patient level (sensitivity analysis).

| Outcome                  | Level       | Studies (datasets) | Effect | 95% CI            | tau^2 (95% CI) | I^2 (95% CI) | 95% prediction |
|--------------------------|-------------|--------------------|--------|-------------------|----------------|--------------|----------------|
| IIP_{binary} % event rate| Site        | 9 (11)             | 50.5%  | 26.3% to 74.5%    | 0.56 (NC)      | 95% (92 to 97%) | 10.4 to 90.0% |
| IIP_{binary} % event rate| Patient     | 6 (6)              | 56.6%  | 23.0% to 87.1%    | 0.74 (NC)      | 96% (93 to 97%) | 4.5 to 97.3%  |
| IIP_{continuous} extent  | Site        | 6 (14)             | 0.58 mm| 0.33 to 0.83 mm   | 0.08 (0.02 to 0.53) | 88% (69 to 98%) | 0 to 1.43 mm* |
| IIP_{continuous} extent  | Patient     | 3 (4)              | 0.64 mm| 0.51 to 0.76 mm   | 0 (0 to .32)   | 0% (0% to 95%)  | 0 to 1.47 mm* |
| IIP > 1 mm_{binary} % event rate | Site  | 5 (5)              | 20.8%  | 8.3 to 37.1%      | 0.14 (NC)      | 84% (63 to 93%) | 4.3 to 60.9 mm |
| IIP > 1 mm_{binary} % event rate | Patient | 4 (4)              | 18.4%  | 6.0 to 35.6%      | 0.13 (NC)      | 82% (53 to 93%) | 1.8 to 73.4%  |

CI, confidence interval; IIP, infraposition of the implant restoration relative to adjacent teeth; NC, non-calculable; PCP, proximal contact point.

* truncated at zero.
APPENDIX S8b  Random-effects meta-regression on the event rates or average values of the primary and secondary outcomes (indirect data) at implant/tooth/contact point level and patient level. All datasets (pertaining to different follow-ups) are extracted from each study and all are included in the analyses. Comparison of results at the implant/site level (main analysis) and at the patient level (sensitivity analysis).

| Outcome | Level   | Factor | Category       | n  | b     | 95% CI        | P  |
|---------|---------|--------|----------------|----|-------|---------------|----|
| IIP<sub>binary</sub> % event rate | Site    | Age    | Per year       | 9  | -0.90%| -4.8%, 3.0%   | 0.60|
|         |         | Sex    | % male (per 10%) | 8  | -11.20%| -35.1%, 12.7% | 0.29|
|         |         | Follow-up | Per year | 10 | 1.90% | -1.6%, 5.3%   | 0.25|
|         |         | Jaw    | % in maxilla (per 10%) | 8 | 19.70% | 5.1%, 34.3% | 0.02|
|         |         | Region | % anterior (per 10%) | 9 | 5.50%  | -1.6%, 12.6%  | 0.11|

| IIP<sub>binary</sub> % event rate | Patient | Age    | Per year       | 5  | -8.90% | -31.0%, 13.2% | 0.29|
|         |         | Sex    | % male (per 10%) | 4  | NC     |              |     |
|         |         | Follow-up | Per year | 5 | 3.30%  | -5.9%, 12.5% | 0.34|
|         |         | Jaw    | % in maxilla (per 10%) | 4 | NC     |              |     |
|         |         | Region | % anterior (per 10%) | 5 | 7.00%  | -4.7%, 18.6% | 0.15|

b, unstandardized meta-regression coefficient; CI, confidence interval; IIP, infraposition of the implant restoration relative to adjacent teeth; NC, non-calculable; PCP, proximal contact point.
Meta-analyses of direct evidence (within- and across-studies) on the primary and secondary outcomes at implant/tooth/contact point level and patient level. Comparison of results at the implant/site level (main analysis) and at the patient level (sensitivity analysis).

| Outcome | Level | Reference | Experimental | n | Effect | 95% CI | P | I² (95% CI) | tau² (95% CI) | 95% prediction |
|---------|-------|-----------|--------------|---|--------|-------|---|------------|--------------|---------------|
| IIPbinary | Site  | Female    | Male         | 3 | OR=0.29| 0.10,0.88| 0.03 | 0% (0%,98%) | 0 (0,55.68) | 0.390.39      |
| IIPbinary | Patient| Female    | Male         | 2 | RR=0.71| 0.51,0.98| 0.04 | 7% (0%,100%)| 0 (0,55.39) | NA            |

CI, confidence interval; IIP, infraposition of the implant restoration relative to adjacent teeth; MD, mean difference; NC, not calculable; OR, odds ratio; PCP, proximal contact point; RR, relative risk.
APPENDIX S9  Sensitivity analysis of Table 2 according to age of included patients in each study. Comparison of results of all studies (main analysis) and the results by including only studies with patients older than 20 years of age (sensitivity analysis)

Indirect random-effects meta-analysis across studies on the pooled event rate or values of the primary and secondary outcomes at implant/tooth/contact point level. All datasets (pertaining to different follow-ups) are extracted from each study, but only the one (Xyz) with the longest follow-up is included in the analysis.

| Outcome                  | Analysis                                    | Studies | Effect | 95% CI          |
|--------------------------|---------------------------------------------|---------|--------|-----------------|
| IIP<sub>binary</sub> % event rate | Any patients                               | 9       | 50.5%  | 26.3% to 74.5%  |
|                          | Only patients with ≥20 years                | 2       | 42.6%  | 2.6% to 90.7%   |
| IIP<sub>continuous</sub> extent in mm | Any patients                               | 6       | 0.58 mm| 0.33 to 0.83 mm |
|                          | Only patients with ≥20 years                | 1       | 0.44 mm| 0.15 to 1.17 mm |
| IIP > 1 mm<sub>binary</sub> % event rate | Any patients                               | 5       | 20.8%  | 8.3 to 37.1%    |
|                          | Only patients with ≥20 years                | 1       | 42.0%  | 23.8% to 61.5%  |
| PCP loss<sub>binary</sub> % event rate | Any patients                               | 9       | 46.3%  | 32.3 to 60.6%   |
|                          | Only patients with ≥20 years                | 5       | 45.8%  | 32.8% to 59.2%  |

CI, confidence interval; IIP, infraposition of the implant restoration relative to adjacent teeth; NC, non-calculable; PCP, proximal contact point
*truncated at zero
APPENDIX S10  Sensitivity analysis of Table 2 according to the number of included implants per study. Comparison of results of all studies (main analysis) and the results by including only studies with at least 100 implants (sensitivity analysis)

| Inclusion                | Outcome                      | Studies | Effect | 95% CI          | tau² (95% CI) | I² (95% CI) |
|--------------------------|------------------------------|---------|--------|-----------------|---------------|-------------|
| All studies              | IIP<sub>binary</sub> % event rate | 9       | 50.5% | 26.3% to 74.5%  | 0.56 (NC)     | 95% (92 to 97%) |
| IIP<sub>continuous</sub> extent in mm | 6   | 0.58 mm | 0.33 to 0.83 mm | 0.08 (0.02 to 0.53) | 88% (69 to 98%) |
| IIP > 1 mm<sub>binary</sub> % event rate | 5 | 20.8% | 8.3 to 37.1% | 0.14 (NC) | 84% (63 to 93%) |
| PCP loss<sub>binary</sub> % event rate | 9 | 46.3% | 32.3 to 60.6% | 0.19 (NC) | 97% (96 to 98%) |

| Studies with >100 implants | IIP<sub>binary</sub> % event rate | - | - | - | - | - |
|----------------------------|----------------------------------|---|---|---|---|---|
| IIP<sub>continuous</sub> extent in mm | - | - | - | - | - |
| IIP > 1 mm<sub>binary</sub> % event rate | - | - | - | - | - |
| PCP loss<sub>binary</sub> % event rate | 4 | 48.6% | 36.6 to 60.6 | 0.06 (NC) | 92% (83 to 96%) |

CI, confidence interval; IIP, infraposition of the implant restoration relative to adjacent teeth; NC, non-calculable; PCP, proximal contact point.