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Dental Implant Failure Rate and Marginal Bone Loss in Smokers Compared to Non-Smokers: A Systematic Review and Meta-Analysis

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Abstract

Background: Although dental implant therapy is considered a predictable treatment modality with reported high survival and success rates, biological complications do occur, and a number of risk factors have been involved. Tobacco smoking is related to many health risks affecting general & oral health.

Objectives: The aim of this systematic review and meta-analysis is to test the null hypothesis of no difference in dental implant failure rates and marginal bone loss between smokers and non-smokers with regards to follow-up time.

Search methods: An extensive electronic search was performed in PubMed, Scopus and EBSCOhost Dentistry and Oral Sciences source to identify relevant articles published up to June 2019. The eligibility criteria included randomized and non-randomized clinical trials & prospective & retrospective observational studies. After a thorough selection process, 23 papers were included. The meta-analysis was expressed in terms of the odds ratio (OR) or standardized mean difference (SMD) with a confidence interval (CI) of 95% and the level of statistical significance was set at $P < 0.05$.

Results: There was a statistically significant difference in marginal bone loss favoring the non-smoking group with a SMD of 1.07 (95% CI 0.67–1.48), demonstrating a statistically significant difference in favor of non-smokers (P

Author's conclusion: Based on the results of this review, the null hypothesis is rejected, and that is in agreement with other reports in the literature. Therefore, the clinical recommendation for a period of abstinence from smoking that at least covers the pre-surgical evaluation & initial therapy, definite implant treatment & immediate post-op phases remains to be very relevant.

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Dental Implant Failure Rate and Marginal Bone Loss in Smokers Compared to non-Smokers: A Systematic Review and Meta-Analysis

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Thesis

Presented to the Faculty of Penn Dental Medicine in Fulfillment of the Requirements for the Degree of Master of Science in Oral Biology

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Results: There was a statistically significant difference in marginal bone loss favoring the non-smoking group with a SMD of 1.07 (95% CI 0.67–1.48), demonstrating a statistically significant difference in favor of non-smokers ($P<0.00001$). A subgroup analysis in smokers revealed a statistically significant increase in marginal bone loss in the maxillary implants compared to the mandible ($P = 0.008$) with a SMD of 1.39 (95% CI 0.35–2.42) although with a high level of heterogeneity ($I2 = 97\%$; $P = 0.0001$). A statistically significant difference ($P < 0.00001$) in implant failure rate in favor of the non-smoking group was also observed, with OR of 2.24 (95% CI 1.90–2.64). Moreover, the subgroup analysis for follow-up time revealed a significant increase in implant failure proportional to the increase in follow-up time ($P = 0.05$), but with considerable heterogeneity ($I2=74.5\%$).

Author's conclusion: Based on the results of this review, the null hypothesis is rejected, and that is in agreement with other reports in the literature. Therefore, the clinical recommendation for a period of abstinence from smoking that at least covers the pre-surgical evaluation & initial therapy, definite implant treatment & immediate post-op phases remains to be very relevant.

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Review of pertinent literature

Methods of evidence-based dental practice was introduced to optimize the decision-making processes in diagnosis and treatment planning, and for comprehensive patient information in preparation of diagnostic and therapeutic interventions, particularly before elective procedures. Outcome anticipation is an important aspect of risk management in contemporary implant dentistry. Recognizing the factors that may potentially place the patient receiving dental implant(s) at a higher risk of implant failure or other adverse conditions allows the practitioner to make informed decisions and refine the treatment approach to optimize the results and improve the predictability of successful therapy.[59] As in other topics, RCTs are one of the most reliable sources of information for clinical practice and therefore are the studies preferred for the elaboration of longitudinal studies in implant dentistry.[73] However, the inclusion of longitudinal observational studies, with high number of participants can potentially increase the amount of viable data. The Early longitudinal studies evaluating osseointegrated dental implants showed satisfactory results.[65,66] Currently, with more than 40 years of scientific evidence, the clinical use of dental implants has been increasing day by day. Nevertheless, few studies have examined follow-up periods for ten years or longer, which is important to enable us to understand the biological aspects of dental implant therapy.[136] Implant-supported prostheses have been shown to have successful long-term outcomes.[19,31,32,83, 91,94] However, numerous local and systemic factors have been hypothesized to affect implant success to various degrees.[59,69,160] Such factors include but are not limited to implant insertion in type III and IV bone qualities,[50] reduced initial stability of the implant, particularly in cases of immediate loading protocol, implant placement in posterior maxilla, radiation therapy sites, drug and alcohol intake, and tobacco smoking. When a cause-effect relationship is being investigated, an accurate definition of the potential cause is

imperative. This is particularly important when the effect is expected to be frequency and dose dependent. In the medical literature, smoking was established to cause a dose-dependent effect on the extent of bone loss and the risk of fracture in long bones.[167] Surprisingly, however, smaller doses of nicotine have been found to stimulate osteoblastic growth.[98] Wide variations in the definition of smoking are encountered in the dental literature in terms of smoking duration, number of cigarettes consumed daily, and categorization of previous smokers, and these variations prevent a detailed analysis of the predictability of measure outcomes. Different patient and implant-related confounding factors have been shown to impact the clinical outcomes associated with dental implants, but these factors are not always considered in the included studies. Many studies investigated the correlation between tobacco smoking and adverse implant-related outcomes, some align with the hypothesis that tobacco smoking increases implant failure rate, but others does not reach the same conclusion.[6,49,120,159] Currently, no consensus has been reached, and no evidence-based guidelines have been generated to help clinicians make informed clinical decisions in utilizing dental implant treatment in tobacco smokers. These shortcomings may be attributed to several factors, like the variability in the design, quality and findings of studies conducted. The considerable heterogeneity among the studies has made direct comparison across studies a difficult task. Therefore, there is a limited number of recent systematic reviews comparing dental implant complications in smokers to non-smokers. Peri-implant mucositis is the most common biological complication associated with dental implants.[73,144] It is characterized by a reversible inflammatory process, demonstrating a color change and redness and bleeding of the peri-implant mucosa, without presenting signs of bone resorption. Probing of the peri-implant sulcus and identifying signs such as the presence of bleeding or suppuration is important for thorough diagnosis of implant health,[173] particularly

peri-implant mucositis. Clinically, peri-implant probing depth is influenced by a number of factors, including the depth of implant placement, the level of peri-implant marginal bone, peri-implant soft tissue phenotype and thickness, type of the prosthetic abutment, emergence profile of the prosthetic restoration, the region in which the implant was placed.[114] Probing depths of >=5 mm must be investigated, as they may be indicative of peri-implant disease. However, peri-implant probing depths were either unreported or reported with wide variations with regard to the exact probing depth value in millimeters or the numbers of sites probed per implant. Therefore, the author elected not to select peri-implant probing depth as an outcome variable in this review. Ever since the first longitudinal studies were conducted to evaluate the clinical performance of implants,[65,66] various authors have proposed different criteria for classifying implant health and success. Nonetheless, up to the current time, no standardization for this classification has been made in the literature and that leads to considerable difficulty in the interpretation and comparison of data among the available studies. Due to the differences in criteria adopted by different authors, it is not always possible to arrive at an absolute mean value for the success rates in systematic reviews. However, in two systematic reviews by Needleman et al (2012)[130] and Papaspyridakos et al (2012)[134] evaluating the success criteria for implants, the criteria of Albrektsson et al. (1986)[68] were related in around 33.3% (n = 78) and 31.7% (n = 41) of the studies included, respectively. This demonstrates that these remain to be the most widely accepted criteria at the present time. In longitudinal studies on osseointegrated dental implants, the terms ‘survival’ and ‘success’ are routinely used. However, these terms continue to generate confusion regarding their actual meanings[154] and are frequently used incorrectly. Knowledge and standardization of these terms is necessary to facilitate communication, comparison, and thorough understanding among dental professionals.[48,73,153,158] Studies evaluating success rates in

implant dentistry are complex because of the large number of confounding variables, such as surgical techniques, materials used, and follow-up period. In addition, several criteria have been proposed for the definition of success[48,62,68,109,143,147,153,172] and the absence of international standardization makes it rather difficult to compare studies.[130,153] While other authors have argued that a period of 5 years may still be too short to enable reliable information to be obtained,[107] a minimum of 5 years of follow-up is necessary[130,137] to properly analyze survival and success rates of dental implants. The majority of longitudinal studies evaluated only the survival rate of dental implants, as a quantitative analysis, potentially underestimating the importance of the data with reference to the overall health and quality of the placed implants. The most probable reason for the preference for survival studies appears to be related to easier methodology for that analysis;[153] i.e. the measurement for statistical analysis is done only by counting the implants remaining in situ. Conversely, evaluating dental implant success involves analysis of more complex parameters and criteria and is more directly associated with the health and quality of the implants. Consequently, the statistical differences between the survival and success rates are typically significant. Smoking has been shown to be a primary risk factor for general health and responsible for many serious diseases, as for 90% of all lung cancers, 70% of chronic lung diseases, 80% of myocardial infarctions before the age of 50, and 30% of chronic ischemic heart diseases and strokes.[51,52,53] There are an estimated 1.3 billion smokers around the world, and 4.9 million people die from tobacco smoking-related diseases every year (WHO).[174] Besides the general role healthcare professionals play in tobacco smoking cessation and prevention, certain aspects pertaining to modern dental implant practice should be considered in tobacco smokers for thorough patient evaluation before oral surgical procedures and implant treatment planning. While the smoking cessation and sustained abstinence well before oral

surgical procedures should be the ultimate goal, nicotine dependence has proven to be a chronic relapsing disorder and is usually characterized by multiple failed quitting attempts.[129] Nevertheless, a number of studies have suggested that adjunctive measures can possibly minimize the negative effects of tobacco smoking on dental implant survival rates.[70,77] Abstinence from smoking for one week before and eight weeks post implant placement has been reported to improve the success rate associated with the Branemark implants.[70] Opting for a two-stage placement and delayed loading protocol with may minimize the accumulation of bacterial biofilms and the diffusion of several of the nearly 4000 chemicals contained in cigarette smoke.[35,162] Placement of dental implant in special populations like tobacco smokers requires consideration of the potential benefits to be gained from the treatment and possible adverse effects. To better appreciate this potential, properly conducted, high-quality systematic reviews and meta-analysis, whenever possible, comparing the survival rate of dental implants, postoperative infection, and peri-implant marginal bone loss (MBL) between smokers and non-smokers are essential to critically summarize the current knowledge and synthesize evidence. Thorough patient information not only about the planned treatment approach and the expected outcomes, but also about risks and risk factors are necessary to support the patient's decision making before dental implant therapy.[155] Moreover, smoking cessation advice, given in conjunction with dental health information may have a marked effect on smokers' attitude toward their habit and provide a powerful incentive to reduce or even quit smoking.[125] When placing dental implants in smokers, the peri-operative use of antibiotics[96] as well as additional local potential preventive measures, like using flat instead of high cover screws, should be considered in an attempt to prevent postoperative complications during the healing period.[18]

Recombinant human parathormone (PTH 1-34), which is an anabolic agent approved for the treatment of patients with osteoporosis that stimulates osteoblast function,[92] has been reported to increase bone volume around implants in the presence of cigarette smoke in animals.[119] It is strongly suggested that the direct exposure of the peri-implant tissues to tobacco smoke products is the main factor causing an increase in dental implant failure rate in smokers compared to non-smokers.[104] The increased risk of post-surgical wound healing complications[105,126,127,146] as well as the risk of peri-implant marginal bone loss and increased implant failure rates[10,116,121] must be emphasized. Delayed wound healing has to be anticipated due to deficient collagen synthesis and production,[106] reduced peripheral blood circulation and capillary bed perfusion[115] and compromised polymorpho-nuclear leucocytes and macrophages functions.[110,124] Furthermore, tobacco smoking was indicated as a significant subject-based risk factor for periodontitis in literature reviews.[132,139] Although not entirely understood, the long-term chronic effect of smoking on periodontitis was found to be due to impairment of periodontal tissues vasculature through vasoconstrictive effects at the end-arterial gingival vessels,[54] multiple function deficiencies of fibroblasts and neutrophils and reduced inflammatory response.[132] Therefore, a regular and strict recall of smoking patients undergoing implant treatment is important for early detection of implant complications. The carbon monoxide generated during combustion of tobacco smoking lowers the oxygen tension in tissues by displacing the oxygen from hemoglobin.[117] Nicotine, which has been found in high concentrations in saliva[101,103] and crevicular fluid[84] of smokers has been reported to have a negative impact on bone regenerative capacity.[71,161] Furthermore, polymorphonuclear neutrophils viability, opsonization & phagocytosis are significantly reduced in smokers compared to non-smokers.[110] Nicotine is the most significant constituent among more than 4000 potentially harmful substances in tobacco

products. It is the principal chemical component that causes tobacco addiction, appears to mediate the vasoconstrictive effects of tobacco smoking, and involved in the pathogenesis of many diseases.[80] The exact mechanism by which tobacco smoke affects the osseointegration process remains to be unclear. However, several chemicals found in tobacco smoke have been shown to reduce the vascularity of the peri-implant tissues, and so may compromise the bone healing process.[132] Approximately 3 mg of nicotine and 20–30 mL of carbon monoxide is inhaled for each cigarette smoked.[151] Nicotine has been related to increased platelet aggregation and interference with the function of fibroblasts, osteoblasts, red blood cells and macrophages.[55,81,102,164,169] In addition, carbon monoxide converts hemoglobin into carboxyhemoglobin rather than oxyhemoglobin due to its 200-fold greater affinity for hemoglobin than oxygen. The formation of carboxyhemoglobin decreases oxygen transportation, resulting in reduced tissue oxygenation and hypoxia.[72,106,117,131,140] Although tobacco smoking is widely accepted as a risk factor for oral health in general,[54] smoking was considered a risk factor for implant treatment since the first publication on this topic by Bain & Moy (1993).[3] Nevertheless, the impact of consideration of the patient's status as a smoker or non-smoker in dental implant treatment planning seems to be uncontroversial, but indistinct. In 1999, a national survey questionnaire to National Health Service (NHS) consultants evaluating their attitudes regarding medical and oral health-related factors considered in patient selection and treatment planning for dental implant placement revealed that, among others, tobacco smoking was one of the most important factors contraindicating dental implant therapy.[75] Another survey among Finnish dentists to evaluate the relationship of various patient characteristics or possible contraindications for dental implant therapy revealed that more dentists practicing in the public or private sectors recommended implant therapy compared to staff of dental schools in case of

smoking patients. Older dentists (40–49 years) were found to be more in favor of implant treatment in smoking patients than younger dentists (30–39 years).[99] Therefore, validation of smoking as a risk factor in treatment decisions may differ among dentists. This impression seems to be confirmed by different attempts made to quantify the number of cigarettes smoked per day in different studies. Human and animal studies have showed the deleterious effects of tobacco smoking on the health of oral tissues. Animal studies[86,123] have demonstrated that nicotine inhibits gene expression of several enzymes that play an important role in the regulation of osteoblast proliferation, differentiation and apoptosis, subsequently affecting bone formation and remodeling. Furthermore, it was shown that exposure to nicotine has a direct effect on blood vessels, producing vasoconstriction which decreases blood perfusion and causes low oxygen and local ischemia.[122,166] In addition to delivering oxygen and nutrients to tissues, blood circulation plays an active role in bone formation and remodeling by mediating the interactions between different bone and vascular cells at different regulatory levels.[93] In a clinical study (AlBandar et al. 2000),[67] tobacco smokers had a higher prevalence of moderate and severe periodontal disease with increased attachment loss and gingival recession compared to non-smokers, indicating worse periodontal conditions in the smokers' group. Furthermore, smokers had more missing teeth than non-smokers. Several review articles identified within this literature search confirmed that smoking is one of the factors related to implant failure by reporting conclusions of several studies showing that smoking is associated with higher failure rates, complications and altered peri-implant tissue conditions.[54,87, 88,149,170] A literature review by Klokkevold and Han (2007)[113] suggested that tobacco smoking may be a significant risk factor with an adverse effect on implant survival and success rates in areas of lower jawbone quality but may not be as significant in sites with better bone. While a review by Levin and Schwartz-Arad (2005)[49] revealed a significant

association between smoking, peri-implant marginal bone loss, reduced survival rate of implants ($0.001 < p < 0.05$) and the outcome of onlay bone grafts ($p < 0.05$) as well. In a recent meta-analysis (Chen et al 2013),[78] smoking was associated with an increased risk of dental implant failure. However, the analysis did not investigate the effects of tobacco smoking on peri-implant MBL. Results from another meta-analysis (Chrcanovic et al. 2015),[60] suggested that insertion of dental implants in smokers affected implant failure rates, the risk of postoperative infection, and peri-implant MBL. It is hypothesized that the increased implant failure rates in tobacco smokers are mainly due to smoking effect on osteogenesis and angiogenesis. The commercially available titanium used in dental implant manufacturing have a wide range of surface topographies or morphologies and chemical and physical properties depending on how it is prepared and handled, examples include turned, acid-etched, sandblasted and acid-etched, sandblasted and fluoride-modified, and oxidized dental implants.[56,57,58] It is known that the surface modifications of different dental implant brands influence the osseointegration process.[168] A retrospective cohort study by Balshe and colleagues (2008)[27] reported that smoking was not significantly associated with implant failure among the moderately rough surface (anodized) implants, while it was associated with implant failure among the group with minimally rough surface implants. Despite the large number of implants in this study ($n = 4607$), the results were not included in the upcoming meta-analysis because the number of placed and the number of failed implants were not separately reported between smokers and non-smokers. The evidence presented by Balshe et al.[27] did not meet all requirements to be included in the current meta-analysis, however it is a valuable addition to the literature due to the great number of implants investigated. In a more recent study by Sayardoust et al. (2013),[16] turned implants had more peri-implant MBL and a higher incidence of failure in smokers, while oxidized implants showed similar MBL and failure

rates in smokers and non-smokers. Such contrasting results indicate that controversy still exists and that there is a need for additional studies to investigate the long-term outcomes of implants with altered surface characteristics in tobacco smokers.[113] The studies included in the current analysis used implants with several different brands and surface characteristics. In a retrospective study investigating success rates of dental implants placed in grafted maxillary sinuses, Kan et al. (1999)[108] reported a 93.04% success rate in non-smokers and an 82.82% in smokers. In another study by the same authors[175] with a longer follow-up period, the success rate for the non-smokers was 82.7% and for smokers was 65.3%. Therefore, in considering the difference in success rates in smokers and non-smokers for implants placed in loose trabecular bone sites that are followed over a longer period of time, the adverse effect of smoking may become more evident. A longer follow-up period can lead to an increase in the failure rate, particularly if it extended beyond functional loading, because other restorative factors can influence implant failure after loading. This may project an underestimation of actual failures in some clinical studies. However, it is difficult to define what would be considered a short follow-up period to evaluate implant failure rate in smokers. Results from the meta-analysis by Chrcanovic et al. (2015)[60] demonstrated that smoking is associated with increased number of dental implant failures regardless of the type of implant surface topography or modification. Additionally, a higher risk ratio was observed with rough-surface implants compared to turned implants in the smoking group. Nevertheless, there is some contradictory evidence that smoking is associated with older turned implant surfaces but not with modern ones. With regard to the bone-implant interface, the detrimental effects of tobacco smoke have a series of local and systemic influences on bone metabolism.[135] Concerning associations with patients' tobacco smoking status, peri-implant bone level is known to be associated with implant prognosis.[61,74,82,143,148,149] The peri-implant marginal bone around the

implant platform is normally a significant indicator for defining good peri-implant health. Misch et al. (2008)[48] classified the implants with marginal bone loss of <2 mm from the time of initial surgery as successful, while according to Albrektsson and Isidor (1993)[62] an implant is regarded as successful when it presents bone resorption of less than 1.5 mm in the first year after prosthetic loading and 0.2 mm in subsequent years. Other authors[147] have proposed that an implant should present a lower bone resorption than one third of the implant length, regardless of the number of years in function. To date, there is no consensus regarding the quantity of peri-implant marginal bone resorption consistent with time after placement, overall health, and success. In a recent meta-analysis by Alfadda (2018),[33] smokers experienced significantly more implant failure and peri-implant marginal bone loss relative to nonsmokers. These findings are in accordance with those of another review conducted by Moraschini et al. (2016).[35] The greater difference in MBL observed between smokers and nonsmokers in association with aging (~0.02 mm/year) may be explained by a combination of the depleting effect of the tobacco chemicals on bone vascularity and the slow, progressive, age-related phase of bone loss in trabecular and cortical bone.[97,111,141] A meta-analysis by Strietzel et al. (2007)[156] on studies in which threaded titanium implants with machined, titanium plasma sprayed (TPS) or Hydroxyapatite (HA)-coated surfaces were predominantly used, revealed a significantly enhanced risk for implant failure among smokers compared to non-smokers. The study compared the implant related odds ratios for implant failure in smokers considering different observation periods. The risk of implant failure for smokers ranged from 2.8 after up to 1 year decreasing to about 2.3 up to 5 years, indicating a higher risk of early implant failure. However, the risk of implant failures in smokers was found to be significantly increased even after 5 years. In an earlier review by Esposito et al. (1998)[87,88] on studies mainly reporting on threaded implants with a machined surface, i.e.

Branemark implants, the consensus was that smoking has a negative influence on implant survival. Furthermore, a comparison between threaded implants with machined and anodic-oxidized surfaces showed no significant influence of smoking on implant failures for implants with an anodic-oxidized surface.[142] However, it is probably worth noting that studies including more modern implants with micro-structured surfaces like sand blasted and/or acid etched surfaces were scarcely published at that time. In the author's opinion, whether these implant surfaces indeed significantly improve outcomes in smokers need to be further explored through studies with larger sample sizes reporting data on implant failure rates in relation to smokers and non-smokers. The findings reported by Strietzel et al. (2007)[156] considering the implant-related ORs for implant failures in smokers were remarkably similar to those published in another study by Hinode et al. (2006)[42] who performed a meta-analysis on the effect of smoking on osseointegrated dental implants, based on implant-related data. This review used a subgroup analysis to examine success in the maxilla versus the mandible. Whereas the overall OR for implant failure was 2.17 (95% CI, 1.67–2.83), the OR in the maxilla was 2.06 (95% CI, 1.61–2.65) and in the mandible was 1.32 (95% CI, 0.72–2.40), meaning the odds of failure was double in the maxilla, but statistically insignificant in the mandible. These two systematic reviews represent a small but growing body of evidence indicating implant failure risk is higher in smokers than in nonsmokers, particularly in the maxilla. In a systematic review by Berglundh et al. (2002)[73] analyzing longitudinal studies of up to 5 years, implant survival rate of 97.5% up to the second stage surgery was observed. In the same year, Davarpanah et al.[85] reported a survival rate of 96.5% for 1583 implants placed in different regions of the maxilla and mandible, with a follow-up period of 5 years as well. These results demonstrated a reduction in dental implant survival rate over time during the follow-up period. Simonis et al. (2010)[153] and Carlsson et al.

(2000)[76] concluded that there was a larger number of implant losses and higher level of peri-implant marginal bone loss in patients who were smokers. These conclusions are supported by numerous other studies that have analyzed the influence of tobacco smoking on the survival and success of dental implants.[6,113,165] A systematic review by Moraschini et al. (2015)[34] revealed a mean survival rate of 94.6% (SD 5.97%) for a total of 7711 implants, with a mean follow-up of 13.4 years. A number of authors from the included studies concluded that bone resorption occurred and was more evident after the first year of prosthetic loading, and in one study (Pikner et al. 2009)[136] it was suggested that implants placed in the mandibular arch tend to present greater marginal bone resorption over the course of time. This review (Moraschini et al. 2015),[34] based on the results of the included studies, presented a mean peri-implant marginal bone loss of 1.3 mm (SD 0.84 mm), and the study that presented the highest mean bone resorption value of 2.67 mm evaluated 316 implants under mandibular overdentures during 12 years of follow-up (van Steenberghe et al. 2001).[163] The results of pertinent studies should be interpreted with caution due to the possible presence of uncontrolled confounding factors and the risk of bias. However, the overall results of most of the recently published studies suggest that placement of dental implants in smokers affects MBL, the incidence of postoperative complications, as well as implant failure rates. In light of the findings of this review, smoking may be associated with significantly increased peri-implant MBL and implant failure rate. Exploring various preventive and interventional measures that can possibly limit the adverse effect of tobacco smoking on implant-related outcomes is highly recommended. Additionally, the potential adverse effects of smoking on treatment outcomes must be explained to the patient before treatment, and the dentists' clinical decisions should be specific to each case. As the risk of implant failure is generally low, individual practitioners will have to decide what modifications to therapy, if any,

should be employed with their patients. In conclusion, smoking is a significant risk factor for dental implant therapy. This should be clearly conveyed to the patient before treatment. A strict recall program throughout the course of the treatment to early detect negative changes in peri-implant tissues or implant failure is necessary.

Background

According to the 9th edition of the Glossary of Prosthodontic Terms,[95] edentulism is defined as the state of being edentulous, i.e. without natural teeth. It is estimated that 178 million Americans are missing at least one tooth & about 40 million are completely edentulous (ACP).[176] The etiology of tooth loss is highly variable, ranging from tooth loss due to dental caries, periodontal disease, trauma or congenital anomalies. Tobacco smoking is a widely spread habit practiced all around the world. In 2016, an estimated 15.5% (37.8 million) of U.S. adults were current cigarette smokers. Of these, 76.1% smoked every day.[44] Tobacco smoking is related to many health risks. It affects general and oral health causing increased risk of periodontal disease, dental caries, oral neoplasms and delayed wound healing. It was reported that there is an association between cigarette smoking and dental implant failure.[3] The adverse effects of smoking and nicotine on oral soft tissue have also been observed in less-successful regenerative procedures and more gingival recession.[138] Higher plaque index (PI) and increased probing depth (PD) have been reported in smokers compared to non-smokers.[25] Furthermore, a 5-year retrospective study comparing different dental implants revealed that smokers have more marginal bone loss (MBL) around implants than non-smokers.[16]

Description of the intervention

The endosteal dental implant: a device placed into the alveolar and/or basal bone of the mandible or maxilla and transecting only one cortical plate.[95] It is the most widely used dental implant type in contemporary dentistry. It is composed of an anchorage component, termed the fixture, which, ideally, is within the bone, a retentive component, termed the abutment and a restorative component in the form of a fixed, removable, or fixed-removable implant supported restoration

replacing single or multiple missing teeth and/or associated tissues. Dental implant survival refers to a dental implant that reside in placement site in the dental arch at the time of evaluation, regardless of any disease signs, symptoms, or history of problems. Dental implant success is usually defined by a set of criteria evaluating the condition and function of the implant at the time of evaluation, i.e. whether or not the implant satisfies the functional & esthetic demands. Dental implant failure often refers to loss of osseointegration and implant mobility that warrants removal of the implant.

How this intervention might work

Brånemark's pioneering work on the phenomenon of osseointegration revolutionized the dental implants practice. Osseointegration is the concept that made dental implant therapy possible. It is defined as the direct structural and functional bone-to-implant contact. Successful osseointegration involves a series of biological events that includes inflammation, bone formation and remodeling.[90] Missing tooth/teeth replacement with dental implants represents an invaluable treatment modality in modern dentistry and can preserve healthy natural teeth structure in cases of partial edentulism.

Why it is important to do this review

Although dental implant therapy is considered a predictable treatment modality with reported high survival and success rates, biological complications do occur and a number of risk factors have been involved, including the patient's medical history, smoking habits, jawbone quality, radiation therapy, parafunctional habits, surgeon's experience and susceptibility to periodontitis. The underlying mechanisms of the detrimental effects of smoking have been studied in vitro and

in vivo in animal and human studies. In vitro studies indicated that nicotine, a component in tobacco smoke, has a negative effect on the osteogenic gene expression in osteoblast cell lines.[145] Furthermore, nicotine combined with bacterial lipopolysaccharide (LPS) has been shown to stimulate the formation of osteoclast-like cells.[157] Animal experiments have demonstrated that nicotine attenuates the expression of a wide range of factors involved in the osteogenic differentiation and formation of extracellular matrix and blood vessels.[171] Additionally, smoking reduces the vascularization of the gingival tissues, impedes the immune response, and promotes a more pathogenic or "dysbiotic" oral microflora.[112] Although the available evidence highlights the potential biological components affected by smoking, the exact mechanism behind the greater marginal bone loss (MBL) and the higher incidence of implant failure in smokers are not fully understood & need further investigation. Although not an absolute contraindication per se, smoking is considered a risk factor for dental implant failure. Several recommendations were suggested to enhance implant survival in smokers.[45] However, despite the plethora of the current available literature, confounding factors and inconsistency in reported outcome measures & implant success criteria is not uncommon.

Objectives

The aim of this systematic review and meta-analysis is to test the null hypothesis of no difference in dental implant failure rates and marginal bone loss between smokers and non-smokers with regards to follow-up time.

Materials and methods

The methodology of this review was adapted from the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[118] The focus question was stated and categorized according to the PICO format (Population, Intervention, Comparison, and Outcome).

Criteria for considering studies for this review

This review sought prospective and retrospective cohort studies, as well as randomized & non-randomized clinical trials that compared implant failure rates and peri-implant marginal bone loss between smokers and non-smokers. In this review, implant failure was regarded as the total loss of the implant. Only studies published in English were eligible for inclusion.

Types of participants

Study participants are adult subjects, with a minimum age of eighteen years or older, that are tobacco smokers and non-smokers who are fully or partially edentulous and received dental implant(s) re-habilitation to overcome problems with conventional removable complete or partial dentures or for providing alternative treatment options for fixed or fixed-removable implant-supported restorations.

Types of intervention

Surgical placement of a single or multiple titanium endosseous dental implant(s) in one or both jaws to replace a single missing tooth or multiple missing teeth.

Types of outcome measures

The outcome measures investigated in this review are the number of failed implants, comprising the dichotomous or binary outcome variable, and the amount of peri-implant marginal bone loss, as a continuous outcome variable, in smokers & non-smokers.

Exclusion criteria:

Letters to the editor, animal studies, in vitro studies, case series, case reports, commentaries and reviews were all excluded. In addition, articles that did not separately report outcome measures for smokers and non-smokers, included patients with congenital/familial medical conditions or uncontrolled autoimmune or systemic diseases or unbalanced metabolic disorders, included subjects with periodontal disease without prior treatment, or were poorly controlled for confounding variables were excluded. Lastly, any studies that did not obtain ethical approval or written informed consent, included fewer than 10 patients in each group, used short (<6 mm) or zygomatic implants or were not available online were also excluded.

Search methods for identification of studies

Electronic searches

An extensive online search of the following databases was performed to locate relevant articles published up to June 2019: PubMed, Scopus, EBSCOhost Dentistry and Oral Sciences Source. To identify studies eligible for inclusion in this review, detailed search strategies were developed for each of the searched databases. These search terms were based on the search strategy originally developed for Medline (OVID) but revised appropriately for each database in an attempt to maximize the efficiency and effectiveness of the search and increase the number of

results. The search strategies incorporated a combination of MeSH (Medical Subject Heading) terms, controlled vocabulary and free text terms. The search strategies for each database are listed in **Table 4**.

Searching other resources

Citations and cross-referencing were comprehensively utilized to further the identification of studies and peer-reviewed dental journals were hand searched for possible related materials. In addition, grey literature was explored using Google Scholar and OpenGrey, until to June 2019.

PICO question: *Does smoking increase implant failure rate and peri-implant marginal bone loss in smokers compared to non-smokers?*

P: tobacco smokers and non-smokers who are fully or partially edentulous

I: surgical placement of a single or multiple titanium endosseous dental implant(s) in one or both jaws to replace a single tooth or multiple missing teeth.

C: comparison of outcome measures between smokers and non-smokers

O: outcome measures of implant failure rate and the extent of peri-implant marginal bone loss

Critical appraisal & assessment of risk of bias in the included studies

The Cochrane collaboration's tool for assessing Risk of Bias (RoB) in randomized trials was utilized to assess randomized clinical trials.[100] Quality assessment for non-randomized studies (prospective and retrospective cohort studies) was performed using the Newcastle–Ottawa scale (NOS).[63] For the categories of 'selection' and 'outcome', studies may obtain a star/point for each item. For the 'comparability' category, two stars/points may be awarded. The highest score that

could be assigned to a study according to the NOS was nine stars/points (highest scientific evidence). Studies scoring six stars/points and above were considered to be of high quality.

Data extraction

Customized data extraction sheet were formulated and the following data were extracted from the included studies (when available): author(s) name(s), publication year, study type, follow-up period, number, gender and age of the subjects, smoking status & description, number & location of implants placed, implant brand, surface characterization, size & dimensions, healing period before loading, marginal bone loss in millimeters +/- standard deviation (SD), implant survival rate, number of failed and placed implants in smokers & non-smokers, *P*-value for implant failure rate, and the number of drop-outs.

Dealing with missing data

The original investigators were contacted by e-mail in cases of missing or unreported data.

Statistical analysis

Dichotomous and continuous variables from the included studies were analyzed through meta-analysis when the same type of data was assessed by at least two studies. For binary outcomes, i.e. implant failure, the estimate of the intervention effect was expressed in the form of odds ratio (OR) with a confidence interval (CI) of 95%. For continuous outcomes, i.e. marginal bone loss, the average and standard deviation (SD) were used to calculate the standardized mean difference (SMD) with a 95% CI. The results were pooled using the fixed-effects model (Mantel–Haens-zel–Peto test) or random-effects model (DerSimonian–Laird test).

Assessment of heterogeneity

The I2 statistical test was used to express the percentage of heterogeneity in the studies. Values up to 25% were classified as indicating low heterogeneity, values of 50% as indicating medium heterogeneity, and values of ≥ 70% as indicating high heterogeneity. The results of the random-effects model were validated when significant heterogeneity was observed ($P < 0.10$). The fixed-effects model was considered when low heterogeneity was observed. The level of statistical significance was set at $P < 0.05$. All data were analyzed using the Review Manager software; version 5.2.8 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; 2014).

Publication bias

Publication bias was explored graphically through a funnel plot. Asymmetry in the funnel plot may indicate possible publication bias.

Results

Literature search

The electronic search yielded 379 titles from the selected databases. Additional 22 relevant articles were identified through other resources. After removal of duplicates, the records were screened by reading the title & abstract (& data tables when available). 30 articles were selected for full-text review. Seven studies were excluded (**Table 3**) after careful analysis, as they did not conform to the eligibility criteria of this review. Therefore, 23 studies; 3 RCTs and 20 observational cohort studies published between 1993 and 2018 were included in the meta-

analysis. The data search and selection process of studies are presented in **Figure 1** as a PRISMA flow diagram.

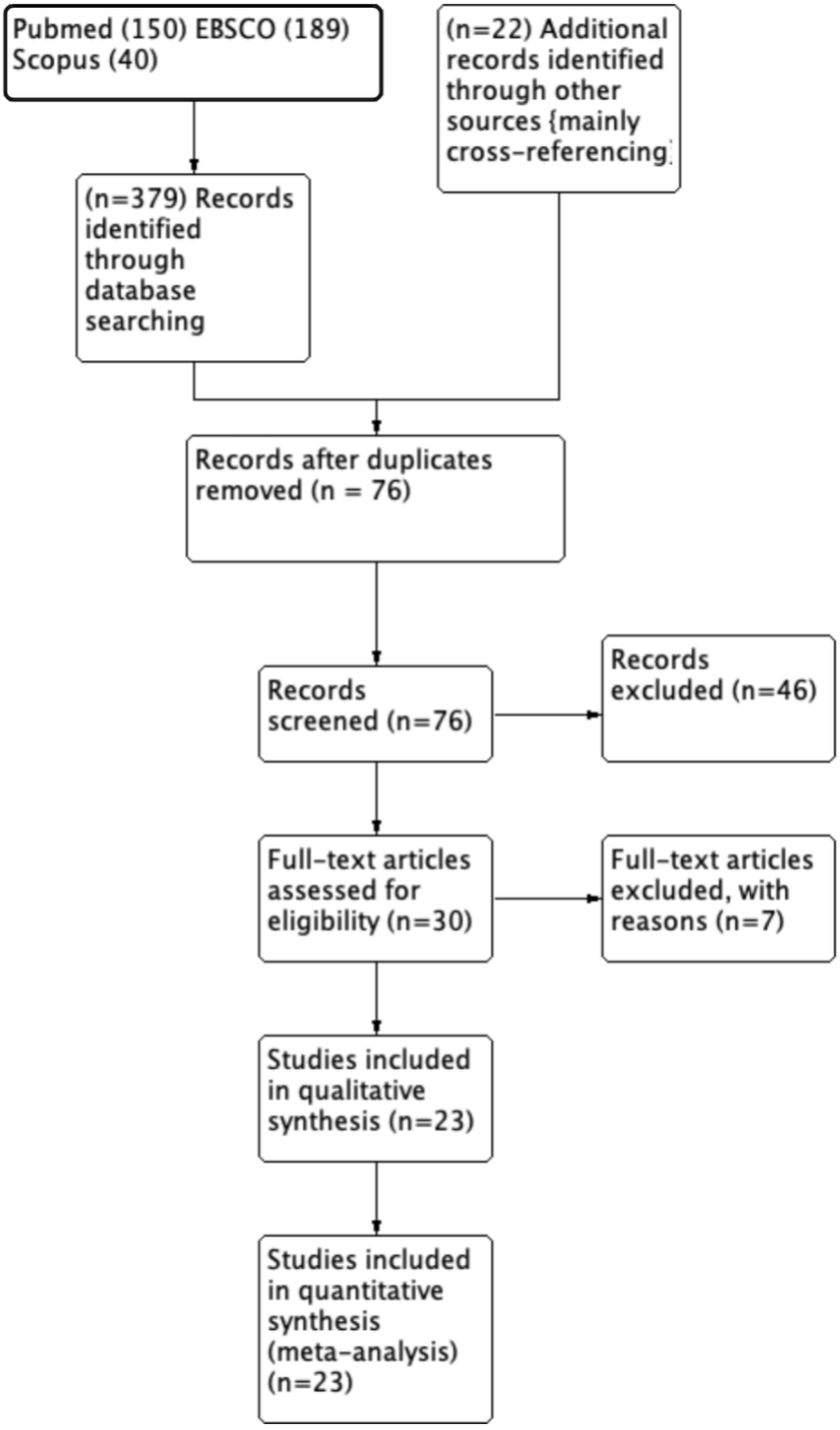

Fig 1: PRISMA flow diagram of the screening and article selection process.

Characteristics of the included studies

Eight prospective and twelve retrospective cohort studies and three randomized clinical trials were included. The number of participants in the studies ranged from 32 to 1727 subjects, and the age range was 17 to 88 years. The follow-up period ranged from 6 to 240 months. The number of implants installed in smokers was 7124 and in non-smokers was 19226. The Branemark system (Nobel Biocare) was the most commonly used implant system. Five studies provided definitions for the smoking habits of the participants in terms of quantity or number of years of smoking, while only two studies did not provide definitions for the smoking habits of the patients investigated. Eleven studies reported a statistically significant difference in the average number of implant failures between smokers and non-smokers. The difference was not statistically significant in only one study. The characteristics of the included studies are presented in **Table 1.**

Quality assessment

The Cochrane RoB tool scores for corresponding randomized controlled trials were included in the forest plot (**Figure 2**) for the 3 included RCTs. For observational studies, only four studies obtained a score of less than six stars on the NOS. The scores for each study are summarized in **Table 2**.

Marginal bone loss

14 out of the 23 included studies reported on the analysis of marginal bone loss. All studies performed this analysis via standardized radiographic measurements from the implant platform to the alveolar bone crest. The marginal bone loss in the group of smokers ranged from 0.07 to

4.65 mm, while in the non-smoking group the marginal bone loss ranged from 0.04 to 3.13 mm. The analysis of marginal bone loss was performed using the random-effects model because of the high level of heterogeneity (I2 = 98%; $P < 0.00001$). A standardized mean difference (SMD) of 1.07 (95% CI 0.67–1.48) was found, demonstrating a statistically significant difference in favor of non-smokers ($P<0.00001$). Four studies analyzed the marginal bone loss between maxillary and mandibular implants in smokers. Despite the high level of heterogeneity (I2 = 97%; $P = 0.00001$), a SMD of 1.39 (95% CI 0.35–2.42) were observed, yielding a statistically significant difference in favor of the mandible ($P < 0.008$). **Figure 2** shows Forest plots for marginal bone loss in smokers compared to non-smokers and for MBL in maxilla versus mandible in the smokers' group.

Implant failure rate

Thirteen studies reported on the number of implant failures in smokers versus non-smokers. The average survival rate of implants varied from 84.2% to 97% in the group of smokers, and from 95.2% to 98.8% in the group of non-smokers. The results of the analysis of implant failure were classified into two subgroups according to the follow-up time, i.e. <5 years & >= 5 years. The fixed-effects model was used for this analysis because of low heterogeneity (I2 = 34%; $P < 0.11$). The total odds ratio was 2.24 (95% CI 1.90–2.64), demonstrating a statistically significant difference in favor of the non-smoking group ($P < 0.00001$). The results for follow up subgroups differences demonstrated a significant increase in implant failure with the increase in follow-up time ($P = 0.05$) although with considerable heterogeneity (I2=74.5%). The overall odds ratio for implant failure rate and the ORs for the subgroup analysis are shown in **Figure 3**.

Publication bias: Analysis of implant failure revealed symmetry of the funnel plot, therefore rejecting the possibility of publication bias (**Figure 4**).

Discussion

Tobacco smoking is an accepted potential risk factor for general and oral health. Investigating the causes of peri-implant marginal bone loss and implant failure is important for predictable implant therapy. Cigarette smoking has different adverse local and systemic effects. Local effects are mainly due to nicotine and cytotoxic vasoactive substances generated in the combustion of tobacco smoke. Systemically, cigarette smoking negatively affects the cellular immunologic response of neutrophils and production of antibodies. Smoking also influences bone metabolism and turn-over. If local absorption of cigarette smoke products had a definite influence on the failure of implants, this may explain the lower rates of mandibular implant failure in smokers as this area is possibly protected by the tongue and more salivary flow. Several clinical studies have shown that the survival of implants can be affected by tobacco smoking. The smoking habits assessed in this review are based on the patients' acknowledgment in the included studies. However, the quantity and frequency of smoking can be a key factor in determining the predictability of success in dental implants treatment. Only five studies included in this review defined or classified smokers, this is a critical factor for risk assessment, but it’s often overlooked or under-reported. In a meta-analysis, homogeneity implies a mathematical compatibility between the results of each individual trial. Potential biases are likely to be greater for non-randomized studies compared with RCTs, so results should always be interpreted with caution when they are included in reviews and meta-analyses. However, narrowing the inclusion criteria increases homogeneity but also excludes the results of more trials, and thus risks the exclusion of

significant data.[152] This was the reason to include non-randomized studies in the present meta-analysis. This issue is important because meta-analyses are frequently conducted on a limited number of RCTs. In meta-analyses, such as these, adding more information from observational studies may aid in clinical reasoning and establish a more solid foundation for causal inferences. In the present meta-analysis, the statistical unit of analysis for 'implant failure' was the implant. It would be technically more correct to adjust for the effect of clustered, correlated observations; however, it is a challenging analytic method and the implant survival is so high that failing to adjust for clustered, correlated observations would have little effect on the estimate and deviation of survival.[79] This systematic review attempted to identify studies comparing the marginal bone loss and implant failure rate between smokers and non-smokers. The search produced observational prospective and retrospective cohort studies and clinical trials. Despite the relatively small number of randomized controlled trials included, the inclusion of a large number of longitudinal observational studies, with large number of participants through a well-defined inclusion and exclusion criteria, in the meta-analysis can potentially increase the amount of information and consolidate the results from the clinical studies. Five different definitions in relation to smoking were reported by the studies, i.e. smoker and non-smoker, smoker and never smoker, low consumption and high consumption, mild smokers and heavy smoker, and one study defined smokers as individuals who smoked half a pack or more of cigarettes a day. The contrast in descriptions and definitions highlights these differences as potential confounding variable. Currently, there is no standardization in the classification of patients regarding the number of cigarettes smoked per day. In addition, other confounding risk factors are known to influence the results by generating publication bias. There is still no consensus in the current evidence regarding the procedures that can minimize the risk of smoking on the health of dental implants.

Two-stage implant placement may decrease the physical contact with tobacco smoke and prevent the accumulation of bacterial biofilms on the implant platform during the healing period, as it is already known that smoking patients tend to have greater bacterial biofilm adhesion. Also, improving the gingival phenotype (increasing the area of keratinized mucosa) in the areas adjacent to implant sites would be a prudent measure. Because tobacco smoking can affect immune function, periodontally susceptible patients may be at a higher risk for dental implant complications, like increased amount of marginal bone loss and implant failure rates. However, a recent meta-analysis that evaluated the interaction between smoking and peri-implantitis concluded that there is low evidence implicating smoking as a risk factor for the development of peri-implant disease.[150] There is a growing evidence in the literature indicating that tobacco smoke ingredients, as nicotine, may delay or inhibit healing after oral surgical procedures. The most accepted theory for the influence of smoking on healing in the oral tissues is the decrease in local blood flow resulting from vasoconstriction, which causes changes in the cell population and the inflammatory process. Results of the present meta-analysis revealed that the marginal bone loss was significantly higher in smokers compared to non-smokers ($P < 0.00001$). A comparison of the maxillary & mandibular arches revealed a significant difference favoring implants placed in the mandible. ($P < 0.008$). It is believed that the maxilla is more permeable to the effects of tobacco smoke possibly due to its increased medullary bone content and vascularity compared to the mandible. The bacterial plaque tends to adhere more quickly on the epithelial cells of smokers. This may cause an increase in the incidence of biological complications, such as peri-implant mucositis and peri-implantitis and consequently an increase in the rate of peri-implant marginal bone loss. Limited number of clinical studies have compared implant marginal bone loss between smokers and non-smokers. Bain and Moy (1993)[3] proposed that tobacco smoking

and decreased quality of available jawbone, could negatively affect healing and increase marginal bone loss, mainly in the maxillary arch. The current review analysis results for implant failure rate showed significant increase in failure rate in smokers compared to non-smokers ($P < 0.00001$). Additionally, the follow-up subgroups comparison revealed that implant failure rate increased with the increase in follow-up time ($P = 0.05$). However, considerable heterogeneity (I2=74.5%) was observed.

Suggestions for future research

A larger number of high-quality longitudinal studies, preferably be RCTs, with a follow-up period of at least 5 years evaluating the clinical performance of implants with emphasis on reporting outcomes for smokers and non-smokers individually, and possibly including implants with various surface characterizations and/or modifications, should be conducted in accordance with the guidelines available in the Consolidated Standards of Reporting Trials (CONSORT) statements.[128] There should be standardization of the success criteria, thereby facilitating communication and comparison of the reported data. Aesthetics is a fundamental factor in dental implant therapy. In spite of this, no success criteria adopted by the studies in this review touched on the individual aesthetic criteria, such as the angle and positioning of the implants and the natural profile of peri-implant soft tissues. Aesthetic outcomes must be part of the evaluation of implant success. Lastly, with the growing popularity of electronic cigarettes and other similar devices, it might be worth-while looking into data generated by evaluation of dental implants placed in individuals who use these devices.

Conclusion

In light of the results of this review, tobacco smokers have a higher risk of biological dental implant complications compared to non-smokers. A statistically significant difference ($P < 0.00001$) in peri-implant marginal bone loss was found between the smoking group and the non-smoking group, in favor of the non-smoking group with a standardized mean difference (SMD) of 1.07 (95% CI 0.67–1.48). Marginal bone loss in smokers was increased in the maxilla compared to the mandible with a SMD of 1.39 (95% CI 0.35–2.42) revealing a statistically significant difference in favor of the mandible ($P < 0.008$). The total odds ratio for implant failure rate was 2.24 (95% CI 1.9–2.64), demonstrating a statistically significant difference in favor of non-smokers ($P < 0.00001$). The results for follow up subgroups differences demonstrated a significant increase in implant failure with the increase in follow-up time ($P = 0.05$) although with considerable heterogeneity (I2=74.5%). Therefore, tobacco smoking patients must be encouraged to quit smoking or at least decrease consumption. Although causality between the measured parameters cannot be assessed with absolute certainty in observational studies, the outcomes of the current investigation indicate that there is a connection between tobacco smoking and increased peri-implant marginal bone loss and implant failure. So, for patients who actively smoke, as in other periodontal & oral surgical procedures, the clinical recommendation for a period of abstinence that at least covers the pre-surgical evaluation, initial therapy, definite implant treatment & immediate post-op phases remain to be very relevant. Therefore, taking into consideration the disparate outcome measures employed to assess dental implant performance and within the limitations of this systematic review, the null hypothesis is rejected, and the alternative hypothesis is accepted, which is in agreement with other related meta-analyses reported elsewhere in the literature.

Table 1: characteristics of included studies

Author & year of publication	Study type Follow-up period in months (mean or range)	No. of subjects No. per group	Age range Mean age Gender	Smoking definition	Number of implants & location	Implant brand & Surface	Implant dimensions	Healing Period for loading (months)	Marginal bone loss (mm) (mean +/- SD)	Implant survival rate (%)	Failed/placed implants in each group	P-value (for implant failure rate)	Drop-outs
Bain 1993	Retrospective 72	540 NR	13–85 55.1 229 M/311 F	Smoker and non-smoker	2194	Branemark Machined	NR x 7,10, 13,15,18,20	6(maxilla) 3(mandible)	NR	S:88.7 NS:95.2	S:44/390 NS:86/1804	<0.001	NR
Haas 1996	Retrospective Up to 108	421 S:107 NS:314	16–88 53.1 171 M/250 F	Smoker and non-Smoker	1366	Branemark, Friatec Machined, rough	NR	3 to 7	S:2.7 +/- 1.87 NS:1.58 +/- 1.42	NR	NR/366 NR/1000	NR	NR
Lindquist 1997	Retrospective 120	45 S:21 NS: 24	(33-64) M: 13 F: 32	Smoker and non-smoker	266	Branemark	NRx10	4	S: 1.3+/- 0.55 NS:0.65+/- 0.2	NR	S:NR/125 NS:2/139	<0.001	1
Kumar 2002	Prospective 18	461 S:72 NS: 389	NR NR NR	Smoker consisted of patients who smoked half a pack or more cigarettes a day	1183	Straumann Rough	NR	1 to 3	NR	S:97 NS:98.3	S:8/269 NS:15/914	<0.05	NR
Schwartz-Arad 2002	Prospective 36	261 S:89 NS: 172	18–67 48 NR	Non-smokers; mild smokers (upto10 cigarettes/day); heavy smokers (>10 cigarettes/ day)	959	NR NR	NR	NR	NR	S:96 NS:98	S:15/380 NS: 12/579	<0.05	NR
Wennstrom 2004	RCT	52 S: 17 NS: 34	NR 59.5 NR	Smoker and non-smoker	149 S: NR NS: NR	Astra Tech (screw-shaped,self-tapping)	NR	NR	S: 0.41 +/- 0.69 NS: 0.30 +/- 0.84	97.3 S: NR NS: NR	NR/50 NR/99	NR	NR

Table 1 cont'd: characteristics of included studies

Galindo-Moreno 2005	Prospective	185 S: 63 NS: 122	NR 49.77 NR	Smoker and non-smoker	514 S: NR NS: NR	148press-fit, 366 screw type	NR	NR	S: 0.45 +/- 0.18 NS: 0.42 +/- 0.12	NR S: NR NS: NR	S: 175 NS: 339	NR	NR
Nitzan 2005	Prospective 9.4-86.6 (mean 45.5)	161 S:59 NS: 102	23–89 57 NR	Non-smokers; mild smokers (upto10 cigarettes/day); heavy smokers (>10 cigarettes/ day)	646	NR NR	NR	NR	S:0.15 +/- 0.09 NS: 0.04 +/- 0.04	NR NR	S:NR/271 NS:NR/375	NR	NR
DeLuca 2006	Prospective cohort	389 S: 285 NS: 104	NR 49.3 NR	Smoker and non-smoker	1330 S: 285 NS: 1045	Branemark	NR	NR	S: NR NS: NR	95.79 S: 94.74 NS: 96.94	S: 26/285 NS: 32/1045	NR	NR
DeLuca & Zarb 2006	Prospective Up to 240	200 S:54 S:146	15–77 52.1 NR	Smoker and non-smoker	1539	Branemark Machined	NR	6(maxilla) 3(mandible)	S:0.07 +/- 0.26 NS:0.04 +/-0.12	NR NR	NR/494 NR/1045	NR	NR
Herzberg 2006	Prospective cohort 56.5	60 S: 21 NS: 39	NR 52 NR	Smoker and non-Smoker	212 S: NR NS: NR	Screw type	NR	NR	S: 0.24 +/- 0.49 NS: 0.09 +/- 0.32	95.5 S: 91 NS: 96.15	S: 5/56 NS: 4/104	NR	NR
Sanchez-Perez 2007	Retrospective 60	66 S:40 NS:26	15–71 43.4 NR	Non-smokers; light smokers (<10 cigarettes/ day); moderate smokers (10–20 cigarettes/day); heavy smokers (>20 cigarettes/day)	165	Biotech Rough	NR	NR	S:2.41 +/- 1.46 NS:3.13 +/- 1.59	S:84.2 NS:98.6	S:15/95 NS:1/70	<0.001	NR
Sverzut 2008	Retrospective 8	650 S:76 S: 574	13–84 42.7 NR	Smoker and non-smoker	1628	NR	NR	NR	NR	S:96.6 NS:97.1	S:7/197 NS:43/1431	0.5994	NR
Anner 2010	Retrospective 1-114	475 S:63	51.96+/- 11.98	NR	1626 NR	NR	NR	NR	NR	NR	S: 21/226 NS: 56/1400	0.0006	17

Table 1 cont'd: characteristics of included studies

		NS:412	M:176 F: 299										
Cavalcanti 2011	Retrospective 60	1727 S:549 NS:1178	17–85 49.2 M:702 F:1025	Smoker and non-smoker	5843	3i, AstraTech, Camlog, Friadent-Dentsply, Nobel Biocare, Straumann, Sweden and Martina, Zimmer Rough	NR	0-9	NR	S:94.5 NS:97.1	S:107/1961 NS:112/3882	0.003	250
Rodriguez-Argueta 2011	Retrospective 6 minmum	295 S:113 NS: 182	21-68 53.1+/-12.5 M:127 F: 168	NR	1033	Nobel Biocare Impladent Astratech (Rough surface)	NR	NR	NR	NR	S: 14/389 NS: 18/644	NR	0
Vandeweghe 2011	Retrospective 60	329 S:41 NS:288	18–84 54 M:141 F:188	Smoker and non-smoker	712	Southern Implants Rough	3.5, 3.75,4,4.3, 5, 6x8.5, 10,10.5, 11.5, 12,13,13.5, 15, 16.5,18	NR	S:1.56+/-0.53 NS:1.32+/-0.38	S:95.2 NS:98.8	S: 5/104 NS: 7/608	0.007	NR
Stoker 2012	RCT 99.6	94 S: 35 NS:59	59.8 M: 28 F: 66	Smoker & never smoker	256	ITI/Bonefit dental implants TPS	NR	3	S: 1.72+/-1.65 NS: 0.92+/-0.8	96.5%	10/256 S:NR/96 NS:NR/160	NR	16
Vervaeke 2012	Retrospective 24	300 S:65 NS:235	17–82 56 M:114 F:186	Smoker and non-smoker	1093	NR NR	3.5, 4,4.5,5x8, 9, 11,13,15,17	NR	S:0.53+/-0.92 NS:0.29+/-0.54	S:96.7 NS:98.7	S:8/244 NS:11/849	0.025	0
Sayardoust 2013	Retrospective 60	80 S: 40 NS:40	NR 57.6 M:38 M F:42	Smoker and non-smoker	80	Branemark; Nobel Biocare Rough	NR	3 to 4	S: 1.39+/-1.57 NS: 1.01+/-1.09	S:89.6 NS:96.9	S:4/40 NS:1/40	<0.05	0

Cha 2014	Prospective cohort	161 S: 18 NS: 143	NR	Smoker and non-smoker	462 S: 48 NS: 414	Implatinium	NR	NR	NR	96.53 S: 85.42 NS: 97.83	S: 7/48 NS: 9/414	NR	NR
Sayardoust 2017b	RCT 3	32 S:16 NS:16	61.8 M:17 F: 15	Smokers: an average of>10 cigarettes/day for>10 years & non-smokers	96 Max:67 Mand: 29	Brånemark, Nobel Biocare Machined, oxidized, & laser-modified	NR	3	S: 2.5+/-0.11 NS: 2.1+/-0.06	NR	S: NR/48 NS: NR/48	NR	0
Al-Aali 2018	Retrospective 60	56 S: 29 NS: 27	35-51 45 NR	Smoker & never smoker	177 Max:100 Mand:77	NR Rough	4.1x10-14	NR	S: 4.65+/-0.68 NS: 1.8+/-0.33	NR	S:NR/86 NS:NR/91	NR	0

Table 1 cont'd: characteristics of included studies

Selection					Comparability of cohorts on the basis of the design or analysis	Outcome			
Authors (Years)	**Representativ-eness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Outcome of interest not present at start**		**Assessment of outcome**	**Was follow-up long enough for outcomes to occur?**	**Adequacy of follow-up of cohorts**	**Total 9/9**
Bain (1993)	0	*	*	*	*0	*	*	0	6/9
Haas (1996)	0	*	*	*	*0	*	*	0	6/9
Lindquist (1997)	*	*	*	*	*0	*	*	0	6/9
Kumar (2002)	0	*	*	*	*0	*	0	0	5/9
Schwartz-Arad (2002)	0	*	*	*	*0	*	*	0	6/9
Galindo-Moreno (2005)	*	*	*	*	*0	*	0	0	6/9
Nitzan (2005)	0	*	*	*	*0	*	*	0	6/9
DeLuca (2006)	0	*	*	*	*0	*	*	0	6/9
DeLuca & Zarb (2006)	0	*	*	*	*0	*	*	0	6/9
Herzberg (2006)	*	0	*	*	*0	*	*	0	6/9
Sanchez-Perez (2007)	*	*	*	*	**	*	*	0	8/9
Sverzut (2008)	0	*	*	*	*0	*	0	0	5/9
Anner (2010)	*	0	*	*	**	*	*	*	8/9
Cavalcanti (2011)	*	*	*	*	*0	*	*	*	8/9
Rodriguez-Argueta(2011)	0	0	*	*	*0	*	0	*	5/9
Vandeweghe (2011)	0	*	*	*	**	*	*	0	7/9
Vervaeke (2012)	0	*	*	*	**	*	*	0	7/9
Sayardoust (2013)	0	*	*	*	**	*	*	0	7/9
Cha (2014)	*	*	*	*	*0	*	0	*	7/9
Al-Aali (2018)	0	0	*	*	*0	*	0	0	4/9

Table 2: Newcastle-Ottawa Scale quality assessment for cohort studies

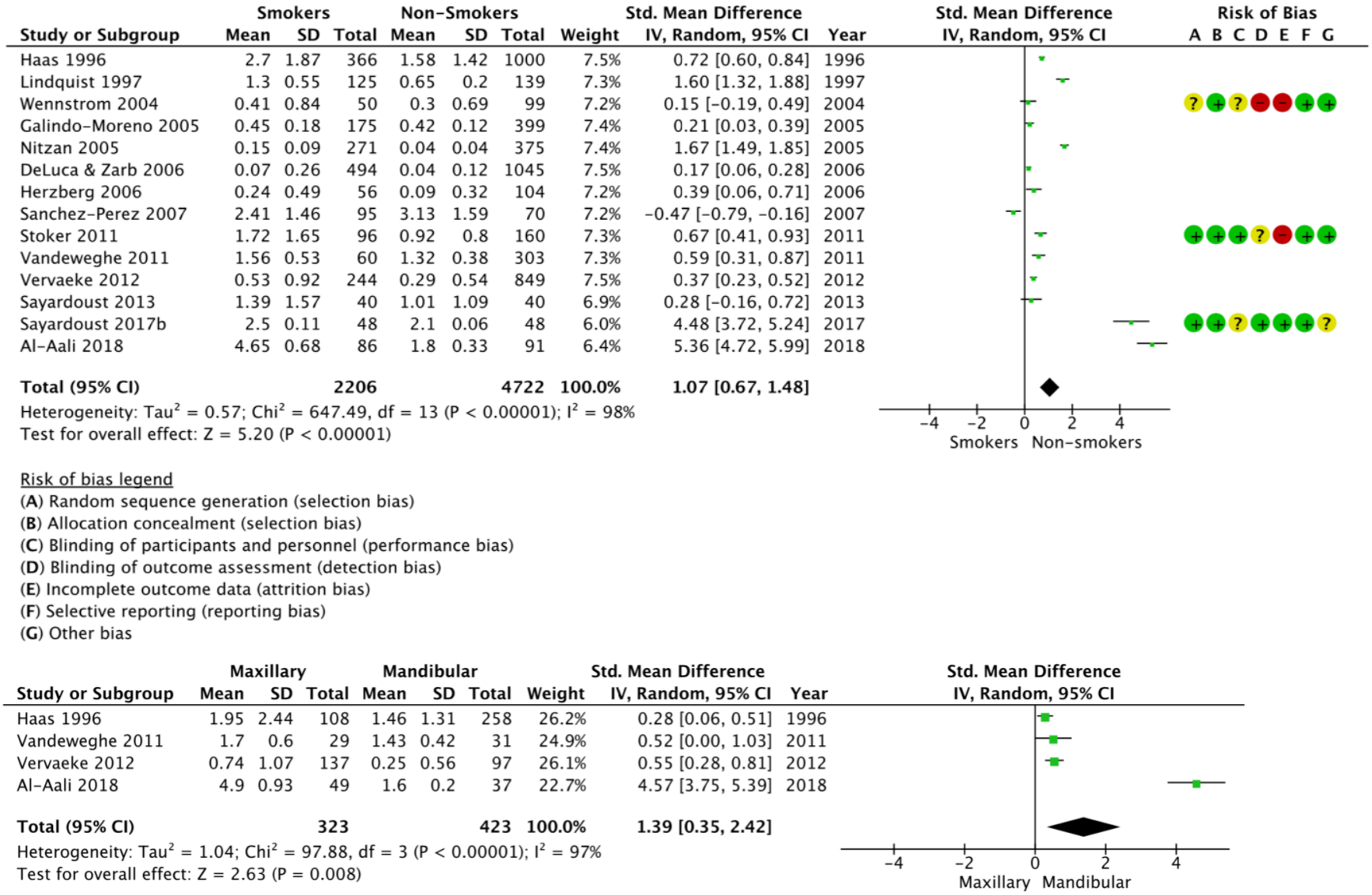

Figure 2: Forest plots for MBL in smokers vs non-smokers and for MBL in maxilla vs mandible in smokers. Also, the Cochrane RoB tool assessment scores for the 3 included RCTs.

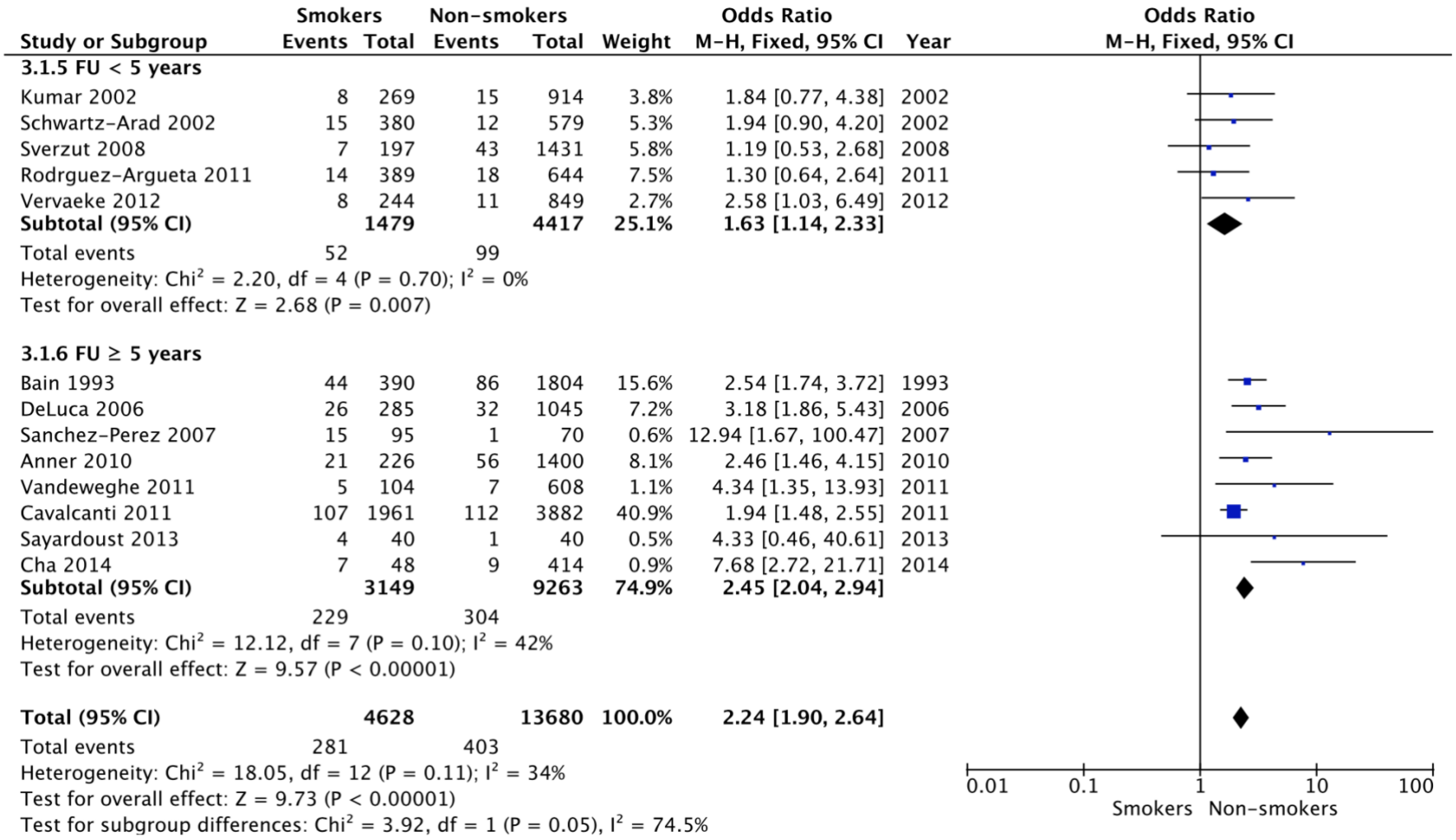

Figure 3: Forest plot for implant failure rate in smokers vs non-smokers with subgroup analysis for follow up time.

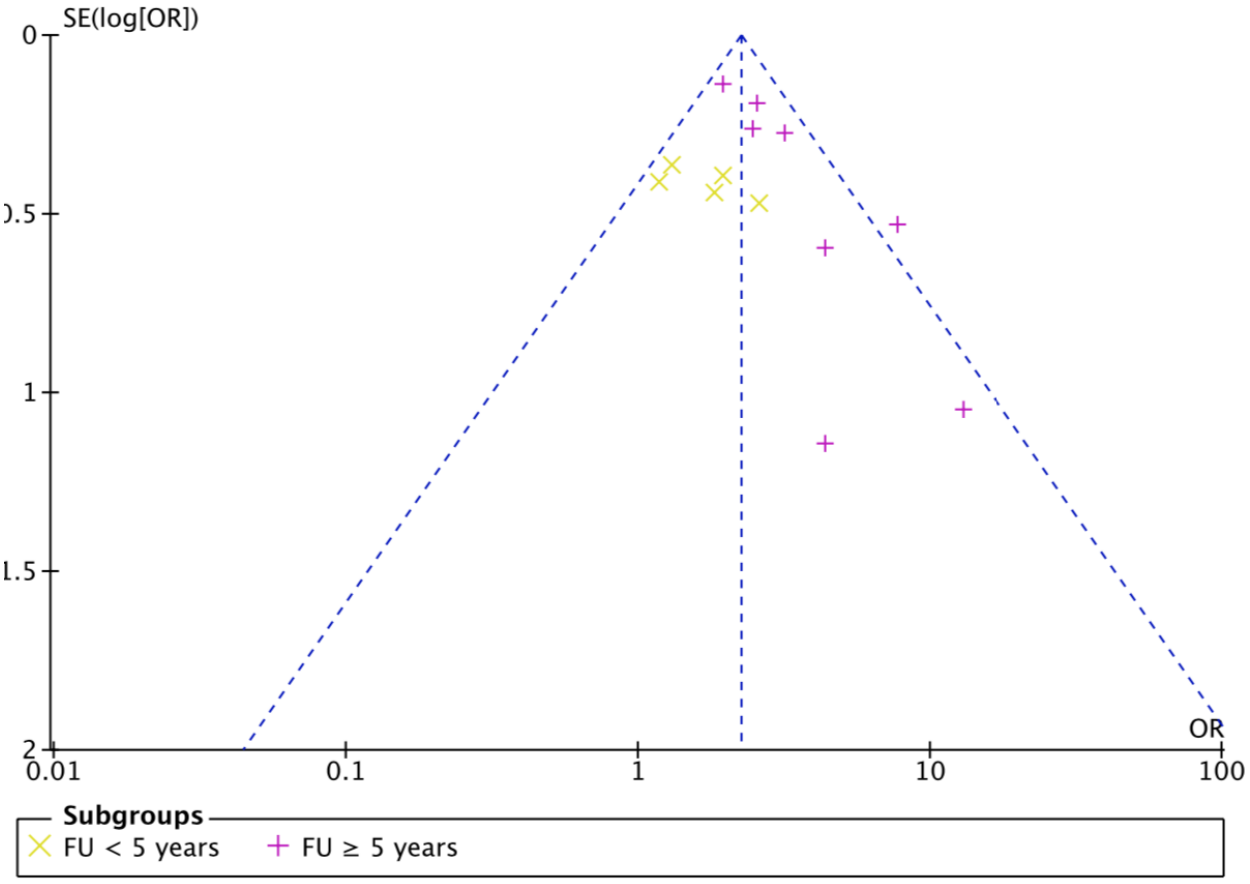

Fig 5: Funnel plot for the studies reporting the outcome measure: implant failure rate.

Characteristics of excluded studies		
Author (year): Title	**Type**	**Reason for exclusion**
Aglietta (2010): A 10-year retrospective analysis of marginal bone-level changes around implants in periodontally healthy and periodontally compromised tobacco smokers	Retrospective	Did not individually report MBL levels or the total number of failed/placed implants at the end of the follow up period and how many were placed in smokers and non-smokers.
Al Amri (2017): Comparison of Peri-Implant Soft Tissue Parameters and Crestal Bone Loss Around Immediately Loaded and Delayed Loaded Implants in Smokers and Non- Smokers: 5-Year Follow-Up Results	Retrospective	Standard deviation for the mean total CBL (crestal bone loss) for smokers and non-smokers is not reported. Though can be estimated through some calculations, its usually inaccurate and can increase heterogeneity in the results. The total number of failed/placed implants at the end of the follow up period and how many were placed in smokers and non-smokers are not reported. Attempted to contact the corresponding author by e-mail but received no reply.
Ata-Ali (2016): Impact of heavy smoking on the clinical, microbiological and immunological parameters of patients with dental implants: a prospective cross-sectional study	Prospective	Did not individually report MBL levels or the number of failed/placed implants in smokers versus non-smokers. Microbiological sampling of the peri-implant sulcus fluid is the main focus of the study.
Balshe (2008): The effects of smoking on the survival of smooth and rough surface dental implants	Retrospective	Did not individually report MBL levels or the number of failed/placed implants in smokers versus non-smokers. The study focused on smooth versus rough implant surface comparison.
Baqain (2012): Early dental implant failure: risk factors	Prospective	Of the 15/399 failed/placed implants, the study did not report how many were placed in smokers and non-smokers. Attempted to contact the corresponding author by e-mail but received no reply.
Sun (2016): Effect of Heavy Smoking on Dental Implants Placed in Male Patients Posterior Mandibles: A Prospective Clinical Study	Prospective	The distribution of the implants placed (n=45) among the heavy smokers and non-smokers is not reported. Also, the study evaluated only 1 implant per patient. The osteogenic jaw bone sampling is the main focus of the study.
Uribarri (2017): Bone Remodeling around Implants Placed in Augmented Sinuses in Patients with and without History of Periodontitis	Prospective	The total number of failed/placed implants at the end of the follow up period and how many were placed in smokers and non-smokers are not reported. The MEAN MBL+/- SD in smokers and non-smokers at the end of the follow up period is not reported. Attempted to contact the corresponding author by e-mail but received no reply.

Table 3: excluded studies and reason(s) for exclusion.

Search strategies	
PubMed	**Results**
(((((((jaw, edentulous[MeSH Terms]) OR jaw, edentulous, partially[MeSH Terms]) OR smoking[MeSH Terms]) OR cigarette smoking[MeSH Terms])) AND ((((((dental implant[MeSH Terms]) OR dental implants[MeSH Terms]) OR dental implantation[MeSH Terms]) OR dental implantation, endosseous[MeSH Terms]) OR endosseous dental implantation[MeSH Terms]) OR osseointegrated dental implantation[MeSH Terms])) AND ((smokers) OR nonsmokers)) AND ((((((((((bone resorption[MeSH Terms]) OR dental implant bone resorption) OR alveolar bone loss[MeSH Terms]) OR marginal bone loss) OR dental implant bone loss) OR periodontal pocket[MeSH Terms]) OR dental implant probing depth) OR peri-implant probing depth) OR peri-implant tissue health) OR survival rates[MeSH Terms]) OR cumulative survival rates[MeSH Terms]) OR dental implant survival)	150
Scopus	**Results**
Smoking OR cigarette smoking AND dental implants OR dental implantation OR endosseous dental implants OR osseointegrated dental implants AND marginal bone loss OR bone resorption OR dental implant bone resorption or dental implant bone loss or dental implant probing depth or peri-implant bone loss	40
EBSCOhost Dentistry & Oral Sciences	**Results**
Smoking AND dental implant complications OR marginal bone loss OR implant failure rate	189
379	**Total**

Table 4: the final Boolean search keywords utilized in different electronic databases. Last search update June 1st, 2019.

References

Included studies:

1. Al-Aali, K. A., Alrabiah, M., Al-Hamdan, R. S., Al-Hamoudi, N., Aldahian, N., & Abduljabbar, T. (2018). Impact of jaw location on clinical and radiological status of dental implants placed in cigarette-smokers and never-smokers: 5-year follow-up results. *Clinical Implant Dentistry and Related Research, 20*(6), 983-987. doi:10.1111/cid.12679

2. Anner, R., Grossmann, Y., Anner, Y., & Levin, L. (2010). Smoking, diabetes mellitus, periodontitis, and supportive periodontal treatment as factors associated with dental implant survival: A long-term retrospective evaluation of patients followed for up to 10 years. *Implant Dentistry, 19*(1), 57-64. doi: 10.1097/ID.0b013e3181bb8f6c

3. Bain, C. A., & Moy, P. K. (1993). The association between the failure of dental implants and cigarette smoking. *The International Journal of Oral & Maxillofacial Implants, 8*(6), 609-615.

4. Cavalcanti, R., Oreglia, F., Manfredonia, M. F., Gianserra, R., & Esposito, M. (2011). The influence of smoking on the survival of dental implants: A 5-year pragmatic multicentre retrospective cohort study of 1727 patients. *European Journal of Oral Implantology, 4*(1), 39-45. doi:21374

5. Cha, H. S., Kim, A., Nowzari, H., Chang, H. S., & Ahn, K. M. (2014). Simultaneous sinus lift and implant installation: Prospective study of consecutive two hundred seventeen sinus lift and four hundred sixty-two implants. *Clinical Implant Dentistry and Related Research, 16*(3), 337-347. doi:10.1111/cid.12012

6. DeLuca, S., Habsha, E., & Zarb, G. A. (2006). The effect of smoking on osseointegrated dental implants. part I: Implant survival. *The International Journal of Prosthodontics, 19*(5), 491-498.

7. DeLuca, S., & Zarb, G. (2006). The effect of smoking on osseointegrated dental implants. part II: Peri-implant bone loss. *The International Journal of Prosthodontics, 19*(6), 560-566.

8. Galindo-Moreno, P., Fauri, M., Avila-Ortiz, G., Fernandez-Barbero, J. E., Cabrera-Leon, A., & Sanchez-Fernandez, E. (2005). Influence of alcohol and tobacco habits on peri-implant marginal bone loss: A prospective study. *Clinical Oral Implants Research, 16*(5), 579-586. doi: CLR1148

9. Herzberg, R., Dolev, E., & Schwartz-Arad, D. (2006). Implant marginal bone loss in maxillary sinus grafts. *The International Journal of Oral & Maxillofacial Implants, 21*(1), 103-110.

10. Haas, R., Haimbock, W., Mailath, G., & Watzek, G. (1996). The relationship of smoking on peri-implant tissue: A retrospective study. *The Journal of Prosthetic Dentistry, 76*(6), 592-596. doi: S0022-3913(96)90435-7

11. Kumar, A., Jaffin, R. A., & Berman, C. (2002). The effect of smoking on achieving osseointegration of surface-modified implants: A clinical report. *The International Journal of Oral & Maxillofacial Implants, 17*(6), 816-819.

12. Lindquist, L. W., Carlsson, G. E., & Jemt, T. (1997). Association between marginal bone loss around osseointegrated mandibular implants and smoking habits: A 10-year follow-up study. *Journal of Dental Research, 76*(10), 1667-1674. doi:10.1177/00220345970760100801

13. Nitzan, D., Mamlider, A., Levin, L., & Schwartz-Arad, D. (2005). Impact of smoking on marginal bone loss. *The International Journal of Oral & Maxillofacial Implants, 20*(4), 605-609.

14. Rodriguez-Argueta, O. F., Figueiredo, R., Valmaseda-Castellon, E., & Gay-Escoda, C. (2011). Postoperative complications in smoking patients treated with implants: A retrospective study. *Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons, 69*(8), 2152-2157. doi: 10.1016/j.joms.2011.02.082

15. Sanchez-Perez, A., Moya-Villaescusa, M. J., & Caffesse, R. G. (2007). Tobacco as a risk factor for survival of dental implants. *Journal of Periodontology, 78*(2), 351-359. doi:10.1902/jop.2007.060299

16. Sayardoust, S., Grondahl, K., Johansson, E., Thomsen, P., & Slotte, C. (2013). Implant survival and marginal bone loss at turned and oxidized implants in periodontitis-susceptible smokers and never-smokers: A retrospective, clinical, radiographic case-control study. *Journal of Periodontology, 84*(12), 1775-1782. doi:10.1902/jop.2013.120608

17. Sayardoust, S., Omar, O., Norderyd, O., & Thomsen, P. (2017). Clinical, radiological, and gene expression analyses in smokers and non-smokers, part 2: RCT on the late healing phase of osseointegration. *Clinical Implant Dentistry and Related Research, 19*(5), 901-915. doi:10.1111/cid.12514

18. Schwartz-Arad, D., Samet, N., Samet, N., & Mamlider, A. (2002). Smoking and complications of endosseous dental implants. *Journal of Periodontology, 73*(2), 153-157. doi:10.1902/jop.2002.73.2.153

19. Stoker, G., van Waas, R., & Wismeijer, D. (2012). Long-term outcomes of three types of implant-supported mandibular overdentures in smokers. *Clinical Oral Implants Research, 23*(8), 925-929. doi:10.1111/j.1600-0501.2011.02237.x

20. Sverzut, A. T., Stabile, G. A., de Moraes, M., Mazzonetto, R., & Moreira, R. W. (2008). The influence of tobacco on early dental implant failure. *Journal of Oral and Maxillofacial*

Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons, 66(5), 1004-1009. doi: 10.1016/j.joms.2008.01.032

21. Vandeweghe, S., & De Bruyn, H. (2011). The effect of smoking on early bone remodeling on surface modified southern implants(R). *Clinical Implant Dentistry and Related Research, 13*(3), 206-214. doi:10.1111/j.1708-8208.2009.00198.x

22. Vervaeke, S., Collaert, B., Vandeweghe, S., Cosyn, J., Deschepper, E., & De Bruyn, H. (2012). The effect of smoking on survival and bone loss of implants with a fluoride-modified surface: A 2-year retrospective analysis of 1106 implants placed in daily practice. *Clinical Oral Implants Research, 23*(6), 758-766. doi:10.1111/j.1600-0501.2011.02201.x

23. Wennstrom, J. L., Ekestubbe, A., Grondahl, K., Karlsson, S., & Lindhe, J. (2004). Oral rehabilitation with implant-supported fixed partial dentures in periodontitis-susceptible subjects. A 5-year prospective study. *Journal of Clinical Periodontology, 31*(9), 713-724. doi:10.1111/j.1600-051X.2004.00568.x

Excluded studies:

24. Aglietta, M., Siciliano, V. I., Rasperini, G., Cafiero, C., Lang, N. P., & Salvi, G. E. (2011). A 10-year retrospective analysis of marginal bone-level changes around implants in periodontally healthy and periodontally compromised tobacco smokers. *Clinical Oral Implants Research, 22*(1), 47-53. Doi: 10.1111/j.1600-0501.2010. 01977.x

25. Al Amri, M. D., Kellesarian, S. V., Abduljabbar, T. S., Al Rifaiy, M. Q., Al Baker, A. M., & Al-Kheraif, A. A. (2017). Comparison of peri-implant soft tissue parameters and crestal bone loss around immediately loaded and delayed loaded implants in smokers and non-smokers: 5-year follow-up results. *Journal of Periodontology, 88*(1), 3-9. doi:10.1902/jop.2016.160427

26. Ata-Ali, J., Flichy-Fernandez, A. J., Alegre-Domingo, T., Ata-Ali, F., & Penarrocha-Diago, M. (2016). Impact of heavy smoking on the clinical, microbiological and immunological parameters of patients with dental implants: A prospective cross-sectional study. *Journal of Investigative and Clinical Dentistry, 7*(4), 401-409. doi:10.1111/jicd.12176

27. Balshe, A. A., Eckert, S. E., Koka, S., Assad, D. A., & Weaver, A. L. (2008). The effects of smoking on the survival of smooth- and rough-surface dental implants. *The International Journal of Oral & Maxillofacial Implants, 23*(6), 1117-1122.

28. Baqain, Z. H., Moqbel, W. Y., & Sawair, F. A. (2012). Early dental implant failure: Risk factors. *The British Journal of Oral & Maxillofacial Surgery, 50*(3), 239-243. doi: 10.1016/j.bjoms.2011.04.074

29. Sun, C., Zhao, J., Jianghao, C., & Hong, T. (2016). Effect of heavy smoking on dental implants placed in male patients' posterior mandibles: A prospective clinical study. *The Journal of Oral Implantology, 42*(6), 477-483. doi:10.1563/aaid-joi-D-16-00078

30. Uribarri, A., Bilbao, E., Marichalar-Mendia, X., Martinez-Conde, R., Aguirre, J. M., & Verdugo, F. (2017). Bone remodeling around implants placed in augmented sinuses in patients with and without history of periodontitis. *Clinical Implant Dentistry and Related Research, 19*(2), 268-279. doi:10.1111/cid.12450

Additional references:

31. Alfadda, S. A., Attard, N. J., & David, L. A. (2009). Five-year clinical results of immediately loaded dental implants using mandibular overdentures. *The International Journal of Prosthodontics, 22*(4), 368-373.

32. Alfadda, S. A. (2014). A randomized controlled clinical trial of edentulous patients treated with immediately loaded implant-supported mandibular fixed prostheses. *Clinical Implant Dentistry and Related Research, 16*(6), 806-816. doi:10.1111/cid.12057

33. Alfadda, S. A. (2018). Current evidence on dental implants outcomes in smokers and nonsmokers: A systematic review and meta-analysis. *The Journal of Oral Implantology, 44*(5), 390-399. doi:10.1563/aaid-joi-D-17-00313

34. Moraschini, V., Poubel, L. A., Ferreira, V. F., & Barboza Edos, S. (2015). Evaluation of survival and success rates of dental implants reported in longitudinal studies with a follow-up period of at least 10 years: A systematic review. *International Journal of Oral and Maxillofacial Surgery, 44*(3), 377-388. doi: 10.1016/j.ijom.2014.10.023

35. Moraschini, V., & Barboza, E. (2016). Success of dental implants in smokers and non-smokers: A systematic review and meta-analysis. *International Journal of Oral and Maxillofacial Surgery, 45*(2), 205-215. doi: 10.1016/j.ijom.2015.08.996

36. Levin, L., Hertzberg, R., Har-Nes, S., & Schwartz-Arad, D. (2008). Long-term marginal bone loss around single dental implants affected by current and past smoking habits. *Implant Dentistry, 17*(4), 422-429. doi:10.1097/ID.0b013e31818c4a24

37. de Oliveira-Neto, O. B., Barbosa, F. T., de Sousa-Rodrigues, C. F., & de Lima, F. J. C. (2018). Risk of bias assessment of systematic reviews regarding dental implant placement in smokers: An umbrella systematic review. *The Journal of Prosthetic Dentistry, 120*(2), 198-203. doi: S0022-3913(18)30076-3

38. Penarrocha, M., Palomar, M., Sanchis, J. M., Guarinos, J., & Balaguer, J. (2004). Radiologic study of marginal bone loss around 108 dental implants and its relationship to

smoking, implant location, and morphology. *The International Journal of Oral & Maxillofacial Implants, 19*(6), 861-867.

39. Queiroz, D. A., Cortelli, J. R., Holzhausen, M., Rodrigues, E., Aquino, D. R., & Saad, W. A. (2009). Smoking increases salivary arginase activity in patients with dental implants. *Clinical Oral Investigations, 13*(3), 263-267. doi:10.1007/s00784-008-0238-0

40. Feloutzis, A., Lang, N. P., Tonetti, M. S., Burgin, W., Bragger, U., Buser, D., . . . Kornman, K. S. (2003). IL-1 gene polymorphism and smoking as risk factors for peri-implant bone loss in a well-maintained population. *Clinical Oral Implants Research, 14*(1), 10-17. doi: clr140102

41. Heitz-Mayfield, L. J., & Huynh-Ba, G. (2009). History of treated periodontitis and smoking as risks for implant therapy. *The International Journal of Oral & Maxillofacial Implants, 24 Suppl*, 39-68.

42. Hinode, D., Tanabe, S., Yokoyama, M., Fujisawa, K., Yamauchi, E., & Miyamoto, Y. (2006). Influence of smoking on osseointegrated implant failure: A meta-analysis. *Clinical Oral Implants Research, 17*(4), 473-478. doi: CLR1244

43. Oates, T. W., Caraway, D., & Jones, J. (2004). Relation between smoking and biomarkers of bone resorption associated with dental endosseous implants. *Implant Dentistry, 13*(4), 352-357. doi:00008505-200413040-00013

44. Jamal, A., Phillips, E., Gentzke, A. S., Homa, D. M., Babb, S. D., King, B. A., & Neff, L. J. (2018). Current cigarette smoking among adults - united states, 2016. *MMWR.Morbidity and Mortality Weekly Report, 67*(2), 53-59. Doi:10.15585/mmwr.mm6702a1

45. Kasat, V., & Ladda, R. (2012). Smoking and dental implants. *Journal of International Society of Preventive & Community Dentistry, 2*(2), 38-41. doi:10.4103/2231-0762.109358

46. Manzano, G., Montero, J., Martin-Vallejo, J., Del Fabbro, M., Bravo, M., & Testori, T. (2016). Risk factors in early implant failure: A meta-analysis. *Implant Dentistry, 25*(2), 272-280. doi:10.1097/ID.0000000000000386

47. McDermott, N. E., Chuang, S. K., Woo, V. V., & Dodson, T. B. (2003). Complications of dental implants: Identification, frequency, and associated risk factors. *The International Journal of Oral & Maxillofacial Implants, 18*(6), 848-855.

48. Misch, C. E., Perel, M. L., Wang, H. L., Sammartino, G., Galindo-Moreno, P., Trisi, P., . . . Valavanis, D. K. (2008). Implant success, survival, and failure: The international congress of oral implantologists (ICOI) pisa consensus conference. *Implant Dentistry, 17*(1), 5-15. doi:10.1097/ID.0b013e3181676059

49. Levin, L., & Schwartz-Arad, D. (2005). The effect of cigarette smoking on dental implants and related surgery. *Implant Dentistry, 14*(4), 357-361. doi:00008505-200512000-00011

50. Lekholm U, Zarb GA. In: Patient selection and preparation. Tissue integrated prostheses: osseointegration in clinical dentistry. Branemark PI, Zarb GA, Albrektsson T, editor. Chicago: Quintessence Publishing Company; 1985. p. 199–209.

51. Fielding, J. A. (1985) Smoking: health effects and control. New England Journal of Medicine 313, 491–498.

52. La Veccia, C., Boyle, P. & Franceschi, S. (1991) Smoking and cancer with emphasis on Europe. European Journal of Cancer 27, 94–104.

53. Peto, R., Lopez, A. D., Boreham, J., Thun, M., Health, C. & Doll, R. (1996) Mortality from smoking worldwide. British Medical Bulletin 52, 12–21.

54. Sham, A. S., Cheung, L. K., Jin, L. J. & Corbet, E. F. (2003) The effects of tobacco use on oral health. Hong Kong Medical Journal 9, 271–277.

55. Sloan A, Hussain I, Maqsood M, Eremin O, El-Sheemy M. The effects of smoking on fracture healing. Surgeon. 2010; 8:111–116.

56. Chrcanovic BR, Pedrosa AR, Martins MD. Chemical topographic analysis of treated surfaces of five different commercial dental titanium implants. Materials Research 2012; 15:372–82.

57. Chrcanovic BR, Lea˜o NLC, Martins MD. Influence of different acid etchings on the superficial characteristics of Ti sandblasted with Al2O3. Materials Research 2013; 16:1006–14.

58. Chrcanovic BR, Martins MD. Study of the influence of acid etching treatments on the superficial characteristics of Ti. Materials Research 2014; 17:373–80.

59. Chrcanovic, B. R., Albrektsson, T., & Wennerberg, A. (2014). Reasons for failures of oral implants. *Journal of Oral Rehabilitation, 41*(6), 443-476. doi:10.1111/joor.12157

60. Chrcanovic, B. R., Albrektsson, T., & Wennerberg, A. (2015). Smoking and dental implants: A systematic review and meta-analysis. *Journal of Dentistry, 43*(5), 487-498. doi: 10.1016/j.jdent.2015.03.003

61. Misch, C. (1993) Implant success or failure: clinical assessment in implant dentistry. In: Misch, C. (ed). Contemporary Implant Dentistry, pp. 29–42. St. Louis: Mosby.

62. Albrektsson T, Isidor F. Consensus report of Session IV. In: Lang NP, Karring T, editors. Proceedings of the 1st European Workshop on Periodontology. London: Quintessence; 1993. p. 365–9.

63. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. Available from: www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

64. Abt, E. (2009). Smoking increases dental implant failures and complications. *Evidence-Based Dentistry, 10*(3), 79-80. doi: 10.1038/sj.ebd.6400670

65. Adell, R., Lekholm, U., Rockler, B., & Branemark, P. I. (1981). A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *International Journal of Oral Surgery, 10*(6), 387-416.

66. Adell, R. (1983). Clinical results of osseointegrated implants supporting fixed prostheses in edentulous jaws. *The Journal of Prosthetic Dentistry, 50*(2), 251-254. doi:0022-3913(83)90026-4

67. Albandar, J. M., Streckfus, C. F., Adesanya, M. R., & Winn, D. M. (2000). Cigar, pipe, and cigarette smoking as risk factors for periodontal disease and tooth loss. *Journal of Periodontology, 71*(12), 1874-1881. doi:10.1902/jop.2000.71.12.1874

68. Albrektsson, T., Zarb, G., Worthington, P., & Eriksson, A. R. (1986). The long-term efficacy of currently used dental implants: A review and proposed criteria of success. *The International Journal of Oral & Maxillofacial Implants, 1*(1), 11-25.

69. Ata-Ali, J., Ata-Ali, F., Penarrocha-Oltra, D., & Galindo-Moreno, P. (2016). What is the impact of bisphosphonate therapy upon dental implant survival? A systematic review and meta-analysis. *Clinical Oral Implants Research, 27*(2), 38. doi:10.1111/clr.12526

70. Bain, C. A. (1996). Smoking and implant failure--benefits of a smoking cessation protocol. *The International Journal of Oral & Maxillofacial Implants, 11*(6), 756-759.

71. Balatsouka, D., Gotfredsen, K., Sorensen, L., Lindh, C. H., & Berglundh, T. (2006). Effect of systemic administration of nicotine on healing in osseous defects. an experimental study in rabbits. part II. *Clinical Oral Implants Research, 17*(5), 488-494. doi: CLR1248

72. Barnoya, J., & Glantz, S. A. (2005). Cardiovascular effects of secondhand smoke: Nearly as large as smoking. *Circulation, 111*(20), 2684-2698. doi:111/20/2684

73. Berglundh, T., Persson, L., & Klinge, B. (2002). A systematic review of the incidence of biological and technical complications in implant dentistry reported in prospective longitudinal studies of at least 5 years. *Journal of Clinical Periodontology, 29 Suppl 3*, 19-3. doi:019

74. Buser, D., Mericske-Stern, R., Bernard, J. P., Behneke, A., Behneke, N., Hirt, H. P., . . . Lang, N. P. (1997). Long-term evaluation of non-submerged ITI implants. part 1: 8-year life table analysis of a prospective multi-center study with 2359 implants. *Clinical Oral Implants Research, 8*(3), 161-172.

75. Butterworth, C. J., Baxter, A. M., Shaw, M. J., & Bradnock, G. (2001). The provision of dental implants in the national health service hospital dental services--a national questionnaire. *British Dental Journal, 190*(2), 93-96. doi: 10.1038/sj.bdj.4800892

76. Carlsson, G. E., Lindquist, L. W., & Jemt, T. (2000). Long-term marginal periimplant bone loss in edentulous patients. *The International Journal of Prosthodontics, 13*(4), 295-302.

77. Cesar-Neto, J. B., Benatti, B. B., Sallum, E. A., Sallum, A. W., & Nociti, F. H.,Jr. (2005). Bone filling around titanium implants may benefit from smoking cessation: A histologic study in rats. *Journal of Periodontology, 76*(9), 1476-1481. doi:10.1902/jop.2005.76.9.1476

78. Chen, H., Liu, N., Xu, X., Qu, X., & Lu, E. (2013). Smoking, radiotherapy, diabetes and osteoporosis as risk factors for dental implant failure: A meta-analysis. *PloS One, 8*(8), e71955. doi: 10.1371/journal.pone.0071955

79. Chuang, S. K., Tian, L., Wei, L. J., & Dodson, T. B. (2001). Kaplan-meier analysis of dental implant survival: A strategy for estimating survival with clustered observations. *Journal of Dental Research, 80*(11), 2016-2020. doi:10.1177/00220345010800111301

80. Ciftci, O., Gunday, M., Caliskan, M., Gullu, H., Guven, A., & Muderrisoglu, H. (2013). Light cigarette smoking and vascular function. *Acta Cardiologica, 68*(3), 255-261. doi:10.2143/AC.68.3.2983419

81. Cobb, T. K., Gabrielsen, T. A., Campbell, D. C.,2nd, Wallrichs, S. L., & Ilstrup, D. M. (1994). Cigarette smoking and nonunion after ankle arthrodesis. *Foot & Ankle International, 15*(2), 64-67. doi:10.1177/107110079401500202

82. Cochran, D. L., Buser, D., ten Bruggenkate, C. M., Weingart, D., Taylor, T. M., Bernard, J. P., . . . Simpson, J. P. (2002). The use of reduced healing times on ITI implants with a sandblasted and acid-etched (SLA) surface: Early results from clinical trials on ITI SLA implants. *Clinical Oral Implants Research, 13*(2), 144-153. doi:130204

83. Cooper, L. F., Reside, G., Stanford, C., Barwacz, C., Feine, J., Abi Nader, S., . . . McGuire, M. (2015). A multicenter randomized comparative trial of implants with different abutment interfaces to replace anterior maxillary single teeth. *The International Journal of Oral & Maxillofacial Implants, 30*(3), 622-632. doi:10.11607/jomi.3772

84. Cuff, M. J., McQuade, M. J., Scheidt, M. J., Sutherland, D. E., & Van Dyke, T. E. (1989). The presence of nicotine on root surfaces of periodontally diseased teeth in smokers. *Journal of Periodontology, 60*(10), 564-569. doi:10.1902/jop.1989.60.10.564

85. Davarpanah, M., Martinez, H., Etienne, D., Zabalegui, I., Mattout, P., Chiche, F., & Michel, J. F. (2002). A prospective multicenter evaluation of 1,583 3i implants: 1- to 5-year data. *The International Journal of Oral & Maxillofacial Implants, 17*(6), 820-828.

86. Deng, Z. L., Sharff, K. A., Tang, N., Song, W. X., Luo, J., Luo, X., . . . He, T. C. (2008). Regulation of osteogenic differentiation during skeletal development. *Frontiers in Bioscience: A Journal and Virtual Library, 13*, 2001-2021. doi:2819

87. Esposito, M., Hirsch, J. M., Lekholm, U., & Thomsen, P. (1998). Biological factors contributing to failures of osseointegrated oral implants. (I). success criteria and epidemiology. *European Journal of Oral Sciences, 106*(1), 527-551.

88. Esposito, M., Hirsch, J. M., Lekholm, U., & Thomsen, P. (1998). Biological factors contributing to failures of osseointegrated oral implants. (II). etiopathogenesis. *European Journal of Oral Sciences, 106*(3), 721-764.

89. Esposito, M., Grusovin, M. G., Coulthard, P., Thomsen, P., & Worthington, H. V. (2005). A 5-year follow-up comparative analysis of the efficacy of various osseointegrated dental implant systems: A systematic review of randomized controlled clinical trials. *The International Journal of Oral & Maxillofacial Implants, 20*(4), 557-568.

90. Esposito, M., Grusovin, M. G., Polyzos, I. P., Felice, P., & Worthington, H. V. (2010). Timing of implant placement after tooth extraction: Immediate, immediate-delayed or delayed

implants? A cochrane systematic review. *European Journal of Oral Implantology, 3*(3), 189-205. doi:19558

91. Esposito, M., Siormpas, K., Mitsias, M., Bechara, S., Trullenque-Eriksson, A., & Pistilli, R. (2016). Immediate, early (6 weeks) and delayed loading (3 months) of single implants: 4-month post-loading from a multicenter pragmatic randomised controlled trial. *European Journal of Oral Implantology, 9*(3), 249-260. doi:36932

92. File, E., & Deal, C. (2009). Clinical update on teriparatide. *Current Rheumatology Reports, 11*(3), 169-176.

93. Fleming, J. T., Barati, M. T., Beck, D. J., Dodds, J. C., Malkani, A. L., Parameswaran, D., . . . Feitelson, J. B. (2001). Bone blood flow and vascular reactivity. *Cells, Tissues, Organs, 169*(3), 279-284. doi:47892

94. Gjelvold, B., Kisch, J., Chrcanovic, B. R., Albrektsson, T., & Wennerberg, A. (2017). Clinical and radiographic outcome following immediate loading and delayed loading of single-tooth implants: Randomized clinical trial. *Clinical Implant Dentistry and Related Research, 19*(3), 549-558. doi:10.1111/cid.12479

95. The glossary of prosthodontic terms: Ninth edition. (2017). *The Journal of Prosthetic Dentistry, 117*(5S), e1-e105. doi: S0022-3913(16)30683-7

96. Gorman, L. M., Lambert, P. M., Morris, H. F., Ochi, S., & Winkler, S. (1994). The effect of smoking on implant survival at second-stage surgery: DICRG interim report no. 5. dental implant CLinical research group. *Implant Dentistry, 3*(3), 165-168.

97. Graafmans, W. C., Ooms, M. E., Bezemer, P. D., Bouter, L. M., & Lips, P. (1996). Different risk profiles for hip fractures and distal forearm fractures: A prospective study. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 6*(6), 427-431.

98. Gullihorn, L., Karpman, R., & Lippiello, L. (2005). Differential effects of nicotine and smoke condensate on bone cell metabolic activity.*Journal of Orthopaedic Trauma, 19*(1), 17-22. doi:00005131-200501000-00004

99. Heinikainen, M., Vehkalahti, M., & Murtomaa, H. (2002). Influence of patient characteristics on finnish dentists' decision-making in implant therapy. *Implant Dentistry, 11*(3), 301-307. doi:00008505-200207000-00017

100. Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., Cochrane Statistical Methods Group. (2011). The cochrane collaboration's tool for assessing risk of bias in randomized trials. *BMJ (Clinical Research Ed.), 343*, d5928. doi:10.1136/bmj.d5928

101. Hoffmann, D., & Adams, J. D. (1981). Carcinogenic tobacco-specific N-nitrosamines in snuff and in the saliva of snuff dippers. *Cancer Research, 41*(11 Pt 1), 4305-4308.

102. Hukkanen, J., Jacob, P.,3rd, & Benowitz, N. L. (2005). Metabolism and disposition kinetics of nicotine. *Pharmacological Reviews, 57*(1), 79-115. doi:57/1/79

103. James, J. A., Sayers, N. M., Drucker, D. B., & Hull, P. S. (1999). Effects of tobacco products on the attachment and growth of periodontal ligament fibroblasts. *Journal of Periodontology, 70*(5), 518-525. doi:10.1902/jop.1999.70.5.518

104. Johnson, G. K., & Guthmiller, J. M. (2007). The impact of cigarette smoking on periodontal disease and treatment. *Periodontology 2000, 44*, 178-194. doi: PRD212

105. Jones, J. K., & Triplett, R. G. (1992). The relationship of cigarette smoking to impaired intraoral wound healing: A review of evidence and implications for patient care. *Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons, 50*(3), 23-40. doi:0278-2391(92)90318-T

106. Jorgensen, L. N., Kallehave, F., Christensen, E., Siana, J. E., & Gottrup, F. (1998). Less collagen production in smokers. *Surgery, 123*(4), 450-455. doi:S0039-6060(98)70167-9

107. Jung, R. E., Pjetursson, B. E., Glauser, R., Zembic, A., Zwahlen, M., & Lang, N. P. (2008). A systematic review of the 5-year survival and complication rates of implant-supported single crowns. *Clinical Oral Implants Research, 19*(2), 119-130. doi: CLR1453

108. Kan, J. Y., Rungcharassaeng, K., Lozada, J. L., & Goodacre, C. J. (1999). Effects of smoking on implant success in grafted maxillary sinuses. *The Journal of Prosthetic Dentistry, 82*(3), 307-311. doi: S0022391399002085

109. Karoussis, I. K., Salvi, G. E., Heitz-Mayfield, L. J., Bragger, U., Hammerle, C. H., & Lang, N. P. (2003). Long-term implant prognosis in patients with and without a history of chronic periodontitis: A 10-year prospective cohort study of the ITI dental implant system.*Clinical Oral Implants Research, 14*(3), 329-339. doi:934

110. Kenney, E. B., Kraal, J. H., Saxe, S. R., & Jones, J. (1977). The effect of cigarette smoke on human oral polymorphonuclear leukocytes.*Journal of Periodontal Research, 12*(4), 227-234. doi:10.1111/j.1600-0765.1977.tb00126.x

111. Khosla, S., & Riggs, B. L. (2005). Pathophysiology of age-related bone loss and osteoporosis. *Endocrinology and Metabolism Clinics of North America, 34*(4), 101-30, xi. doi: S0889-8529(05)00090-3

112. Kinane, D. F., & Chestnutt, I. G. (2000). Smoking and periodontal disease. *Critical Reviews in Oral Biology and Medicine: An Official Publication of the American Association of Oral Biologists, 11*(3), 356-365.

113. Klokkevold, P. R., & Han, T. J. (2007). How do smoking, diabetes, and periodontitis affect outcomes of implant treatment? *The International Journal of Oral & Maxillofacial Implants, 22 Suppl*, 173-202.

114. Lang, N. P., Berglundh, T., & Working Group 4 of Seventh European Workshop on Periodontology. (2011). Periimplant diseases: Where are we now? consensus of the seventh european workshop on periodontology. *Journal of Clinical Periodontology, 38 Suppl 11*, 178-181. doi:10.1111/j.1600-051X.2010. 01674.x

115. Lehr, H. A. (2000). Microcirculatory dysfunction induced by cigarette smoking. *Microcirculation (New York, N.Y.: 1994), 7*(6 Pt 1), 367-384.

116. Lemons, J. E., Laskin, D. M., Roberts, W. E., Tarnow, D. P., Shipman, C.,Jr, Paczkowski, C., . . . English, C. (1997). Changes in patient screening for a clinical study of dental implants after increased awareness of tobacco use as a risk factor. *Journal of Oral and Maxillofacial Surgery: Official Journal of the American Association of Oral and Maxillofacial Surgeons, 55*(12 Suppl 5), 72-75. doi: S0278239197000554

117. Leow, Y. H., & Maibach, H. I. (1998). Cigarette smoking, cutaneous vasculature and tissue oxygen: An overview. *Skin Research and Technology: Official Journal of International*

Society for Bioengineering and the Skin (ISBS) [and] International Society for Digital Imaging of Skin (ISDIS) [and] International Society for Skin Imaging (ISSI), 4(1), 1-8. doi:10.1111/j.1600-0846.1998.tb00077.x

118. Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., . . . Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration.*PLoS Medicine, 6*(7), e1000100. doi: 10.1371/journal.pmed.1000100

119. Lima, L. L., Cesar Neto, J. B., Cayana, E. G., Nociti, F. H.,Jr, Sallum, E. A., & Casati, M. Z. (2013). Parathyroid hormone (1-34) compensates the negative effect of smoking around implants. *Clinical Oral Implants Research, 24*(9), 1055-1059. doi:10.1111/j.1600-0501.2012.02502.x

120. Lin, T. H., Chen, L., Cha, J., Jeffcoat, M., Kao, D. W., Nevins, M., & Fiorellini, J. P. (2012). The effect of cigarette smoking and native bone height on dental implants placed immediately in sinuses grafted by hydraulic condensation. *The International Journal of Periodontics & Restorative Dentistry, 32*(3), 255-261.

121. Lindquist, L. W., Carlsson, G. E., & Jemt, T. (1996). A prospective 15-year follow-up study of mandibular fixed prostheses supported by osseointegrated implants. clinical results and marginal bone loss. *Clinical Oral Implants Research, 7*(4), 329-336.

122. Ma, L., Zheng, L. W., Sham, M. H., & Cheung, L. K. (2010). Uncoupled angiogenesis and osteogenesis in nicotine-compromised bone healing. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 25*(6), 1305-1313. doi:10.1002/jbmr.19

123. Ma, L., Zwahlen, R. A., Zheng, L. W., & Sham, M. H. (2011). Influence of nicotine on the biological activity of rabbit osteoblasts. *Clinical Oral Implants Research, 22*(3), 338-342. doi:10.1111/j.1600-0501.2010.02088.x

124. MacFarlane, G. D., Herzberg, M. C., Wolff, L. F., & Hardie, N. A. (1992). Refractory periodontitis associated with abnormal polymorphonuclear leukocyte phagocytosis and cigarette smoking. *Journal of Periodontology, 63*(11), 908-913. doi:10.1902/jop.1992.63.11.908

125. Macgregor, I. D. (1996). Efficacy of dental health advice as an aid to reducing cigarette smoking. *British Dental Journal, 180*(8), 292-296. doi:10.1038/sj.bdj.4809067

126. Meechan, J. G., Macgregor, I. D., Rogers, S. N., Hobson, R. S., Bate, J. P., & Dennison, M. (1988). The effect of smoking on immediate post-extraction socket filling with blood and on the incidence of painful socket. *The British Journal of Oral & Maxillofacial Surgery, 26*(5), 402-409.

127. Miller, P. D.,Jr. (1988). Regenerative and reconstructive periodontal plastic surgery. mucogingival surgery. *Dental Clinics of North America, 32*(2), 287-306.

128. Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gotzsche, P. C., Devereaux, P. J., . . . CONSORT. (2012). CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery (London, England), 10*(1), 28-55. doi: 10.1016/j.ijsu.2011.10.001

129. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. (2014). No title. doi: NBK179276

130. Needleman, I., Chin, S., O'Brien, T., Petrie, A., & Donos, N. (2012). Systematic review of outcome measurements and reference group(s) to evaluate and compare implant success and failure. *Journal of Clinical Periodontology, 39 Suppl 12*, 122-132. doi:10.1111/j.1600-051X.2011.01836.x

131. Nolan, J., Jenkins, R. A., Kurihara, K., & Schultz, R. C. (1985). The acute effects of cigarette smoke exposure on experimental skin flaps. *Plastic and Reconstructive Surgery, 75*(4), 544-551. doi:10.1097/00006534-198504000-00018

132. Palmer, R. M., Wilson, R. F., Hasan, A. S., & Scott, D. A. (2005). Mechanisms of action of environmental factors--tobacco smoking.*Journal of Clinical Periodontology, 32 Suppl 6*, 180-195. doi: CPE786

133. Pandis, N. (2011). The evidence pyramid and introduction to randomized controlled trials. *American Journal of Orthodontics and Dentofacial Orthopedics: Official Publication of the American Association of Orthodontists, its Constituent Societies, and the American Board of Orthodontics, 140*(3), 446-447. doi: 10.1016/j.ajodo.2011.04.016

134. Papaspyridakos, P., Chen, C. J., Singh, M., Weber, H. P., & Gallucci, G. O. (2012). Success criteria in implant dentistry: A systematic review. *Journal of Dental Research, 91*(3), 242-248. doi:10.1177/0022034511431252

135. Pereira, M. L., Carvalho, J. C., Peres, F., & Fernandes, M. H. (2010). Simultaneous effects of nicotine, acrolein, and acetaldehyde on osteogenic-induced bone marrow cells cultured on plasma-sprayed titanium implants. *The International Journal of Oral & Maxillofacial Implants, 25*(1), 112-122.

136. Pikner, S. S., Grondahl, K., Jemt, T., & Friberg, B. (2009). Marginal bone loss at implants: A retrospective, long-term follow-up of turned branemark system implants. *Clinical Implant Dentistry and Related Research, 11*(1), 11-23. doi:10.1111/j.1708-8208.2008.00092.x

137. Pjetursson, B. E., Tan, K., Lang, N. P., Bragger, U., Egger, M., & Zwahlen, M. (2004). A systematic review of the survival and complication rates of fixed partial dentures (FPDs) after an observation period of at least 5 years. *Clinical Oral Implants Research, 15*(6), 667-676. doi: CLR1120

138. Raes, S., Rocci, A., Raes, F., Cooper, L., De Bruyn, H., & Cosyn, J. (2015). A prospective cohort study on the impact of smoking on soft tissue alterations around single implants. *Clinical Oral Implants Research, 26*(9), 1086-1090. doi:10.1111/clr.12405

139. Ramseier, C. A. (2005). Potential impact of subject-based risk factor control on periodontitis. *Journal of Clinical Periodontology, 32 Suppl 6*, 283-290. doi: CPE798

140. Rees, T. D., Liverett, D. M., & Guy, C. L. (1984). The effect of cigarette smoking on skin-flap survival in the face lift patient. *Plastic and Reconstructive Surgery, 73*(6), 911-915. doi:10.1097/00006534-198406000-00009

141. Riggs, B. L., Khosla, S., & Melton, L. J.,3rd. (2002). Sex steroids and the construction and conservation of the adult skeleton. *Endocrine Reviews, 23*(3), 279-302. doi:10.1210/edrv.23.3.0465

142. Rocci, A., Martignoni, M., & Gottlow, J. (2003). Immediate loading of branemark system TiUnite and machined-surface implants in the posterior mandible: A randomized open-ended clinical trial. *Clinical Implant Dentistry and Related Research, 5 Suppl 1*, 57-63.

143. Roos, J., Sennerby, L., Lekholm, U., Jemt, T., Grondahl, K., & Albrektsson, T. (1997). A qualitative and quantitative method for evaluating implant success: A 5-year retrospective analysis of the branemark implant. *The International Journal of Oral & Maxillofacial Implants, 12*(4), 504-514.

144. Roos-Jansaker, A. M., Lindahl, C., Renvert, H., & Renvert, S. (2006). Nine- to fourteen-year follow-up of implant treatment. part II: Presence of peri-implant lesions. *Journal of Clinical Periodontology, 33*(4), 290-295. doi: CPE906

145. Rothem, D. E., Rothem, L., Soudry, M., Dahan, A., & Eliakim, R. (2009). Nicotine modulates bone metabolism-associated gene expression in osteoblast cells. *Journal of Bone and Mineral Metabolism, 27*(5), 555-561. doi:10.1007/s00774-009-0075-5

146. Sands, T., Pynn, B. R., & Nenniger, S. (1993). Third molar surgery: Current concepts and controversies. part 2. *Oral Health, 83*(5), 19, 2-30.

147. Schnitman, P. A., & Shulman, L. B. (1979). Recommendations of the consensus development conference on dental implants. *Journal of the American Dental Association (1939), 98*(3), 373-377. doi: S0002-8177(79)83016-0

148. Schubert, U., Kleber, B. M., Strietzel, F. P., & Dorfling, P. (2001). CrossLaps and beta-glucuronidase in peri-implant and gingival crevicular fluid. *The International Journal of Oral & Maxillofacial Implants, 16*(2), 252-258.

149. Sennerby, L., & Roos, J. (1998). Surgical determinants of clinical success of osseointegrated oral implants: A review of the literature. *The International Journal of Prosthodontics, 11*(5), 408-420.

150. Sgolastra, F., Petrucci, A., Severino, M., Gatto, R., & Monaco, A. (2015). Smoking and the risk of peri-implantitis. A systematic review and meta-analysis. *Clinical Oral Implants Research, 26*(4), e62-e67. doi:10.1111/clr.12333

151. Sherwin, M. A., & Gastwirth, C. M. (1990). Detrimental effects of cigarette smoking on lower extremity wound healing. *The Journal of Foot Surgery, 29*(1), 84-87.

152. Shrier, I., Boivin, J. F., Steele, R. J., Platt, R. W., Furlan, A., Kakuma, R., . . . Rossignol, M. (2007). Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *American Journal of Epidemiology, 166*(10), 1203-1209. doi: kwm189

153. Simonis, P., Dufour, T., & Tenenbaum, H. (2010). Long-term implant survival and success: A 10-16-year follow-up of non-submerged dental implants. *Clinical Oral Implants Research, 21*(7), 772-777. doi:10.1111/j.1600-0501.2010.01912.x

154. Smith, D. E., & Zarb, G. A. (1989). Criteria for success of osseointegrated endosseous implants. *The Journal of Prosthetic Dentistry, 62*(5), 567-572. doi:0022-3913(89)90081-4

155. Strietzel, F. P. (2003). Patient's informed consent prior to implant-prosthetic treatment: A retrospective analysis of expert opinions.*The International Journal of Oral & Maxillofacial Implants, 18*(3), 433-439.

156. Strietzel, F. P., Reichart, P. A., Kale, A., Kulkarni, M., Wegner, B., & Küchler, I. (2007). Smoking interferes with the prognosis of dental implant treatment: A systematic review and meta-analysis. *Journal of Clinical Periodontology, 34*(6), 523-544. doi:10.1111/j.1600-051X.2007.01083.x

157. Tanaka, H., Tanabe, N., Shoji, M., Suzuki, N., Katono, T., Sato, S., . . . Maeno, M. (2006). Nicotine and lipopolysaccharide stimulate the formation of osteoclast-like cells by increasing macrophage colony-stimulating factor and prostaglandin E2 production by osteoblasts. *Life Sciences, 78*(15), 1733-1740. doi: S0024-3205(05)00994-X

158. ten Bruggenkate, C. M., van der Kwast, W. A., & Oosterbeek, H. S. (1990). Success criteria in oral implantology. A review of the literature. *The International Journal of Oral Implantology: Implantologist, 7*(1), 45-51.

159. Testori, T., Weinstein, R. L., Taschieri, S., & Del Fabbro, M. (2012). Risk factor analysis following maxillary sinus augmentation: A retrospective multicenter study. *The International Journal of Oral & Maxillofacial Implants, 27*(5), 1170-1176.

160. Ting, M., Tenaglia, M. S., Jones, G. H., & Suzuki, J. B. (2017). Surgical and patient factors affecting marginal bone levels around dental implants: A comprehensive overview of systematic reviews. *Implant Dentistry, 26*(2), 303-315. doi:10.1097/ID.0000000000000565

161. Ueng, S. W., Lee, M. Y., Li, A. F., Lin, S. S., Tai, C. L., & Shih, C. H. (1997). Effect of intermittent cigarette smoke inhalation on tibial lengthening: Experimental study on rabbits. *The Journal of Trauma, 42*(2), 231-238. doi:10.1097/00005373-199702000-00008

162. van Steenberghe, D. (1997). Outcomes and their measurement in clinical trials of endosseous oral implants. *Annals of Periodontology, 2*(1), 291-298. doi:10.1902/annals.1997.2.1.291

163. van Steenberghe, D., Quirynen, M., Naert, I., Maffei, G., & Jacobs, R. (2001). Marginal bone loss around implants retaining hinging mandibular overdentures, at 4-, 8- and 12-years follow-up. *Journal of Clinical Periodontology, 28*(7), 628-633. doi: cpe280704

164. Waeber, B., Schaller, M. D., Nussberger, J., Bussien, J. P., Hofbauer, K. G., & Brunner, H. R. (1984). Skin blood flow reduction induced by cigarette smoking: Role of vasopressin. *The American Journal of Physiology, 247*(6 Pt 2), 895. doi:10.1152/ajpheart.1984.247.6.H895

165. Wallace, R. H. (2000). The relationship between cigarette smoking and dental implant failure. *The European Journal of Prosthodontics and Restorative Dentistry, 8*(3), 103-106.

166. Wang, Y., Wan, C., Deng, L., Liu, X., Cao, X., Gilbert, S. R., . . . Clemens, T. L. (2007). The hypoxia-inducible factor alpha pathway couples angiogenesis to osteogenesis during skeletal development. *The Journal of Clinical Investigation, 117*(6), 1616-1626. doi:10.1172/JCI31581 [doi]

167. Ward, K. D., & Klesges, R. C. (2001). A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcified Tissue International, 68*(5), 259-270. doi:10.1007/bf02390832

168. Wennerberg, A., & Albrektsson, T. (2010). On implant surfaces: A review of current knowledge and opinions. *The International Journal of Oral & Maxillofacial Implants, 25*(1), 63-74.

169. Winniford, M. D., Wheelan, K. R., Kremers, M. S., Ugolini, V., van den Berg, E.,Jr, Niggemann, E. H., . . . Hillis, L. D. (1986). Smoking-induced coronary vasoconstriction in patients with atherosclerotic coronary artery disease: Evidence for adrenergically mediated alterations in coronary artery tone. *Circulation, 73*(4), 662-667. doi: 10.1161/01.cir.73.4.662

170. Wood, M. R., Vermilyea, S. G., & Committee on Research in Fixed Prosthodontics of the Academy of Fixed Prosthodontics. (2004). A review of selected dental literature on evidence-based treatment planning for dental implants: Report of the committee on research in fixed

prosthodontics of the academy of fixed prosthodontics. *The Journal of Prosthetic Dentistry, 92*(5), 447-462. doi: S0022391304005207

171. Yamano, S., Berley, J. A., Kuo, W. P., Gallucci, G. O., Weber, H. P., & Sukotjo, C. (2010). Effects of nicotine on gene expression and osseointegration in rats. *Clinical Oral Implants Research, 21*(12), 1353-1359. doi:10.1111/j.1600-0501.2010.01955.x

172. Zarb, G. A., & Albrektsson, T. (1998). Consensus report: Towards optimized treatment outcomes for dental implants. *The Journal of Prosthetic Dentistry, 80*(6), 64-4. doi: S0022-3913(98)70048-4

173. Zitzmann, N. U., & Berglundh, T. (2008). Definition and prevalence of peri-implant diseases. *Journal of Clinical Periodontology, 35*(8 Suppl), 286-291. doi:10.1111/j.1600-051X.2008.01274.x

174. WHO (2005) Tobacco and Health. The role of health professionals in tobacco control. WHO Library Catalogue-in-Publication, pp. 7–8. www.who.int/tobacco/resources/publications

175. Kan JY, Rungcharassaeng K, Kim J, Lozada JL, Goodacre CJ. Factors affecting the survival of implants placed in grafted maxillary sinuses: a clinical report. Journal of Prosthetic Dentistry 2002;87:485–9.

176. Avinash B., Wu J. ACP Public Relations Committee. 2014 NPAW articles.