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Systematic Review

Association between IL-1A, IL-1B and IL-1RN Polymorphisms and Peri-Implantitis: A Systematic Review and Meta-Analysis

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Featured Application: Feature Application: The evaluation of genetic polymorphisms may have great clinical relevance since they can be measured before the onset of the disease and may be of great benefit for treatment planning and prognosis at an early stage.

Abstract: Recent studies report that individuals with polymorphisms in the genes that encode for interleukin (IL)-1α and IL-1β (IL-1A and IL1B, respectively) and for IL-1 receptor antagonist (IL-1RN) may be more susceptible in developing peri-implantitis. Therefore, the current systematic review evaluates what is reported about the role of genetics, more specifically of single nucleotide polymorphisms (SNP) on IL-1 and variable number of tandem repeats (VNTR) on IL-1RN, in the development of peri-implantitis. This systematic review was carried out by screening PubMed, B-on, Cochrane and Scopus databases, for articles English, Spanish, and Portuguese, with no limit regarding the publication year. Eight articles were selected for systematic review and four for meta-analytic syntheses. Our results show that although there is a lack of consensus in the literature, there seems to be an association between IL-1A, IL-1B, and IL-1RN polymorphisms with peri-implantitis. The results of the meta-analysis showed that patients who have the polymorphic allele at position +3954 of the IL-1B gene have on average almost twice the risk of developing peri-implantitis (*odds ratio* = 1.986, 95% confidence interval).

Keywords: genetics; peri-implantitis; interleukin-1; interleukin-1 receptor antagonist; interleukin-1 genotype; genetic polymorphisms; peri-implant disease

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1. Introduction

Dental implants are now considered as an effective and predictable treatment modality for the functional and aesthetic rehabilitation of either partially or completely edentulous patients [1,2]. This rehabilitation method has a success rate of more than 90% for implants in function for more than five years [3]. However, despite the high success rates associated with implant rehabilitation, biological complications may arise in the peri-implant soft tissues, such as peri-implantitis, which can compromise the permanence of the implant [4]. Peri-implantitis is a plaque-associated pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa

and progressive loss of supporting bone [5,6]. This definition is in accordance with the more recent classification of periodontal and peri-implant diseases (American Academy of Periodontology—AAP and European Federation of Periodontology—EFP 2018) [6].

According with the Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, there is strong evidence from animal and human experimental studies that plaque is the etiological factor for peri-implant mucositis, which is assumed to precede peri-implantitis [6]. Data indicate that patients diagnosed with peri-implant mucositis may develop peri-implantitis, especially in the absence of regular maintenance care. However, the features or conditions characterizing the progression from peri-implant mucositis to peri-implantitis in susceptible patients have not been identified [6].

With a growing number of dental implants inserted, the potential number of sites for implant-associated diseases increases [7]. But the actual value of the incidence/prevalence of this disease is uncertain since the method of classifying peri-implantitis has varied between authors over the years and, in addition, few studies follow up and evaluate the sample for several years [8]. The characteristics of the populations included also vary between studies, which may influence the results [8]. In a systematic review carried out by Atieh et al., the prevalence of peri-implantitis obtained per patient was 18.8% while the prevalence per implant was 9.6% [9]. Lee et al. conducted a systematic review and meta-analysis, that included forty-seven articles, and concluded that the mean prevalence of peri-implantitis, at implant and subject level was 9.25% and 19.83%, respectively [10].

There are some similar features in the sequence of immunopathological events in peri-implant and periodontal infections [11]. Both are initiated primarily by Gram-negative anaerobic bacteria, while the inflammatory process goes faster and deeper around implants than around natural teeth and thus is a more significant problem for patients with dental implants [12]. However, Becker et al. in a study in which the transcriptome profiling using mRNA from patients suffering from either peri-implantitis or periodontitis was compared, the authors observed that these two pathologies react in a different way [13]. These differences may be explained by the anatomy, which is very different comparing the scar tissue in peri-implantitis with the specialized fibers inserting the surface of the teeth. In peri-implantitis tissue, transcripts associated to innate immune responses, and defense responses were dominating, while in periodontitis tissues, bacterial response systems prevailed [13].

Research evidence indicates that implant complications tend to be clustered in a subset of individuals rather than being randomly distributed in the population implying that patient's host response might play a role for the implant success [14,15].

Interleukin-1 (IL-1) is the pivotal mediator of the immune-inflammatory response that acts both in response to bacterial infection and in bone metabolism [16]. IL-1 family has at least 11 cytokines; clustered on the long arm of chromosome 2q, and the three most studied members are IL-1A, IL-1B, and IL-1RN genes, which encode the agonistic proteins IL-1α and IL-1β, and IL-1 receptor antagonist (IL-1Ra), respectively [17]. The effect of IL-1 is determined by the balance between IL-1α, IL-1β, and IL-1Ra through competitive binding of IL-1Ra to the IL-1 receptor to block the activity of IL-1α or IL-1β. IL1 is strongly induced by lipopolysaccharides from the cell walls of Gram-negative bacteria and acts either directly or indirectly to initiate and amplify inflammatory responses through inducing expression of a substrate of effectors including cytokines/chemokines and matrix metalloproteinases [18].

The variations of IL-1 gene cluster, including IL-1A and IL-1B genes, and the variations of IL-1 RN are the most commonly studied functional polymorphisms for peri-implantitis.

Many studies have investigated different single nucleotide polymorphisms (SNPs) in the IL-1 genes as a risk factor for peri-implantitis. Among them, the IL-1A −889 C/T (rs1800587) and IL-1B +3954 C/T (rs1143634) have been mostly investigated [19]. The IL-1B-511 (rs16944) is also studied in some studies. These polymorphisms are characterized by the substitution of cytosine with thymine in the DNA sequence, which has been demonstrated to be associated with directly changed levels of gene expression and secreted cytokines,

respectively [20]. In the IL-1RN gene, there is a genetic polymorphism located in intron 2 which is composed of a variable number of tandem repeats (VNTR) of 86 base pairs length. Several studies have analyzed the relationship between these polymorphisms and peri-implantitis. However, studies have yielded conflicting results on this issue [21–26].

A clarification of the genetic basis associated with peri-implant pathology could be used to predict peri-implantitis occurrence and to improve treatment and monitoring of patients with dental implants [21].

Most of these studies had a relatively small sample size and thus had insufficient statistical power to detect the genetic associations. Some of them do not refer to confounding variables such as periodontal condition, ethnicity and smoking habits. Furthermore, many studies, including published systematic reviews, assess the relationship of these polymorphisms with the peri-implant disease, pooling in the same group patients with bone loss, implant loss, and peri-implantitis [27–29]. However, peri-implant tissue health can exist around implants with variable levels of bone support [6]. In addition, an implant can fail without having an associated chronic inflammatory reaction as occurs in peri-implantitis.

Therefore, we performed a systematic review and meta-analysis, quantitatively synthesizing previous studies, to evaluate the association of common functional polymorphisms in the IL1 and IL-1RN genes with susceptibility to peri-implantitis.

2. Materials and Methods

2.1. Study Design

The guidelines of PRISMA were followed while reporting this systematic review and meta-analysis.

The research question used for this systematic review was: "What is the importance of the interleukin-1 genotype (IL-1A −889 (rs1800587), IL-1B −511 (rs16944), and IL-1B +3954 (rs1143634)) and the IL-1 receptor antagonist genotype (IL-1 RN (rs2234663)) in the development of peri-implantitis, in adults, smokers or not, after at least one year of the implant in function?". In addition, the PECO nomenclature was also used:

P (Population)—Adult patients
E (Exposure)—Genotype including selected polymorphisms of interleukin-1 and its antagonist
C (Control)—Genotype not including selected polymorphisms of interleukin-1 and its antagonist
O (Outcomes/Outcome)—Development of peri-implantitis

A search protocol was specified in advance and registered at PROSPERO (International Prospective Register of Systematic Reviews ID 322662).

2.2. Search Strategy

Two authors (J.M.C.) (S.D.) extracted the specific studies from the databases, and the same authors removed duplicates and irrelevant studies. Discrepancies, if occurred, were resolved by a third researcher (P.M.).

Systematic searches were performed on the PubMed, B-on, Cochrane and Scopus literature databases for studies published until January 2022.

The MESH terms and other keywords were used in combination, and Boolean operators such as AND and/or OR and/or NOT were added to obtain more relevant studies regarding the topic in question [30].

We used a specific search strategy with the following focused key terms:

("dental implants" or "oral implants") and ("polymorphism" or "interleukins" or "interleukin-1"); ("peri-implantitis") and ("interleukin-1" or "interleukins") and ("gene polymorphism" OR "genotype") not animal.

2.3. Inclusion and Exclusion Criteria

The inclusion criteria were: (1) Human case-control studies; (2) peri-implantitis as the outcome of interest in functional implants with at least one year follow up; (3) studies reporting IL-1A −889, IL-1B −511, IL-1B +3954 and IL-1RN (VNTR), and composite geno-

type of IL-1A −889/IL-1B +3954 polymorphisms; (4) articles written in English, Spanish or Portuguese.

The exclusion criteria were: (1) Studies that included patients with uncontrolled systemic diseases; (2) studies in which patients with peri-implantitis were included in a general category disease group of peri-implant diseases or other conditions (presence of suppuration, development of fistula, radiographic bone loss or implant loss).

The author (S.D.) screened all the titles and abstracts based on the eligibility criteria and included/excluded studies for full-text review. Another author (J.M.C.) rechecked relevant articles. Discrepancies, if occurred, were resolved by a third researcher (P.M.).

2.4. Data Extraction

One author (S.D.) independently extracted the information or data from each study and another author (J.M.C.) rechecked them.

2.5. Risk of Bias Assessment

Two authors (S.D. and P.M.) evaluated the quality of included articles using the Joanna Brigs Institute (JBI) checklist [31]. This tool evaluates "cross-sectional analytical" studies regarding eight domains. These domains evaluate if the criteria in the sample were clearly defined, if the study subjects and the setting were described in detail, if the confounding factors were identified and strategies to deal with, and if the outcomes were measured in a valid and reliable way.

2.6. Statistical Analysis

Statistical analysis was performed using the Open Meta [Analyst] for Windows 8 (built 04/06/2015) software, from Center for Evidence Synthesis in Health (Brown University, Providence, RI, USA), which allowed us to obtain all meta-analysis and meta-regression plots, which are described later [32]. Allele frequencies against peri-implantitis incidence were converted in odds ratios effect size and associated 95% confidence intervals in a binomial model framework. Model parameters were estimated applying the restricted maximum likelihood method.

Heterogeneity was assessed using the I^2 index and it was considered high if it was above 50%. A high I^2 value means that the authors of the different articles analyzed are not in consensus. To counteract this value, covariates can be added [33].

We used 95% confidence intervals and considered the *p*-value test results lower than 0.05 to correspond to a statically significant result.

A subgroup analysis was done in relation of the odds ratio (OR) of the ethnicity in the difference in the frequency of the mutated allele between the disease and control group.

Meta-regressions were carried out for longitude and latitude of the sample's provenance, the mean age, the percentage of males and females, the representative ratio of the mutated allele, sample size and year of publication.

3. Results

3.1. Study Selection

Initially, 324 articles were obtained from all databases. After excluding the duplicates, 218 articles remained, of which the titles and abstracts were read. Since 199 were not included in the theme of this systematic review, they were excluded, leaving only 19. These were read in full and, as eleven articles did not meet the inclusion and exclusion criteria, only eight articles remained, which were included in this systematic review [21–26,34,35]. However, only four of these articles contained eligible quantitative data, and were included in the meta-analysis [21,23,24,26].

A PRISMA flowchart was carried out to systematize the selected information throughout the different research phases (Figure 1).

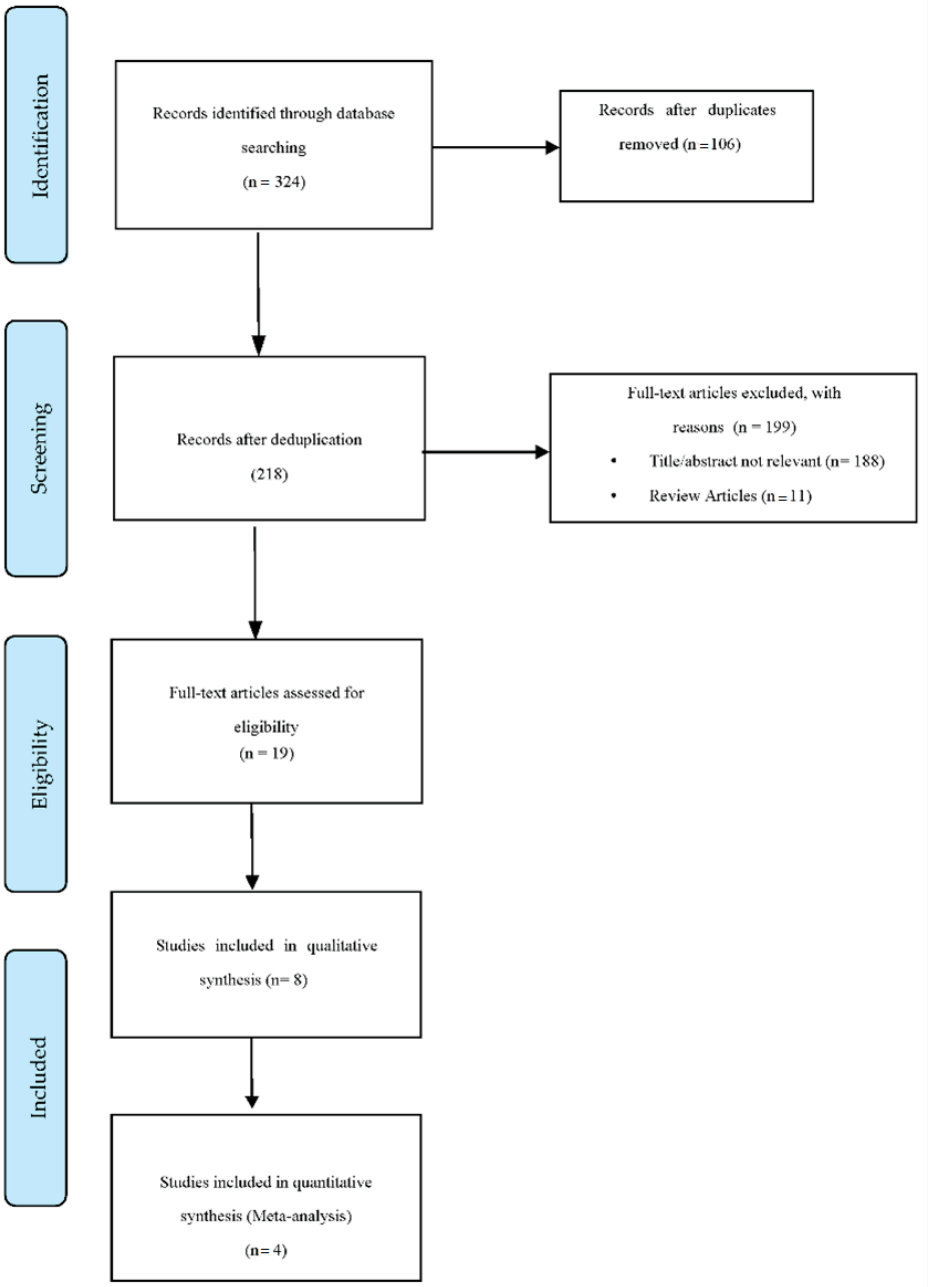

Figure 1. Flow chart of the study selection.

3.2. Results of the Bias Risk Assessment

In order to know the risk of bias in the articles, by completing the JBI checklist, a Traffic Plot-type graph was obtained (Figure A1), where it is possible to clearly observe the risk of bias for each article selected for this systematic review. None of the articles had three or more high risk judgments and they were all included in the review.

3.3. Characteristics of the Studies

The Table 1 provides the characteristics of eight articles [21–26,34,35] included in the systematic review. Four articles included individuals from Europe [21,25,34,35], two from Asia [24,26], one from North Africa [22] and one from South America [23]. Five studies reported IL-1A −889 polymorphism [21,22,24,25,34], two IL-1B −511 [21,23], seven IL-1B +3954 polymorphism [21–26,34], two IL-1RN (VNTR) polymorphism [21,35] and five composite genotype of IL-1A −889 and IL-1B +3954 polymorphisms [21,22,24,25,34].

Table 1. Systematic review table of the eight articles included in the present study.

Year & Author	Type of Study	Polymorphisms Evaluated	Geographic Region	Inclusion Criteria	Exclusion Criteria	Smoking Habits	Time of Implant in Function (Months)	Outcome
Garcia-Delaney, 2015 [34]	Case-control	IL-1A −889 IL-1B +3954 IL-1RN +2018	Spain	Systemically healthy patients; Peri-implantitis group: BOP or SUP (+); BL > 2 mm Control group: BOP (−); SUP (−); BL < 2 mm	- Cases with incomplete data or with dubious diagnosis	All smokers	≥18	IL-1 genotypes do not seem to be good predictors of peri-implantitis in the great majority of smoking patients. Furthermore, no synergic effect was found between IL-1 genotypes and heavy smokers. Patients with a previous history of periodontitis were more prone to peri-implantitis.
Hamdy, 2011 [22]	Case-control	IL-1A −889 IL-1B +3954	Egypt	Systematically healthy patients; Peri-implantitis group: BOP (+); PPD > 4 mm; BL (+)	- Smokers; - History of antibiotic intake or periodontal treatment in previous 6 months	Non-smokers	≥36 (implant placement)	The combination of the polymorphism in IL-1A −889 and IL-1B +3954, in patients with inflamed periodontal or peri-implant tissues, may act as a risk factor that increases tissue destruction. IL-1 gene polymorphism (IL-1A −889 and IL-1B +3954) may have a negative effect on treatment outcomes of peri-implantitis.
He, 2019 [24]	Case-control	IL-1A −889 IL-1B +3954 TNFα −308	China	Peri-implantitis group: PPD ≥ 4 mm; BOP (+); GI (+); BL involving ≥ 2 threads compared to prosthetic placement Control group: Healthy peri-implant tissue; PPD < 3mm; BOP (−); BL (−)	- Smokers; - Pregnant or lactation; - General health problems (diabetes mellitus, HIV infection); - Intake of any antibiotics and anti-inflammatories in the last 3 months.	Non-smokers	≥24	The IL-1A −889 or IL-1B +3954 genetic polymorphisms were associated with the risk of peri-implantitis and periodontal status.
Lachmann, 2007 [25]	Case-control	IL-1A −889 IL-1B +3954	Germany	- Systemic health in general; - Absence of medical conditions that compromise the immune system. Peri-implantitis group—PPD > 4 mm; BOP (+); BL (+)	ND	ND	≥12	The composite IL-1A −889 and IL-1B +3954 genotype investigated exerted only little influence on the peri-implant crevicular immune response, and this influence appeared to be of limited impact in sites with established peri-implantitis lesions.
Laine, 2006 [21]	Case-control	IL-1A −889 IL-1B +3954 IL-1B −511 IL-1RN (VNTR)	Sweden	Peri-implantitis group: BL involving ≥ 3 threads; BOP and/or SUP (+)	ND	Peri-implantitis group—76% smokers Control group—49% smokers	≥24	IL-1RN gene polymorphism is associated with peri-implantitis and may represent a risk factor for this disease.
Melo, 2011 [23]	Case-control	IL-1B +3954 IL-1B −511 IL-6 −174	Brazil	- No medical history of chronic illness; - No history of antibiotic therapy or use of steroidal or AINE medications in the 6 months prior to the study. Control group: no mucosal bleeding, PD ≤ 4 mm, BOP and SUP (−)	- Smokers; - Pregnant or lactation; - Periodontitis	Non-smokers	ND	There was no correlation between the concentration of IL-1β and IL-6 in the crevicular sulcular fluid present in healthy or diseased osseointegrated implants in comparison with healthy teeth. The studied genetic polymorphisms had no influence on peri-implant disease.
Petkovic-Curcin, 2017 [35]	Case-control	IL-6 −174 IL-10 −1082 TNF-α −308 CD14 −159 IL-1RN (VNTR)	Serbia	Peri-implantitis group: PPD ≥ 4 mm, BOP +, GI (+); PI (+) and BL involving ≥ 2 threads compared to prosthetic replacement Control group: Healthy peri-implant tissue, BOP (−), PPD < 4 mm, BL (−)	ND	C—42% smokers PI—71% smoker	≥24	Smoking and the presence of TNFα-308 polymorphism may increase the risk for peri-implantitis, while CD14-159 polymorphism decreases the risk. The results also indicate significant association of CD14-159, TNFα-308, and IL6-174 genotypes and clinical parameters in the Serbian population.

Table 1. *Cont.*

Year & Author	Type of Study	Polymorphisms Evaluated	Geographic Region	Inclusion Criteria	Exclusion Criteria	Smoking Habits	Time of Implant in Function (Months)	Outcome
Saremi, 2021 [26]	Case-control	IL-1B +3954 IL-10 −819 IL-10 −592 TNF-α −308 TNF-α −857	Iran	- No history of periodontitis Peri-implantitis group: PPD > 5 mm; BOP (+) with or without SUP; BL ≥ 2 mm Control group: PPD < 4 mm; BL (−)	- Oral and periodontal diseases (except caries), - Current orthodontic treatment; - History of systemic diseases or any complication that compromises the immune system (diabetes, HIV, hepatitis, chemotherapy); - Pregnant or lactation	ND	≥12	Genetic polymorphisms of IL-10 −819, IL-10 −592 and IL-1B +3954 may play a role in the pathogenesis of peri-implantitis and increase its risk of occurrence.

(+)—presence, (−)—absent, BL—bone loss, BOP—bleeding on probing, SUP—suppuration, GI—gingival index, ND—non-defined, PPD—probing pocket depth, PI—plaque index, VNTR—Variable number of tandem repeats, AINE—non-steroid anti-inflammatory.

The Table A1 provides the percentage of men and women, from which it is possible to conclude that there is a predominance of female individuals in five of the eight articles [21,23,25,26,34]. The mean age varies between 41 and 67 years. The mean age of the sample of each study was considered, since between the group with peri-implantitis and the control group there was no difference in mean age of more than five years.

The mean percentage of the mutated allele in the sample are indicated in four of the eight articles [21,23,24,26]. Some articles only indicated the genotype of the individuals, without referring to whether they were homozygous or heterozygous for the mutated allele, which could influence the results.

3.4. Meta-Analysis

To carry out the meta-analysis, only four articles were used, as explained above [21,23,24,26]. However, due to the lack of information and the different types of polymorphisms analyzed by each article, it was only possible to perform the meta-analytic study for the IL-1B +3954 polymorphism, which was the only common polymorphism in the previously selected articles. In addition, these four articles contained information about the amount of mutated alleles in the sample.

Figure 2 shows the odds ratio (OR) meta-analysis as a forest plot. The OR values extracted from each study are graphically illustrated. This graph performs an analysis of heterogeneity that is expressed in the form of I^2, in %, and presents the mean value of the ORs and the respective uncertainty in the form of a 95% confidence interval. On the left, the authors and the year of the included studies are indicated, followed by the corresponding analytical values obtained.

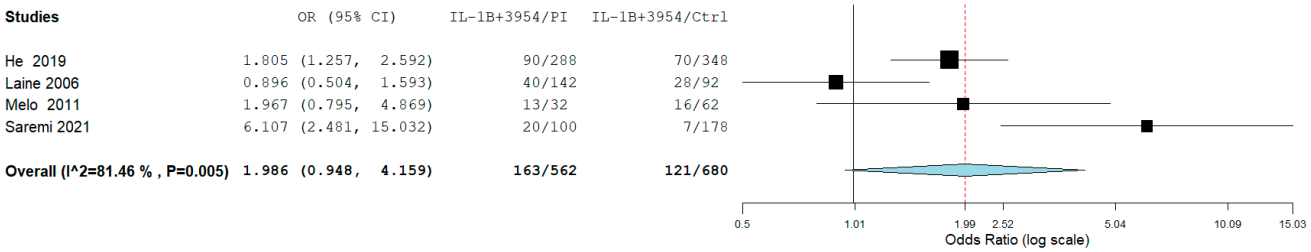

Figure 2. Meta-analysis Forest Plot. (OR—odds ratio, CI—confidence interval, PI—peri-implantitis group, Ctrl—control group). Laine et al., 2006 [21]; Melo et al., 2011 [23]; He et al., 2019 [24]; Saremi et al., 2021 [26].

The odds ratio of these studies is 1.986 (chi square test, $p < 0.001$), which means that this polymorphism increases the risk of carriers of the mutated allele in the IL-1B +3954 to have peri-implantitis, by almost twice, as compared to the control group, patients that do not have this polymorphism.

The I^2 in this case is quite high, which may indicate that the authors are not in agreement with the results they present.

3.5. Subgroup Analysis

The subgroup analyses (based on the ethnicity) of the association between the frequency of the mutated allele in the IL-1B +3954 gene and the risk of peri-implantitis is shown in Figure 3. The results showed that the ethnicity, Asian, is one factor that affects the difference in frequencies of the mutated allele in the IL-1 B3954 gene between the disease and the control groups (OR = 3.088, chi square test, $p < 0.001$). The ethnicity, Caucasian, does not affect the difference in frequencies of the mutated allele in the IL-1 B3954 gene between the disease and the control groups (OR = 0.896, chi square test, $p = 0.709$). Regarding mixed ethnicity, further studies are needed to understand its influence in the difference in frequencies of the mutated allele in the IL-1 B3954 gene between peri-implantitis and control groups (OR = 1.967, chi square test, $p = 0.140$).

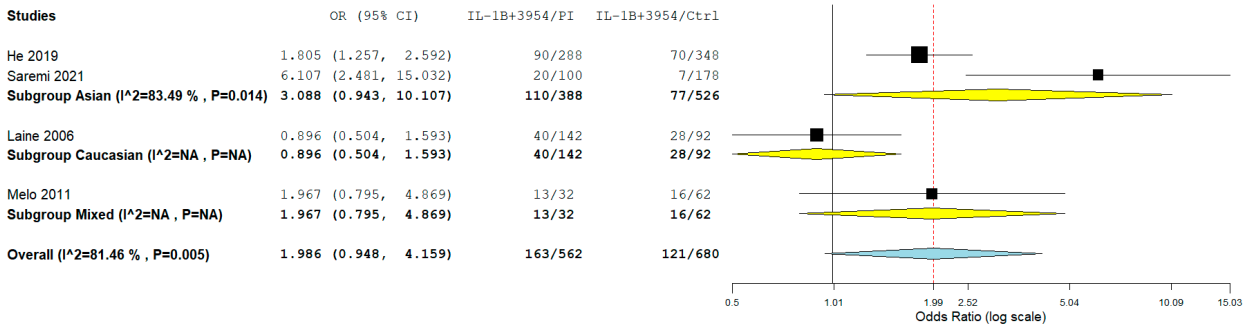

Figure 3. The subgroup analyses (based on the ethnicity) of the association between the frequency of the mutated allele in the IL-1B +3954 gene and the risk of peri-implantitis. (OR—odds ratio, CI—confidence interval, PI—peri-implantitis group, Ctrl—control group). Laine et al., 2006 [21]; Melo et al., 2011 [23]; He et al., 2019 [24]; Saremi et al., 2021 [26].

3.6. Meta-Regression

Regarding meta-regressions, in all there is a limitation, since there are only four points represented in the graphs, only four articles were analyzed. There is, therefore, a limitation to being able to extrapolate this trend to other populations or other geographic regions. Therefore, further studies are recommended in order to confirm this trend.

The size of the circles in all figures represents the weight that this article contributed to the average. Since the OR logarithm is proportional to the OR, with negative coefficient, as the latitude increases, there is a tendency for the OR to decrease, and in this case the trend is statistically supported/significant since the *p*-value obtained was 0.025 (Figure 4). The result of the coefficient statistical test in the longitude-relative meta-regression presents a value of $p = 0.295$, so it is not statistically significant (Figure A2).

Regarding the mean age, the *p*-value in this meta-regression has a value of 0.005, thereby it is statistically significant (Figure 5).

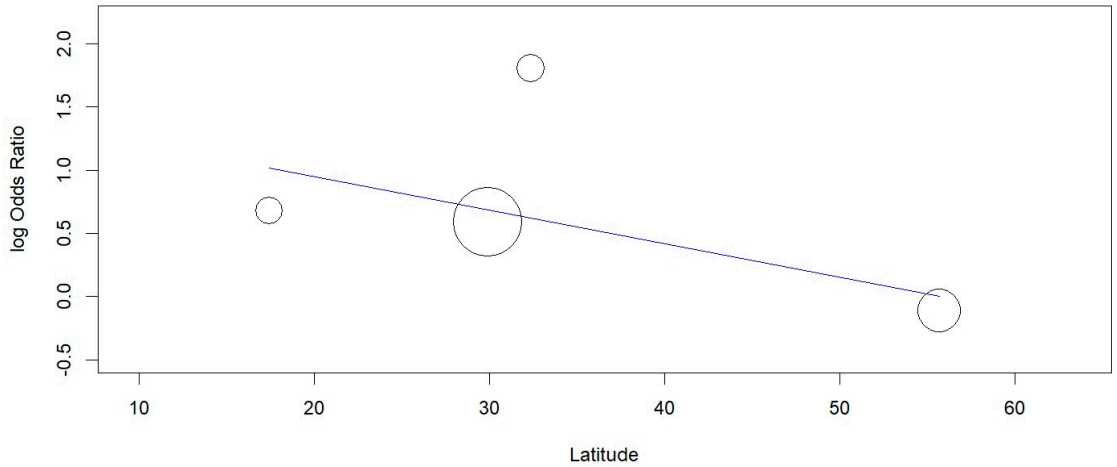

Figure 4. Log OR meta-regression for IL-1B +3954 polymorphism as a function of latitude covariate (*p*-value = 0.025, coefficient = −0.026).

Analyzing the meta-regression analysis regarding the percentage of male subjects, it is possible to conclude that, as the proportion of male individuals increases, there is an increase in the OR, therefore, there is an increase in risk, however, it is not statistically significant (Figure A3).

We can also observe that as the percentage of the mutated allele increases, the OR decreases. It is necessary to consider that the value of the mutated allele corresponds to the entire sample, both for control patients and patients with peri-implantitis. The effect

of the lower percentage of the mutated allele on the risk for peri-implantitis is statistically significant (p-value < 0.05) (Figure 6).

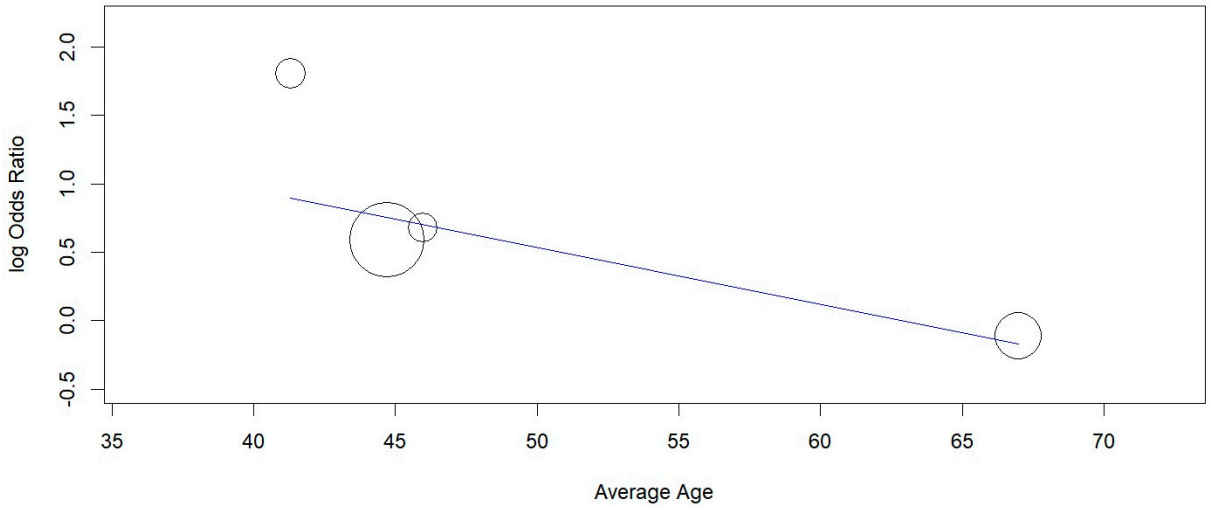

Figure 5. Log OR meta-regression for the IL-1B +3954 polymorphism as a function of the mean age covariate (p-value = 0.005, coefficient = −0.041).

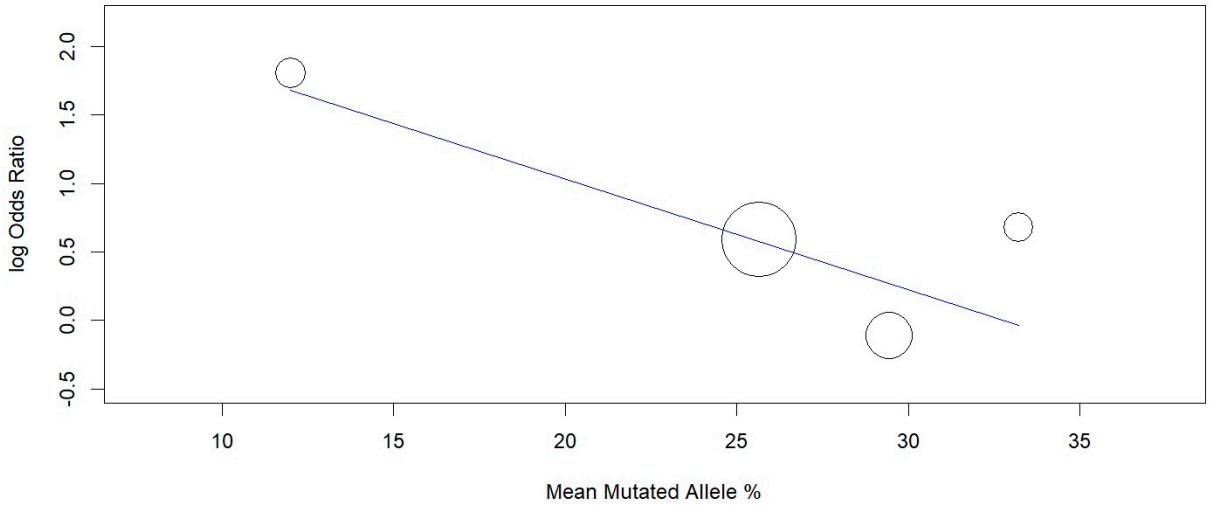

Figure 6. Log OR meta-regression for the IL-1B +3954 polymorphism as a function of the covariate percentage of the mutated allele in the s ample (p-value = 0.003, coefficient = −0.081).

Performing a meta-regression analysis regarding the year of publication (Figure 7) and the sample size (Figure A4) of the included studies, we can conclude that the effect of year of publication is statistically significant while the effect of the sample size is not statistically significant. We can observe that as the year of publication increases, the risk for peri-implantitis also increases.

Through the interpretation of this meta-analysis, we were able to analyze the historical perspective from the oldest to the most recent article. From the Figure 8, we concluded that, with these successive assessments, there is an increased risk of carriers of the IL-1B +3954 polymorphism to have peri-implantitis.

3.7. Sensitivity Analysis

Both "leave-one-out" and "cumulative analysis" were performed within the sensitivity analysis for the IL-1B +3954 polymorphism study effects sizes. Results are illustrated in Figure A5. All studies seem to have had a balanced contribution to the pooled results although recent studies seem to overestimate the effect in comparison with previous ones.

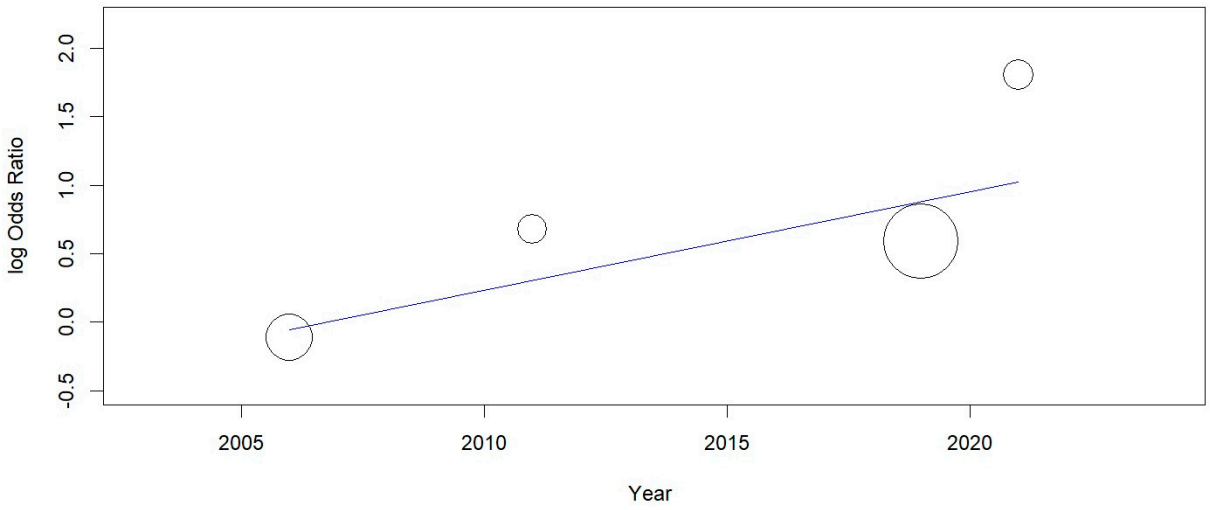

Figure 7. Log OR meta-regression for the IL-1B +3954 polymorphism as a function of the year of publication (*p*-value = 0.014, coefficient = 0.067).

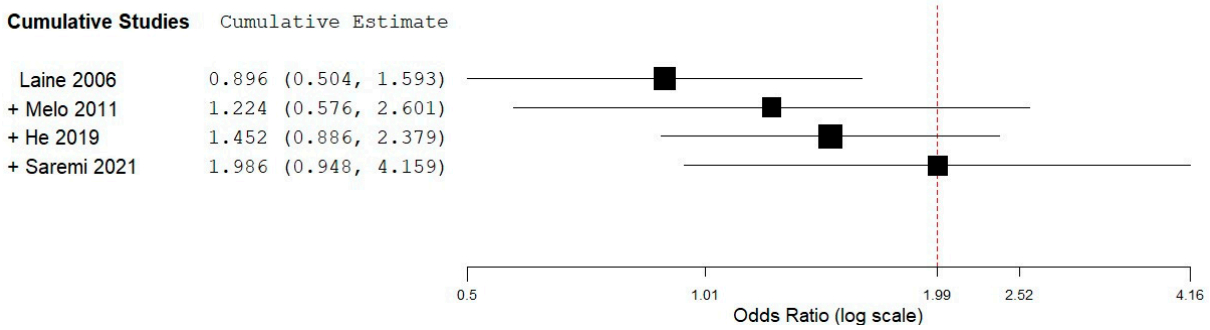

Figure 8. Forest Plot of the cumulative meta-analysis for the IL-1B +3954 polymorphism. Laine et al., 2006 [21]; Melo et al., 2011 [23]; He et al., 2019 [24]; Saremi et al., 2021 [26].

4. Discussion

This study aimed to verify if there is an association between the polymorphisms of the IL-1A, IL-1B, and IL-1RN genes and peri-implantitis. It is a relevant topic since, if this association is confirmed, it is possible to identify patients who have this polymorphism and the physician's approach can be adjusted in order to prevent the onset of this disease, considered a public health problem. Genetic polymorphisms are constant and can be measured before disease onset, thus it could be of great benefit for treatment planning and prognosis in an early stage. Despite the fact that peri-implantitis etiology and pathology are complex, the identification of genetic biomarkers associated with peri-implantitis risk could be a valuable tool in daily clinical practice. They could be used for early identification of individuals predisposed to increased peri-implantitis risk, and this would help practitioners (after estimating dental implants prognosis) in individualizing their treatment plan.

The future of disease diagnosis must involve not only identifying more susceptible patients but also identifying disease-associated biomarkers. Biomarkers are biological indicators with high prognostic and predictive value that can be related to the onset or development of a pathology. Frequently they must be able to predict the presence of a disease or its progression. A recent paper that has focused on five promising host derived biomarkers as candidate for early diagnosis of periodontitis, IL-1 β was one of them [36].

After a systematic search, which is described in the flowchart in Figure 1, eight articles were obtained for the present systematic review [21–26,34,35].

Table 1 shows the general conclusions of each of the eight articles. Four of these articles concluded that individuals with the IL-1 gene polymorphisms had a higher risk for the development of peri-implantitis [21,22,24,26]. These results are in agreement with

what is found in the systematic review of Dereka et al. [27]. In this systematic review, the authors observed that in two of the three studies which evaluated peri-implantitis in relation to IL-1 genotype, the findings indicate that IL-1RN, IL-1A –899, IL-1B +3954 gene polymorphisms were correlated to increased peri-implant tissue infection and destruction [27]. In 2008, Huynh-Ba et al. carried out a systematic review [37] where two articles were included [38,39], and they concluded that there is not enough evidence to support or refute an association between the IL-1 genotype status and peri-implantitis. It should be mentioned that the articles included in this review evaluated peri-implantitis based on bone loss [37,38].

The number of studies in the literature evaluating this association is limited and some of these do not refer to confounding variables such as periodontal condition, ethnicity, and smoking status. These factors may explain the differences found between the different studies. The ethnicity of the populations included in the studies varies and there are studies that include patients who smoke and others who do not. On the other hand, the definition of peri-implantitis varies between studies, which makes comparisons between studies difficult. In our systematic review, we only included articles in which peri-implantitis was the evaluated outcome. From 2018, with the new Classification of Periodontal and Peri-implant Diseases and Conditions, it will be easier to standardize the definition of peri-implantitis between studies [6]. This new classification is the product of the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions organized jointly by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) to create a consensus knowledge base for a new classification to be promoted globally.

Furthermore, some aspects such as the surface and position of the implants (anterior or posterior), the type of prosthetic restoration used (removable or fixed), type of retention (screw or cemented), the need for guided bone regeneration before or at the time of implant placement, general oral cavity health conditions were not referred or varied between studies. The techniques of DNA isolation also differ between studies, with some studies obtaining DNA from oral mucosal cells using swabs [22–25,34] and others using mouthwashes [21]. Other authors obtain DNA from blood [26,35].

Within the limits of this systematic review, it might be concluded that there is no obvious association between specific genetic polymorphism of IL-1 and IL-1RN and peri-implantitis, although a tendency should be underlined showing the potential link between IL-1 genotype and peri-implantitis.

For the meta-analysis, it was only possible to include four articles [21,23,24,26] since, in order to obtain a more real result on the true influence of the polymorphism in the disease, allele frequencies were evaluated. The remaining studies were excluded as they did not mention whether the patients were homozygous or heterozygous for the mutated allele, which may influence the interpretation of the results. The common polymorphism in these four studies was IL-1B +3954, which was evaluated.

In the present study, it was found that individuals who had the polymorphism in the IL-1B +3954 had an almost twice higher risk of developing peri-implantitis (OR 1.986). This result is in agreement with a meta-analysis performed by Jin et al. where the association between IL-1A −889, ILB +3954, IL-1B -511, composite genotype of IL-1A −889 and ILB +3954, and TNF-α −308 and risk of peri-implant disease (PID) was evaluated [29]. The PID included implant failure/loss, marginal bone loss and peri-implantitis. When a subgroup analysis is performed, it is observed that only IL-1B +3954 is associated with a higher risk of peri-implantitis (OR 1.87).

In a meta-analysis carried out by Liao et al., that included four articles regarding the relationship of IL-1 polymorphisms and peri-implantitis, the composite genotype of IL-1 −889 and IL-1B +3954 was associated with increased risk of peri-implantitis (OR 2.34) [19]. The inclusion criteria differed from the present study, which allowed the authors to assess the relationship between the composite genotype and peri-implantitis.

In a recent meta-analysis, which evaluated association between interleukin-1 polymorphisms and susceptibility to PID, the authors observed that there was no association between IL−1A −889, IL−1B −511 and IL−1RN (VNTR) polymorphisms and the risk of PID [28]. In contrast, an association was observed between the composite genotype of IL−1A −889 and IL−1B +3954 and PID. In addition, the T allele and CT genotype of IL−1B +3954 polymorphism were also associated with an elevated risk of PID. In subgroup analysis no association was found between the polymorphisms evaluated and the risk of peri-implantitis [28]. However, the results of the study have to be interpreted with caution because the authors included in the same group of PID, patients with peri-implantitis, patients with marginal bone loss and patients with implant failure. However, bone loss can occur with or without the sign of infection, whereas peri-implantitis is an inflammatory lesion associated with loss of supporting bone around implant [5]. On the other hand, not all implant failures are caused by peri-implantitis and not all peri-implantitis lead to implant loss.

Regarding meta-regressions carried out in our meta-analysis, we observed that as the latitude increases, there is a tendency for the OR to decrease, so with increasing latitude, the risk for peri-implantitis decreases. The result of the coefficient statistical test in the longitude-relative meta-regression is not statistically significant. The influence of ethnic and racial variations in the frequency of gene polymorphisms in terms of the genetic susceptibility to a specific disease has been reported [40,41]. It has been demonstrated that there is low prevalence of the periodontitis-associated IL-1A +4845 and IL-1B +3954 gene polymorphisms in Chinese (2.3%) [41] compared with that reported for Caucasians (36%) [40]. The IL-1A +4845 polymorphism is more than 99% in linkage disequilibrium with the IL-1A –889 polymorphism (if one is present, the other usually is present) [42]. In our study, it was observed that in populations where the allele frequency of the mutated allele is higher, the risk of peri-implantitis is lower. Furthermore, in a subgroup analysis we also found that the Asian population was at a greater risk for the disease than the Mixed or Caucasian subgroup. This is not in agreement with the information that exists regarding certain geographic areas, such as the Asian continent. In these areas, there is a low prevalence of the mutated allele in the population and a lower risk for inflammatory diseases such as periodontitis, compared to other geographic areas. We were only able to evaluate four articles in our meta-analysis so we can´t extrapolate these results.

Through the interpretation of our meta-analysis, we were able to analyze the historical perspective from the oldest to the most recent article. We concluded that with these successive assessments, there is an increased risk of carriers of the IL-1B +3954 polymorphism to have peri-implantitis. This finding may be related to a more adequate definition of peri-implantitis over the years in the various published studies.

In carrying out this work, there were some limitations. Not all articles presented information about the follow-up period, the inclusion and exclusion criteria were not similar between the various articles and there were parameters that some articles evaluated while others did not. In addition, there were also factors, such as age, gender, and ethnicity, which were not analyzed in the same way in all studies. These factors contributed to the heterogeneity obtained in this work.

The definition of peri-implantitis itself was not the same in all studies. Another limitation is the fact that some of the articles referred only to the genotype of the individuals and in this study the allele frequency was studied, since it is more specific.

The number of studies in the literature evaluating this association is limited, had small samples and some of them do not refer to confounding variables such as periodontal condition, ethnicity and smoking status. The inequality of these study designs necessitates the conduction of further studies using proper methodologies and from different ethnic groups. A clarification of the genetic basis associated with peri-implant pathology could be used to predict peri-implantitis occurrence and to improve treatment and monitoring of patients with dental implants.

5. Conclusions

It is possible to conclude that there are still no studies with an adequate sample size or sufficient studies to reach robust conclusions about the influence of interleukin 1 and interleukin 1 receptor antagonist polymorphisms on the development of peri-implantitis. However, the available evidence, while constrained by the above mentioned issues, shows that there seems to be a possible influence of these polymorphisms on the development of the disease. Regarding the meta-analysis performed, it was observed that individuals with the polymorphism in the IL-1B +3954 gene have a higher risk for the development of peri-implantitis.

Nevertheless, there is a need for further studies, with larger samples and in different ethnic groups, to increase scientific evidence about the possible role of these polymorphisms in the development of peri-implantitis.

Author Contributions: Conceptualization, J.M.C. and S.D.; methodology, S.D. and P.M.; software, P.M.; validation, J.M.C., S.D. and P.M.; formal analysis, J.M.C., S.D. and P.M.; investigation, J.M.C. and S.D.; resources, J.M.C. and P.M.; data curation, J.M.C., S.D. and P.M.; writing—original draft preparation, J.M.C. and S.D.; writing—review and editing J.M.C., A.C.R., P.M., S.N. and R.C.A.; funding acquisition, J.M.C. and R.C.A. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data used to support the findings of this study are included in the article.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

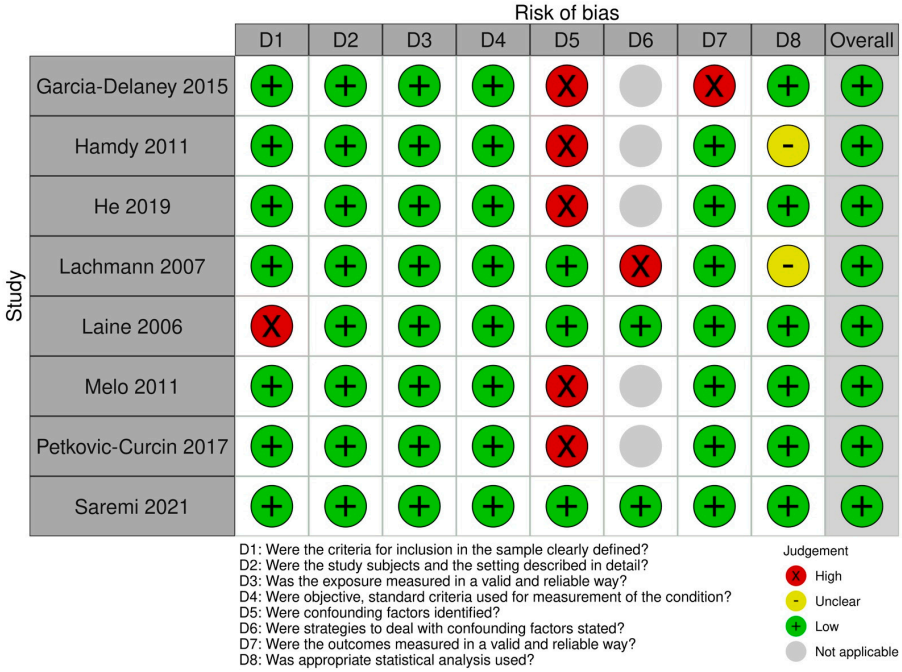

Figure A1. Risk of bias assessment of the included studies. Laine et al., 2006 [21]; Lachmann et al., 2007 [25]; Hamdy et al., 2011 [22]; Melo et al., 2011 [23]; Garcia-Delaney et al., 2015 [33]; Petkovic-Curcin et al., 2017 [34]; He et al., 2019 [24]; Saremi et al., 2021 [26].

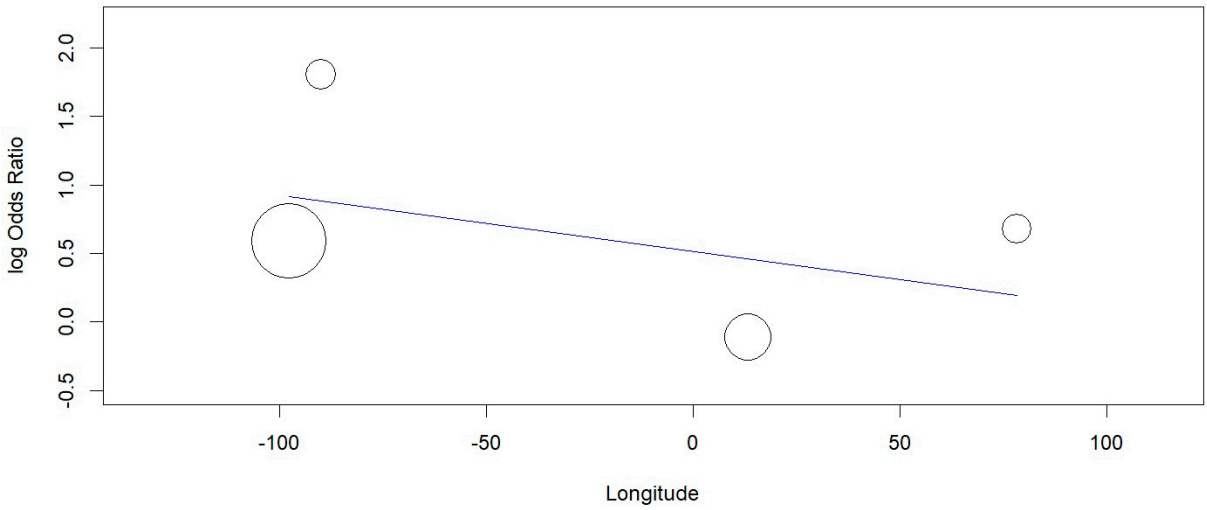

Figure A2. Log OR meta-regression for the IL-1B +3954 polymorphism as a function of the longitude covariate (p-value = 0.295, coefficient = −0.004).

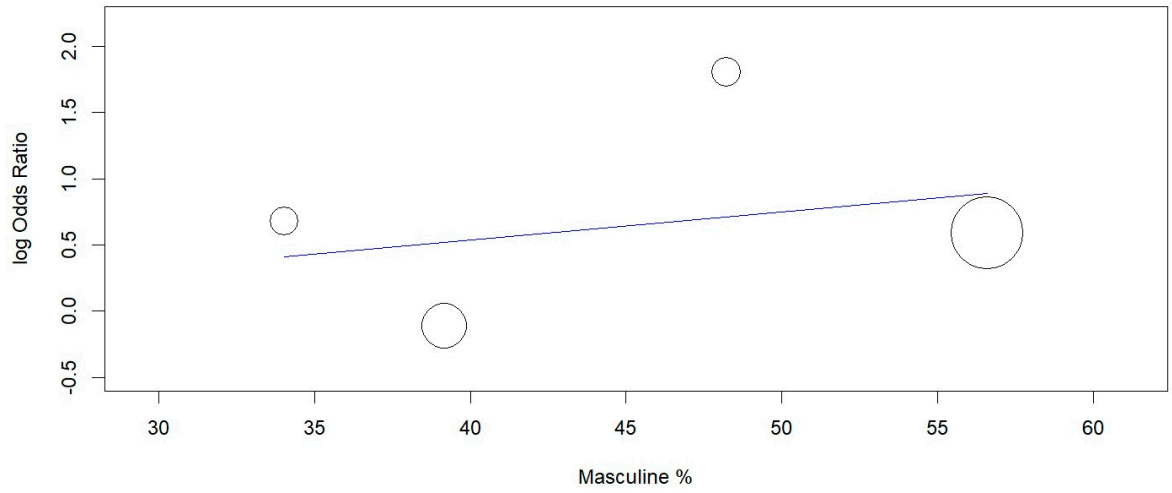

Figure A3. Log OR meta-regression for IL-1B +3954 polymorphism as a function of the covariate percentage of male subjects (p-value = 0.531, coefficient = 0.021).

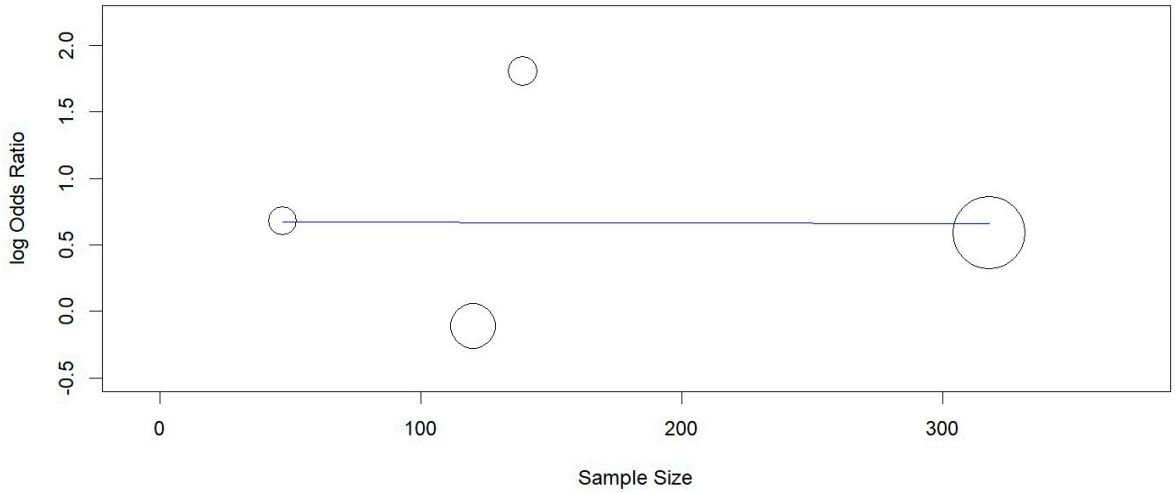

Figure A4. Log OR meta-regression for the IL-1B +3954 polymorphism as a function of sample size (p-value = 0.989, coefficient = −0.000).

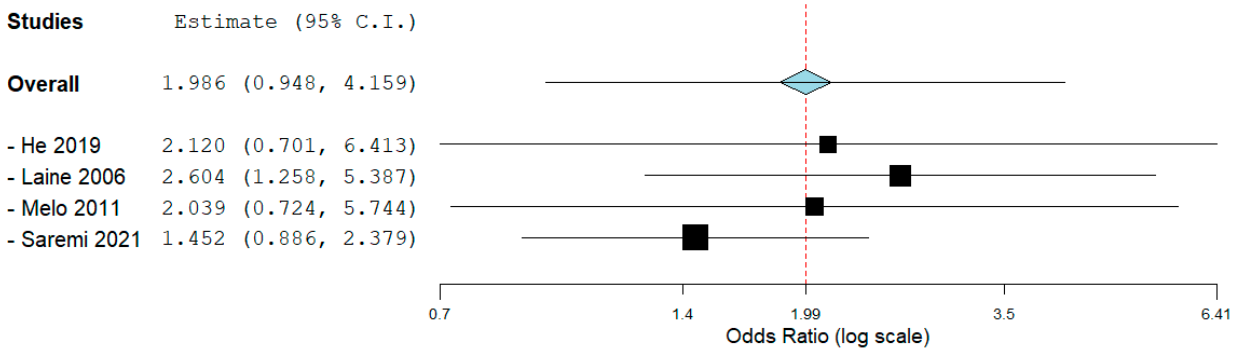

Figure A5. Sensitivity Analysis (CI—confidence interval). Laine et al., 2006 [21]; Melo et al., 2011 [23]; He et al., 2019 [24]; Saremi et al., 2021 [26].

Table A1. Systematic review table relating to the sample characteristics of the different articles.

Year & Author	Latitude; Longitude (Degrees)	Sample Size	M/F (%)	Average Age of the Sample	Mean % of Mutated Allele
Garcia-Delaney, 2015 [33]	32.363890; −86.298190	Total: 54 PI: 27 Control: 27	37/63	53	ND
Hamdy, 2011 [22]	−35.052770; 147.349560	Total: 50 PI: 25 Control: 25	76/24	41	ND
He, 2019 [24]	29.894920; −97.677800	Total: 318 PI: 144 Control: 174	57/43	45	IL-1B +3954: 25.65
Lachmann, 2007 [25]	−13.848923; −171.751145	Total: 29 PI: 11 Control: 18	34/66	66	ND
Laine, 2006 [21]	55.702888; 13.194710	Total: 120 PI: 71 Control: 49	39/61	67	IL-1B +3954: 29.45
Melo, 2011 [23]	17.433660; 78.339010	Total: 47 PI: 16 Control: 31	34/66	46	IL-1B +3954: 33.22
Petkovic-Curcin, 2017 [34]	40.772770; −111.839100	Total: 98 PI: 34 Control: 64	71/29	58 *	ND
Saremi, 2021 [26]	32.331050; −90.170660	Total: 139 PI: 50 Control: 89	49/51	41	IL-1B +3954: 12

ND—non-defined, PI—peri-implantitis group, * In this article, the median age of the sample is exceptionally represented.

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