Long-term Outcomes of Periodontal Regenerative Procedures for the Treatment of Intrabony Periodontal Defects: A Systematic Review and Meta-analysis

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Abstract

Aims: The present systematic review and meta-analysis aimed to evaluate the long-term efficacy of periodontal regenerative procedures for the treatment of intrabony periodontal defects after at least 5 years of follow-up.

Materials and methods: Electronic literature database search was performed in CINAHL, EMBASE, PubMed, and Web of Science. Additionally, a manual search of literature was performed. Studies conducted in human subjects with intrabony periodontal defects treated using periodontal regenerative therapy and a minimum follow-up period of 5-years were included. Studies had to provide quantitative outcomes for change in clinical attachment level (CAL; primary outcome variable), tooth retention, change in pocket probing depth (PPD) or radiographic vertical defect fill. Data from included studies were pooled to estimate effect size.

Results: Thirty-eight citations met the inclusion criteria. Quantitative analysis showed a mean gain in CAL of 3.47 mm ($p<0.001$; 95% CI: 3.13; 3.82) after at least 5 years following therapy. Tooth retention rate was 92.8% (95% CI: 0.91; 0.94) and 87.7% (95% CI: 0.83; 0.91) after at least 5 years and 10 years of follow-up, respectively. The pooled data demonstrated a mean reduction of 4.06 mm in PPD ($p<0.001$; 95% CI: 3.65; 4.48) and a mean radiographic vertical defect fill of 3.69 mm ($p<0.001$; 95% CI: 2.83; 4.55).

Conclusions: Periodontal regenerative procedures for the treatment of intrabony defects result in long-term tooth retention, defect reduction, and lasting improvements in clinical attachment level and pocket probing depth.

Keywords: Guided Tissue Regeneration, Meta-analysis, Periodontal Attachment Loss, Periodontal Diseases, Tooth Loss, Treatment Outcome

Introduction

Periodontitis is characterized by microbial-associated and host-mediated inflammation that results in the loss of tooth-supporting structures (Tonetti *et al.*, 2018). Untreated periodontitis results in further disease progression and ultimately the loss of dentition (Tonetti *et al.*, 2018). This is a dental public health concern as approximately 11% of the world population suffers from severe periodontitis (Kassebaum *et al.*, 2014). The goal of periodontal therapy is to prevent further progression of the disease, and if possible, regenerate the previously lost periodontal tissues. Treatment of periodontitis includes both non-surgical and surgical approaches (Heitz-Mayfield and Lang, 2013). Although periodontal health may be re-established using non-surgical therapy (Heitz-Mayfield and Lang, 2013), this treatment approach has its own limitations (Caffesse *et al.*, 1986). It is well established that in the presence of persistent inflammation and residual deep pockets after non-surgical therapy, periodontal surgical therapy is the subsequent intervention (Rateitschak-Pluss *et al.*, 1992).

Surgical periodontal treatment includes resective and regenerative interventions. Resective treatment is a periodontal surgical technique that involves periodontal

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debridement and resolution of osseous defects (Carnevale and Kaldahl, 2000). A resective treatment approach may prevent further progression of periodontal disease by reducing probing depths and providing more hygienic gingival tissue morphology. However, excessive tissue recession during the surgery may lead to an open furcation, esthetic concerns, and an increase of tooth mobility (Carnevale and Kaldahl, 2000). In addition, resective surgery does not result in periodontal regeneration and re-establishment of the periodontal attachment apparatus. Therefore, several treatment modalities have been developed to achieve periodontal regeneration (Kao *et al*., 2015; Reynolds *et al*., 2015; Wang *et al*., 2005).

Regenerative procedures involve reconstruction of cementum, periodontal ligament (PDL), and alveolar bone around a tooth (Wang *et al*., 2005). Periodontal regeneration can be accomplished by various bone replacement grafting materials, guided tissue regeneration (GTR) with various barrier membranes, application of biological factors, or any combinations of the above (Kao *et al*., 2015; Reynolds *et al*., 2015). Although a variety of regenerative materials and techniques have been utilized for periodontal regeneration, clinicians still face uncertainty regarding the predictably and long-term success of currently available periodontal regenerative modalities.

Previous meta-analysis and systematic reviews have shown promising clinical outcomes for periodontal regenerative approaches using various materials and techniques (Figueira *et al*., 2014; Kao *et al*., 2015; Trombelli *et al*., 2002; Wu *et al*., 2017). However, the majority of the studies that were analyzed in those systematic reviews had short-term follow-ups (Figueira *et al*., 2014; Kao *et al*., 2015; Trombelli *et al*., 2002; Wu *et al*., 2017). It is crucial to assess the long-term success and predictability of regeneration treatment by focusing on studies with long-term follow-ups. Therefore, the objective of this systematic review and meta-analysis was to assess the long-term clinical, radiographic, and patient-centered outcomes of periodontal regenerative approaches for the treatment of intrabony periodontal defects after at least 5 years of follow up.

Materials and methods

The present systematic review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher *et al*., 2015). The study protocol was registered in PROSPERO database (# CRD42019124626). The focus question was defined as "What is the long-term efficacy of periodontal regenerative procedures in adult human subjects for the treatment of intrabony periodontal defects after at least 5 years of follow up in terms of clinical outcomes, radiographic outcomes, and patient-centered outcomes?"

Eligibility criteria

A Participants, Interventions, Comparators, Outcomes, Time-frame (PICOT) framework was used utilizing these elements: (1) Population: studies conducted in adult human subjects presented with intra-bony periodontal defects were included; (2) Intervention: included studies had to have an intervention group consisting of patients with one or multiple periodontal intra-bony defects treated utilizing periodontal regenerative procedures such as guided tissue regeneration, bone replacement grafts, biological agents, or any combinations of the above; (3) Comparator: studies with or without a comparator group were included; (4) Outcome: all included studies had to provide quantitative outcomes for at least one of the following variables: tooth retention, changes in clinical attachment level (CAL), changes in pocket probing depth (PPD), radiographic vertical defect fill, or any patient-centered outcomes; (5) Time-frame: all included studies must have at least five years follow-up period.

All study designs with a comparison from baseline were considered for inclusion in order to present all existing evidence. For studies with multiple groups, only groups where periodontal regenerative procedures had been performed were included.

Exclusion criteria

The exclusion criteria were as follows: a) studies that do not report baseline or follow-up data; b) studies that did not fulfill the definitions for PICOT; c) studies that included same patient population reporting same outcome variable as other included studies; d) studies that included teeth with furcation defects without reporting data independently for intrabony defects; e) studies that did not clearly describe the experimental methodology or outcome parameters; f) *in vitro* studies, animal studies, editorials, reviews, case reports, and non-English citations.

Search strategy

The following electronic databases were searched from the start of the database through January 2019: CINAHL, EMBASE, PubMed, and Web of Science. Details of the electronic search strategy are presented in the supplementary Appendix. To expand the searches, the tables of contents of the following scientific journals were searched from January 1990 to January 2019: *Journal of Dental Research, Journal of Periodontology*, *Journal of Clinical Periodontology*, *Journal of Periodontal Research,* and *International Journal of Periodontics and Restorative Dentistry*. In addition, the reference list of all included articles and relevant narrative or systematic reviews were screened.

Study selection

Two investigators (K.N. and N.E.) independently reviewed the results of the systematic literature search.

Disagreements regarding the inclusion of the studies were resolved through discussion and consensus, and consultation by a third author (S.B.).

Data extraction

Two investigators (K.N. and J. Sze) independently reviewed and extracted data from the included studies using a predetermined data extraction table. Details of the methodology for data extraction are outlined in the supplementary Appendix.

Quality assessment

Risk of bias assessment was performed for randomized controlled trials using the Cochrane Collaboration's revised tool for assessing risk of bias in randomised trials (RoB2) (Sterne *et al*., 2019). These five domains were assessed: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Risk-of-bias judgement for each domine rated as low risk of bias, Some concerns, or high risk of bias. Then, overall risk-of-bias judgement was determined according to the Cochrane Handbook recommendations (Higgins *et al*., 2019). Quality assessment for non-randomized studies was performed using Newcastle-Ottawa Quality Assessment Scale for Cohort studies (Wells *et al*., 2014). This assessment tool appraises the methodological quality of the studies based on three categories of Selection (4 items), Comparability (1 item), and Outcome (3 items). Each citation can receive a maximum of one star for each item within the Selection and Outcome categories, and two stars for the Comparability category. Hence, each included study could receive a maximum of nine stars.

Quantitative analysis

Quantitative analyses were done to pool the data for each outcome variable. The primary outcome variable was the mean changes in CAL. The secondary outcome variables were tooth retention, mean changes in PPD, and mean radiographic vertical defect fill. For the dichotomous outcome variable, the included studies had to report the sample size and the number of events. For continuous outcome variables, the sample size and the mean and standard deviation values at baseline and follow-up examinations had to be reported. All statistical analyses were done using a software package (Comprehensive Meta-Analysis Software Version 3, Biostat Inc., Englewood, NJ, USA).

Data from the included studies were pooled to estimate the effect size. The planned summary measures were event rate for dichotomous outcomes and weighted mean differences and 95% confidence intervals (CI) for continuous outcomes. Cochran-Q statistic and I^2 statistic tests were performed to assess the heterogeneity across studies. Random effect model was used when a significant heterogeneity present across the studies, determining by P value of <0.05 from Cochran-Q statistic and I^2 value of $> 25\%$. Otherwise, a fixed effect model was used to pool data. Fixed effect model was used to perform meta-analysis for the tooth retention variable. Random effect model was used for mean changes in CAL, mean changes in PPD, and mean radiographic vertical defect fill due to the presence of significant heterogeneity. Forest plots were produced to graphically represent individual and combined effect sizes.

Subgroup analyses were also performed to compare the outcomes of randomized clinical trials with those of non-randomized studies. Sensitivity analyses were done to assess the effects of the inclusion of non-randomized studies on the outcomes of this study. The effect size was estimated after excluding the studies with non-randomized design. Potential publication bias for each outcome variable was assessed using the funnel plots and Begg and Mazumdar rank correlation test.

Results

Study Selection

A flow diagram of the literature search results is illustrated in Figure 1. The electronic and manual literature search identified a total of 1,906 articles. 1,719 citations were excluded after screening of titles and abstracts. The full-text of the remaining 187 articles were reviewed, and 38 articles met the inclusion criteria (Tables 1 and 2; studies 1-38).

Study Characteristics

Characteristics of the included studies are presented in Table 1 and Table 2. Seventeen studies were randomized clinical trials (studies 2, 5, 6, 7, 12, 13, 14, 15, 18, 19, 24, 25, 26, 27, 30, 31, 35), thirteen studies had a prospective design (studies 1, 3, 8, 9, 11, 16, 17, 21, 22, 28, 29, 37, 38), and eight studies had a retrospective design (studies 4, 10, 20, 23, 32, 33, 34, 36). The majority of studies were conducted in Europe, and in academic settings. Sixteen studies were supported by non-industrial funding sources, (studies 1, 2, 5, 7, 13, 14, 15, 20, 25, 26, 28, 31, 34, 35, 36, 38) eight studies were partially or completely supported by industrial funding sources (studies 6, 9, 11, 12, 16, 18, 27, 33), and the other studies did not report the funding sources. The follow-up period of all included studies ranged from 5 years to 20 years.

Smoker subjects were included in eighteen studies (studies 2, 5, 6, 7, 8, 15, 16, 17, 20, 21, 25, 26, 31, 33, 34, 35, 36, 37). The morphology of the treated defects were reported in twenty three studies (studies 5, 9, 10, 11, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 36), while the other studies did not provide information on this variable.

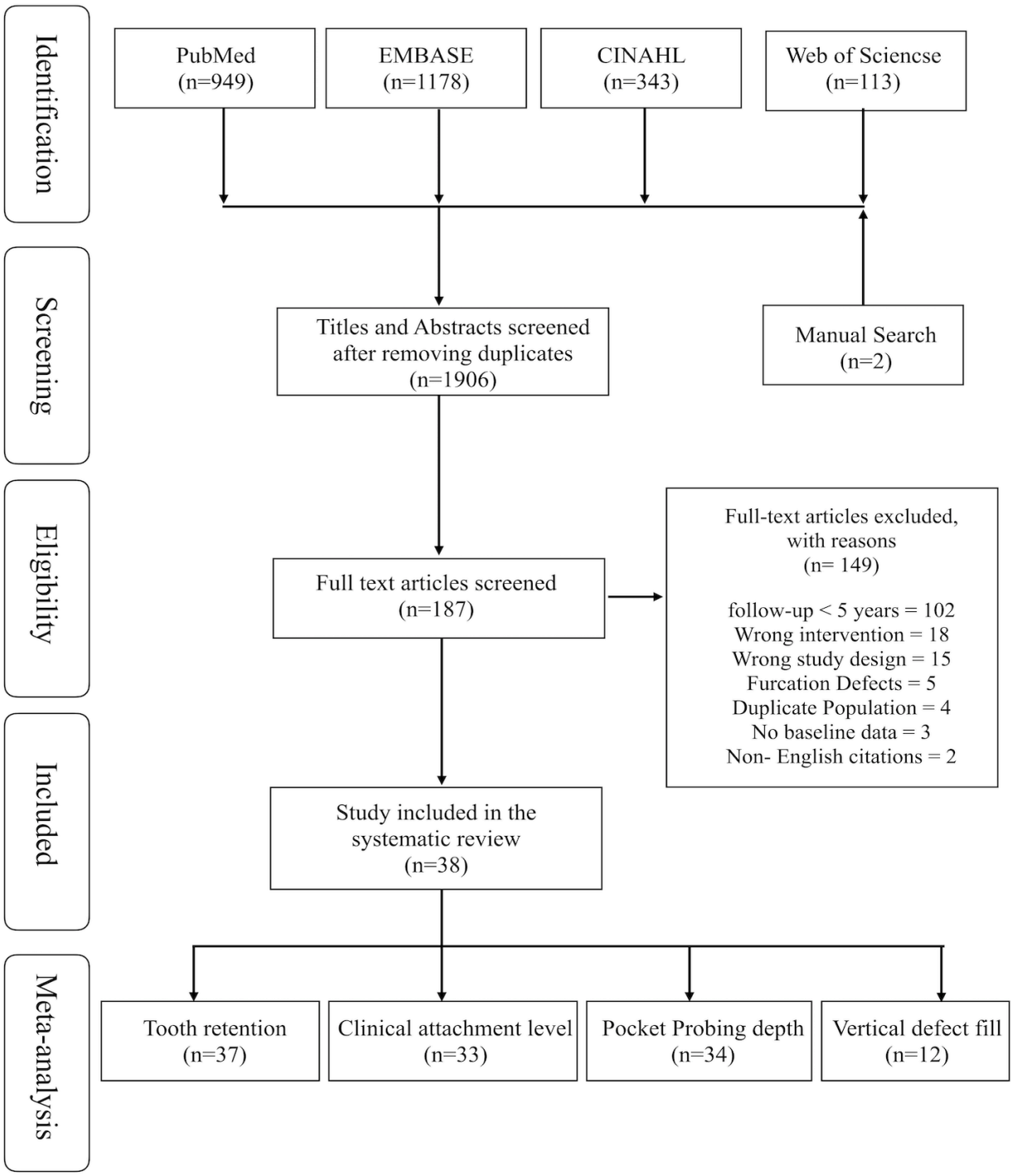

Figure 1. Study selection flow diagram.

Eight studies conducted periodontal regenerative therapy using barrier membranes only (studies 1, 2, 3, 4, 5, 6, 7, 8), three studies used bone replacement grafts only (studies 9, 10, 11), and seven studies used both barrier membranes and bone replacement grafts (studies 12, 13, 14, 15, 16, 17, 18). Four studies applied biological factors only (studies 19, 20, 21, 22), three studies used barrier membranes and biological factors (studies 23, 24, 25), four studies used bone replacement grafts and biological factors (studies 26, 27, 28, 29), and three studies used barrier membranes, bone replacement grafts, and biological factors (studies 30, 31, 32). The remaining six studies were conducted using combination periodontal regenerative therapies (studies 33, 34, 35, 36, 37, 38).

Administration of prophylactic antibiotics prior to regenerative therapy was reported in seven studies (studies 4, 7, 8, 17, 18, 31, 37). Primary wound closure was achieved in twenty-two studies (studies 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 13, 17, 18, 20, 22, 24, 25, 30, 31, 32, 36, 37), while the remaining studies did not report information on primary closure achievement. Maintenance protocol was reported in all included studies.

Table 1. Characteristic of included studies: study characteristics and patient characteristics

Study Characteristics							Patients characteristics				
#	Study and Year	Study Design	Country	Setting	Funding	Follow-up (yr)	Groups	# of Patients	Mean Age ± SD (yr)	Smokers (n)	# of M/F
Periodontal regenerative therapy using barrier membrane only											
1	Cortellini *et al*. 1999	Prosp	Italy	NR	Non-ind	5.6 + 1.6[a]	G	16	49.6 + 7.7	0	5/11
2	Cortellini *et al*. 2017	RCT; P	Italy	NR	Non-ind	20	G1	15	39.3 ± 6.4	2	5/10
							G2	15	43.7 + 9.6	2	9/6
3	Eickholz *et al*. 2002	Prosp	Germany	Acad	NR	5	G	NR	NR	NR	NR
4	Eickholz *et al*. 2007	Retro	Germany	Acad	NR	5	G	37	NR	NR	NR
5	Nickles *et al*. 2009	RCT	Germany	Acad	Non-ind	10 ± 1	G	16	NR	4	8/8
6	Pretzl *et al*. 2008	RCT; SM	Germany	Acad	Ind-assoc	10 ± 0.5	G1 G2	12	46.1 ± 10.1	3	3/9
7	Pretzl *et al*. 2009	RCT; SM	Germany	Acad	Non-ind	10 ± 0.5	G1 G2	15	42.1 ± 12.8	3	3/12
8	Stavropoulos *et al*. 2004	Prosp	Denmark	Acad	NR	6-7	G	21	41	8	10/11
Periodontal regenerative therapy using bone replacement grafts only											
9	De Bruyckere *et al*. 2018	Prosp	Belgium	Acad and PP	Ind-assoc	5	G	95	NR	0	NR
10	Persson *et al*. 2000	Retro	USA	Acad	NR	9.7 ± 3.6	G	24	NR	NR	NR
11	Yukna *et al*. 1998	Prosp	USA	PP	Ind	5-6.5	G	22	NR	NR	NR
Periodontal regenerative therapy using barrier membrane and bone replacement grafts											
12	Mengel *et al*. 2006	RCT; SM	Germany	Acad	Ind	5	G1 G2	16	45	0	5 /11
13	Nygaard-Ostby *et al*. 2010	RCT; P	Norway	PP	Non-ind	10	G1	20	53.7 ± 1.4	0	11/9
							G2	20	52.6 ± 1.5	0	9 /11
14	Orsini *et al*. 2008	RCT; SM	NR	NR	Non-ind	6	G1 G2	12	42	0	7/5

Table 1 continued overleaf...

Table 1 continued...

15	Sculean *et al*. 2007a	RCT; P	Germany	Acad	Non-ind	5	G	14	NR	2	NR
16	Slotte *et al*. 2007	Prosp	Sweden	Acad	Ind-assoc	5	G	24	57 ± 9	8	11/13
17	Stavropoulos *et al*. 2005	Prosp	Denmark	Acad	NR	5	G	15	NR	5	NR
18	Stavropoulos *et al*. 2010	RCT; P	Denmark	Acad	Ind-assoc	6	G1 G2 G3	15 15 15	NR	NR	NR
Periodontal regenerative therapy using biological factors only											
19	Bhutda *et al*. 2013	RCT; SM	India	Acad	NR	5	G	15	40.66 ± 2.96	0	NR
20	Farina *et al*. 2007	Retro	Italy	Acad	Non-ind	6-8	G	6	NR	1	NR
21	Heden *et al*. 2006	Prosp	Sweden	Acad	NR	5	G	114	56.65[a]	33a	59/55[a]
22	Sculean *et al*. 2007b	Prosp	NR	NR	NR	9	G	21	43 ± 8.5	0	NR
Periodontal regenerative therapy using barrier membrane and biological factors											
23	Mitani *et al*. 2015	Retro	Japan	Acad	NR	5	G1 G2	12 12	44.3 ± 3.5 45.5 ± 3.3	0 0	2/10 3/9
24	Sculean *et al*. 2006	RCT; SM	Germany	Acad	NR	8	G1 G2	16	NR	0	10/6
25	Sculean *et al*. 2008b	RCT; P	Germany	Acad	Non-ind	10	G1 G2 G3	14 14 14	NR	3 3 4	NR
Periodontal regenerative therapy using bone replacement grafts and biological factors											
26	Dori *et al*. 2013a	RCT: P	Hungary	Acad	Non-ind	10	G1 G2	12 12	NR NR	1 1	8/16
27	Dori *et al*. 2013b	RCT; P	Hungary	Acad	Ind-assoc	5	G1 G2	13 13	NR	0 0	12/14
28	Okuda *et al*. 2013	Prosp	Japan	Acad	Non-ind	5	G	25	NR	0	NR
29	Sculean *et al*. 2008a	Prosp	NR	NR	NR	5	G	11	45.8 ± 14	0	4 /7

Table 1 continued overleaf...

Table 1 continued...

Periodontal regenerative therapy using barrier membrane, bone replacement grafts and biological factors											
30	Ceteinkaya *et al*. 2014	RCT; SM	Turkey	Acad	NR	5	G1 G2	15 15	NR	0	NR
31	Cieplik *et al*. 2018	RCT; SM	Germany	Acad	Non-ind	13	G1 G2	25	42b	5	10/15
32	De Sanctis *et al*. 2013	Retro	Italy	Acad	NR	7-18	G1	47	NR	NR	NR
							G2	34	NR	NR	NR
							G3	56	NR	NR	NR
Combination periodontal regenerative therapies											
33	Broseler *et al*. 2017	Retro	Germany	PP	Ind	5-10	G	176	49.9	44	80/96
34	Cortellini *et al*. 2004	Retro	Italy	NR	Non-ind	8 + 3.4	G	175	44.5 ±10.2	56	75/100
35	Cortellini *et al*. 2011	RCT; P	Italy	PP	Non-Ind	5	G	25	46.3 ± 8.9	2	10/15
36	Nickles *et al*. 2017	Retro	Germany	Acad	Non-ind	5	G	41	62 b	6	24/17
37	Roccuzzo *et al*. 2018	Prosp	Italy	PP	NR	10	G	48	44.3 ± 8.5	4	20/28
38	Silvestri *et al*. 2011	Prosp	Italy	PP	Non-ind	9	G	84	48 ± 5.6	NR	32/52

[a] Calculated by the authors based on the number of patient/sites that completed at least a five-year follow-up
[b] Median range; mean age was not reported
F: female; G: group; M: male; n: number; NR: not reported; SD: standard deviation; yr: year
Design: P: parallel group design; Prosp: prospective; RCT: randomized controlled trial; Retro: retrospective; SM: split-mouth design
Setting: Acad: academic setting; PP: private practice setting
Funding: Ind: industry supported; Ind- assoc: industry Associated; Non-ind: non-Industry

Table 2. Characteristic of included studies: defect characteristics and surgical considerations

#	Study and Year	Groups	Defect Characteristics: No. of defects: Baseline	Follow-up	Extracted	Drop-out	Location	Type of teeth	Morphology (n)	Surgical Considerations: Pre-op antibiotics	Grafting material	Membrane	Biologic factors	Root Conditioning	Primary closure	Maintenance protocol
Periodontal regenerative therapy using barrier membrane only																
1	Cortellini *et al*. 1999	G	16	11 a	0	5	Both	All	NR	NR	No	Non-R	No	No	Yes	Yes
2	Cortellini *et al*. 2017	G1	15	14	0	1	Both	All	NR	NR	No	Non-R	No	NR	Yes	Yes
		G2	15	13	0	2				NR	No	Non-R	No	NR	Yes	Yes
3	Eickholz *et al*. 2002	G	16	16	0	0	Both	NR	NR	NR	No	R (n=9); Non-R (n=7)	No	NR	Yes	Yes
4	Eickholz *et al*. 2007	G	60	50	2	8	Both	All	NR	Yes	No	R (n=11) Non-R (n=39)	No	NR	Yes	Yes
5	Nickles *et al*. 2009	G	23	18	4	1	Both	All	3-wall (NR), 2-wall (NR)	NR	No	R	No	NR	Yes	Yes
6	Pretzl *et al*. 2008	G1	12	7	1	4	Both	All	NR	NR	No	Non-R	No	NR	Yes	Yes
		G2	12	8	1	3				NR	No	R	No	NR	Yes	Yes
7	Pretzl *et al*. 2009	G1	15	9	2	4	Both	All	NR	Yes	No	R	No	NR	Yes	Yes
		G2	15	11	0	4				Yes	No	R	No	NR	Yes	Yes
8	Stavropoulos *et al*. 2004	G	28	25	3	0	NR	NR	NR	Yes	No	R	No	NR	Yes	Yes
Periodontal regenerative therapy using bone replacement grafts only																
9	De Bruyckere *et al*. 2018	G	95	71	0	24	Both	All	3-wall (NR), 2-wall (NR), 1-wall (NR)	NR	XG	No	No	No	Yes	Yes
10	Persson *et al*. 2000	G	24	17	0	7	NR	NR	3-wall (NR), 2-wall (NR)	NR	Al	No	No	NR	NR	Yes
11	Yukna *et al*. 1998	G	NR	20	0	NR	NR	NR	3-wall (NR), 2-wall (NR), 1-wall (NR)	NR	AP	No	No	Yes	Yes	Yes
Periodontal regenerative therapy using barrier membrane and bone replacement grafts																
12	Mengel *et al*. 2006	G1	22	22	0	0	NR	All	NR	No	No	R	No	NR	NR	Yes
		G2	20	20	0	0				No	AP	No	No	NR	NR	Yes

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Table 2 continued...

13	Nygaard-Ostby *et al*. 2010	G1	20	13	2	5	Both	Non-M	NR	NR	Auto	No	No	NR	Yes	Yes
		G2	20	13	1	6				NR	Auto	R	No	NR	Yes	Yes
14	Orsini *et al*. 2008	G1	12	12	0	0	Both	NR	3-wall (NR), 2-wall (NR)	NR	Auto and AP	No	No	NR	NR	Yes
		G2	12	12	0	0				NR	Auto	R	No	NR	NR	Yes
15	Sculean *et al*. 2007a	G	14	10	0	4	Both	NR	3-wall (1), 2-wall (7), 1-2 wall (2)	NR	XG	R	No	No	NR	Yes
16	Slotte *et al*. 2007	G	24	24	0	0	Both	All	3-wall (4), 2-wall (9), 1-wall (11)	No	XG	R	No	NR	NR	Yes
17	Stavropoulos *et al*. 2005	G	15	11	2	2	NR	NR	2-wall (11), 1-wall (4)	Yes	XG	R	No	NR	Yes	Yes
18	Stavropoulos *et al*. 2010	G1	15	12	0	3	Both	NR	mainly 2-wall (NR) and 1-wall (NR)	Yes	No	R	No	NR	Yes	Yes
		G2	15	10	1	4				Yes	XG	R	No	NR	Yes	Yes
		G3	15	11	2	2				Yes	XG	R	No	NR	Yes	Yes
Periodontal regenerative therapy using biological factors only																
19	Bhutda *et al*. 2013	G	15	15	0	0	Man	PM, M	3-wall (8), 2-wall (5), combined (2)	NR	No	No	EMD	Yes	NR	Yes
20	Farina *et al*. 2007	G	6	6	0	0	NR	Non-M	NR	NR	No	No	EMD	Yes	Yes	Yes
21	Heden *et al*. 2006	G	146	102	28	16	Both	All	3-wall (6%), 2-wall (56%), 1-wall (38%)	NR	No	No	EMD	Yes	NR	Yes
22	Sculean *et al*. 2007b	G	26	26	0	0	Both	All	3-wall (2), 2-wall (16), 1-2 wall (6), 1-wall (2)	NR	No	No	EMD	Yes	Yes	Yes
Periodontal regenerative therapy using barrier membrane and biological factors																
23	Mitani *et al*. 2015	G1	15	15	0	0	NR	All	3-wall (7), 2-wall (8)	NR	No	No	EMD	Yes	NR	Yes
		G2	13	13	0	0			3-wall (4), 2-wall (9)	NR	No	Non-R	No	NR	NR	Yes
24	Sculean *et al*. 2006	G1	16	10	0	6	NR	NR	3-wall (1), 2-wall (8), 1-wall (1)	NR	No	No	EMD	Yes	Yes	Yes
		G2	16	10	0	6			3-wall (2), 2-wall (7), 1-wall (1)	NR	No	R	No	NR	Yes	Yes

Table 2 continued overleaf...

Table 2 continued...

		G1	14	10	0	4			3-wall (1), 2-wall (6), 1-2 wall (3)	NR	No	No	EMD	Yes	Yes	Yes
25	Sculean *et al*. 2008b	G2	14	10	0	4	NR	NR	3-wall (1), 2-wall (6), 1-2 wall (3)	NR	No	R	No	NR	Yes	Yes
		G3	14	9	0	5			3-wall (1), 2-wall (7), 1-2 wall (1)	NR	No	R	EMD	Yes	Yes	Yes
26	Dori *et al*. 2013a	G1	12	11	0	1	Both	All	3-wall (2), 2-wall (8), 1- to 2- wall (1)	NR	XG	No	EMD	Yes	NR	Yes
		G2	12	11	0	1			3-wall (3), 2-wall (7), 1- to 2- wall (1)	NR	AP	No	EMD	Yes	NR	Yes
27	Dori *et al*. 2013b	G1	13	12	0	1	Both	All	2-wall (6), 1- to 2- wall (6)	NR	XG	No	EMD and PRP	Yes	NR	Yes
		G2	13	12	0	1			2-wall (5), 1- to 2- wall (7)	NR	XG	No	EMD	Yes	NR	Yes
28	Okuda *et al*. 2013	G	25	22	0	3	Both	NR	3-wall (14), 2-wall (3), 1-wall (5)	NR	AP and Auto cell sheets	No	PRP	NR	NR	Yes
29	Sculean *et al*. 2008a	G	11	11	0	0	Both	All	2-wall (NR), 1-wall (NR)	NR	XG	No	EMD	Yes	NR	Yes
Periodontal regenerative therapy using barrier membrane, bone replacement grafts and biological factors																
30	Ceteinkaya *et al*. 2014	G1	15	11	0	4	Both	PM, M	3-wall (3), 2-wall (8)	NR	No	R	PRP	NR	Yes	Yes
		G2	15	11	0	4			3-wall (4), 2-wall (7)	NR	AP	R	No	NR	Yes	Yes
31	Cieplik *et al*. 2018	G1	25	19	3	3	Both	All	3-wall (11), 2-wall (4), 1-wall (0), combined (10)	Yes	AP	R	No	Yes	Yes	Yes
		G2	25	18	4	3			3-wall (11), 2-wall (3), 1-wall (0), combined (11)	Yes	AP	R	PRP	Yes	Yes	Yes
32	De Sanctis *et al*. 2013	G1	47	47	0	0	Both	NR	NR	NR	No	Non-R	No	No	Yes	Yes
		G2	34	34	0	0				NR	No	No	EMD	Yes	Yes	Yes
		G3	56	56	0	0				NR	XG (NR); AP (NR)	No	EMD	Yes	Yes	Yes
Combination periodontal regenerative therapies																
33	Broseler *et al*. 2017	G	1008	378	27	603	NR	NR	2-wall (73.5%), 1-wall (26.5%)	NR	XG	No (46.13%); R (53.87%)	No (89.98%); EMD (10.02%)	NR	NR	Yes

Table 2 continued overleaf...

Table 2 continued...

34	Cortellini *et al*. 2004	G	175	155a	4	16	Both	NR	NR	NR	No (NR); AP (NR)	R (NR); Non-R (NR)	No	NR	NR	Yes
35	Cortellini *et al*. 2011	G	25	23	2	0	Both	All	NR	NR	No (n=16); AP (n=5); XG (n=4)	No (n=15); R (n=8); Non-R (n=2)	No (n=8); EMD (n=17)	No (n=8); Yes (n=17)	NR	Yes
36	Nickles *et al*. 2017	G	41	41	0	0	Both	All	3-wall (NR), 2-wall (NR), 1-wall (NR)	NR	No (n=38); XG (n=3)	No (n=39); R (n=1); Non-R (n=1)	No (n=3); EMD (n=38)	No (n=3); Yes (n=38)	Yes	Yes
37	Roccuzzo *et al*. 2018	G	48	35	1	12	Both	Non-M	NR	Yes	No (n=5); XG (n=31)	No (n=29); R (n=7)	EMD	Yes	Yes	Yes
38	Silvestri *et al*. 2011	G	120	92a	4	24	Both	All	NR	NR	No (n=54); Auto (n=5);XG (n=41); NR (n=20)	No (n=47); R (n=46); Non-R (n=7); NR (n=20)	No (n=53); EMD (n=67)	NR	NR	Yes

[a] Calculated by the authors based on the number of patient/sites that completed at least a five-year follow-up
G: group; NR: not reported;
Location: Both: both maxilla and mandible; Mand: mandible
Type of teeth: All: all type of teeth included; M: Molars; Non-M: non-molars; P: premolars
Grafting material: Al: allograft; AP: alloplast; Auto: autologous graft; XG: xenograft
Membrane: Non-R: non-resorbable; R: resorbable
Growth factor: EMD: Enamel Matrix Derivative; PRP: platelet-rich plasma

Quality assessment

The results of quality assessment for the included studies are presented in Table 3, Table 4, and the Appendix.

Quantitative Analyses

Meta-analyses were possible to perform for the following outcome variables: tooth retention (37 studies), changes in CAL (primary outcome variable; 33 studies), changes in PPD (34 studies), and radiographic vertical defect fill (12 studies). No study report data on patient-centered outcomes.

Tooth retention

Tooth retention data was reported in 37 studies with 55 periodontal regenerative treatment groups. In total, periodontal regeneration procedures were performed for 2565 teeth with intrabony defects in 1492 patients at the baseline. After a minimum of 5 years follow-up period, 1747 teeth were re-evaluated. 1665 teeth that were treated with periodontal regeneration procedures were retained, while 82 teeth were extracted. Quantitative analysis revealed a tooth retention rate of 92.8% for periodontal regenerative procedures after at least 5 years follow-up (Figure 2A; Event rate=0.928; 95%CI=0.91-0.94; heterogeneity I^2<0.001%; τ<0.001; fixed model).

The effect of the study design on the 5-year tooth retention outcomes was assessed in the sub-group analysis. 17 randomized clinical trials with 32 periodontal regenerative treatment groups and 20 non-randomized studies with 23 treatment groups were compared. The subgroup analysis demonstrated that tooth retention rate was 90.8% for randomized clinical trials (Appendix Figure 1; Event rate=0.908; 95%CI=0.87-0.93) and 93.6% for non-randomized studies (Appendix Figure 2; Event rate=0.936; 95%CI=0.92-0.95). This difference was not statistically significant between randomized clinical studies and non-randomized studies (p=0.082).

Eleven studies with 19 periodontal regenerative treatment groups provide the data on tooth retention after at least 10 years of follow-up. In these studies,

Table 3. Summary of risk of bias assessment for the included randomized controlled studies using Cochrane Collaboration's tool for assessing risk of bias.

Study	Randomisation	Deviations from Intended interventions	Missing Data	Measurement of outcome	Selection of reported result	Overall risk of Bias
Bhutda *et al*. 2013	low	low	low	Some concerns	low	Some concerns
Ceteinkaya *et al*. 2014	low	low	low	low	low	low
Cieplik *et al*. 2018	low	low	low	low	low	low
Cortellini *et al*. 2011	low	low	low	Some concerns	low	Some concerns
Cortellini *et al*. 2017	low	low	low	low	low	low
Dori *et al*. 2013a	low	low	low	low	low	low
Dori *et al*. 2013b	low	low	low	low	low	low
Mengel *et al*. 2006	low	low	low	low	low	low
Nickles *et al*. 2009	Some concerns	low	low	Some concerns	low	Some concerns
Nygaard-Ostby *et al*. 2010	low	low	low	low	low	low
Orsini *et al*. 2008	low	low	low	Some concerns	low	Some concerns
Pretzl *et al*. 2008	low	low	low	Some concerns	low	Some concerns
Pretzl *et al*. 2009	low	low	low	low	low	low
Sculean *et al*. 2006	Some concerns	low	low	low	low	Some concerns
Sculean *et al*. 2007a	low	low	low	low	low	low
Sculean *et al*. 2008b	low	low	low	low	low	low
Stavropoulos *et al*. 2010	low	low	low	low	low	low

Table 4. Summary of the quality assessment for the included non-randomized controlled studies using Newcastle-Ottawa quality assessment scale

Studies	Selection				Comparability	Outcome			Total (9 Max)
	Item 1	Item 2	Item 3	Item 4	Item 1	Item 1	Item 2	Item 3	
Broseler *et al*. 2017	*		*	*		*	*		5
Cortellini *et al*. 1999	*		*	*	**	*	*		7
Cortellini *et al*. 2004	*		*	*	**	*	*	*	8
De Bruyckere *et al*. 2018	*		*	*	**	*	*		7
De Sanctis *et al*. 2013	*		*	*		*	*	*	6
Eickholz *et al*. 2002	*		*	*		*	*		5
Eickholz *et al*. 2007	*		*	*	*	*	*		6
Farina *et al*. 2007	*		*	*		*	*	*	6
Heden *et al*. 2006	*		*	*		*	*		5
Mitani *et al*. 2015	*		*	*	**	*	*	*	8
Nickles *et al*. 2017	*		*	*	**	*	*	*	8
Okuda *et al*. 2013	*		*	*	**	*	*		7
Persson *et al*. 2000	*		*	*	*	*	*		6
Roccuzzo *et al*. 2018	*		*	*	**	*	*		7
Sculean *et al*. 2007b	*		*	*	**	*	*	*	8
Sculean *et al*. 2008a	*		*	*	**	*	*	*	8
Silvestri *et al*. 2011	*		*	*	**	*	*		7
Slotte *et al*. 2007	*		*	*		*	*	*	6
Stavropoulos *et al*. 2004	*		*	*	*	*	*	*	7
Stavropoulos *et al*. 2005	*		*	*	*	*	*		6
Yukna *et al*. 1998	*		*	*	*	*	*		6

606 teeth with intrabody defects in 511 subjects were treated using periodontal regeneration procedures. After at least 10 years follow-up, 351 teeth were re-examined. 317 teeth were retained, while 34 teeth were lost. Quantitative analysis revealed a tooth retention rate of 87.7% after at least a 10 years follow-up period (Figure 2B; Event rate=0.877; 95%CI=0.83-0.91; heterogeneity I^2<0.001%; τ<0.001; fixed model). The subgroup analysis found that the tooth retention rate in eight randomized clinical trials with 16 periodontal regenerative treatment groups was 88.2% (Appendix Figure 3; Event rate=0.882; 95%CI=0.83-0.92). The tooth retention rate for three included non-randomized studies was 86.9% (Appendix Figure 4; Event rate=0.869; 95%CI=0.80-0.92). The sub-group analysis found no significant differences for this variable between randomized clinical trials and non-randomized studies (p=0.729).

Changes in clinical attachment level (Primary outcome variable)

Data on the mean changes in CAL (Primary outcome variable) were reported in 33 articles with 51 periodontal regenerative treatment groups. A total of 1131 teeth with intrabony defects were treated with periodontal regenerative procedures at baseline, and 1075 teeth were examined after at least 5 years of follow-up. The meta-analysis revealed that the CAL significantly increased after at least 5 years of follow-up compared to the baseline (p<0.001). The weighted mean gain in CAL was 3.47 mm (Figure 3; 95%CI=3.13-3.82; heterogeneity I^2=83.25%; τ=1.09; random effect model).

The sub-group analysis was performed to assess the effect of the study design on the outcome of the analysis for changes in CAL. Seventeen randomized clinical trials with 32 periodontal regenerative treatment groups and 16 non-randomized studies with 19 treatment groups were compared. The subgroup analysis demonstrated that weighted mean gain in CAL was 3.28 mm for randomized clinical trials (Appendix Figure 5; p<0.001; 95%CI=2.88-3.68), and it was 3.76 mm for non-randomized studies (Appendix Figure 6; p<0.001; 95%CI=3.24-4.27). No statistically significant differences were found for this variable between randomized clinical trials and non-randomized studies (p=0.154).

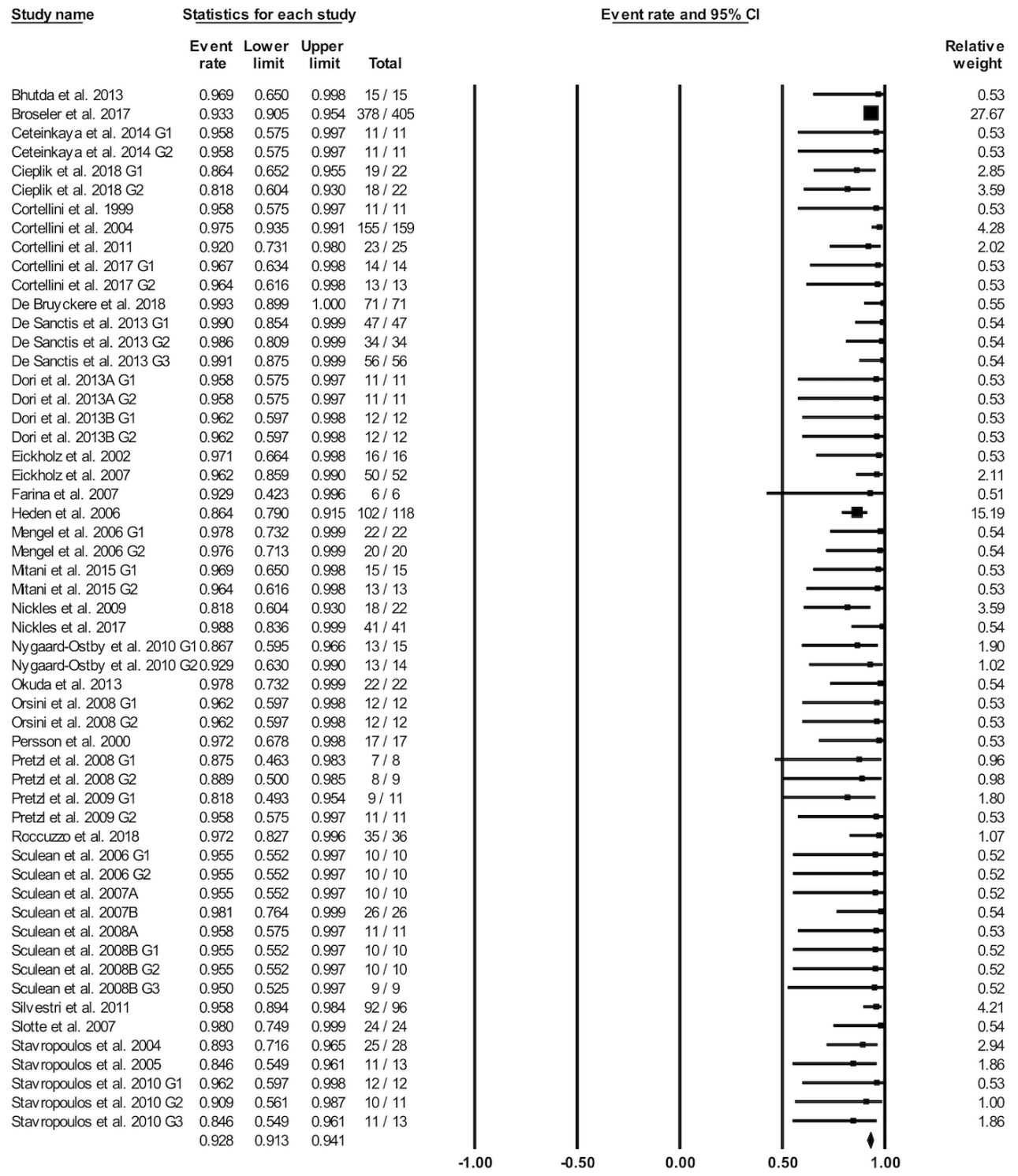

Figure 2A. Forest plot for tooth retention after at least 5 years following periodontal regenerative procedures

Changes in pocket probing depth

Thirty-four included studies with 52 periodontal regenerative treatment groups reported the PPD measurements. In total, 2055 teeth with intrabony defects received periodontal regenerative treatment at baseline, and 1397 teeth were assessed after at least 5 years. The pooled data demonstrated a mean reduction of 4.06 mm in PPD after a minimum of five years following periodontal regenerative procedures (Figure 4A; $p<0.001$; 95%CI=3.65-4.48; heterogeneity $I^2=93.69\%$; $\tau=1.43$; random effect model).

The quantitative data on PPD was reported in 17 randomized clinical trials with 32 regenerative treatment groups and in 17 non-randomized studies with 20 groups. Sub-group analysis revealed that there were no statistically significant differences in PPD between the two study designs ($p=0.711$). The weighted mean reduction in PPD was found to be 4.0 mm for randomized clinical studies (Appendix Figure 7; $p<0.001$; 95%CI=3.54-4.46) and 4.16 mm for non-randomized studies (Appendix Figure 8; $p<0.001$; 95%CI=3.44-4.88).

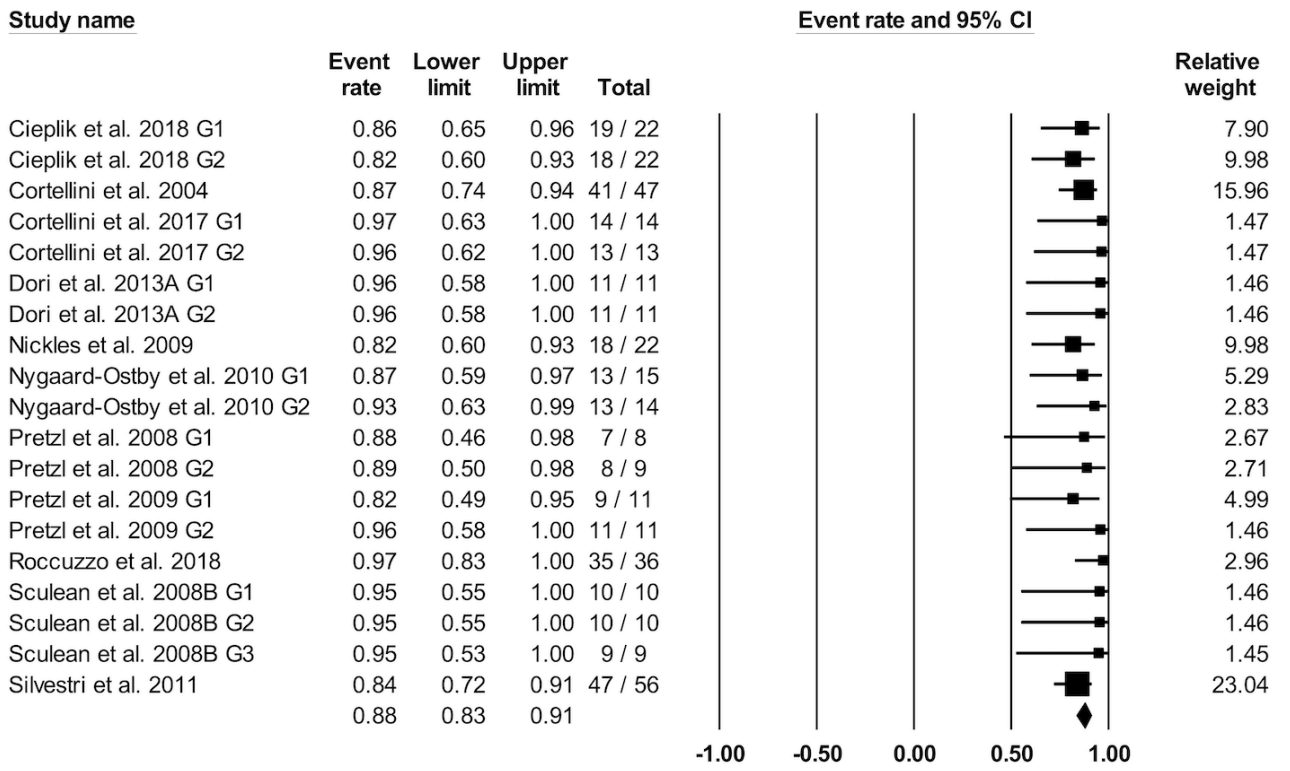

Figure 2B. Forest plot for tooth retention after at least 10 years following periodontal regenerative procedures

Radiographic vertical defect fill

The quantitative data for radiographic vertical defect fill was reported in 12 studies with 16 periodontal regenerative treatment groups. These studies included a total of 1337 teeth with intrabony defects at baseline that were treated using periodontal regenerative modalities. After a minimum of 5 years follow-up period, 544 teeth were re-examined. The quantitative analysis found a mean vertical defect fill of 3.69 mm in intrabony defects treated with periodontal regenerative procedures after at least 5 years post-operatively (Figure 4B; $p<0.001$; 95%CI=2.83-4.55; heterogeneity $I^2=91.33\%$; $\tau=1.49$; random effect model).

Among the included studies for this analysis, five were randomized clinical trials with nine periodontal regenerative treatment groups, and seven were non-randomized studies with seven treatment groups. No statistically significant differences in radiographic vertical defect fill were found between the two study designs ($p=0.647$). After at least 5 years follow-up period, the weighted mean radiographic defect fill was 3.85 mm for randomized clinical trials (Appendix Figure 9; $p<0.001$; 95%CI=1.83-5.87) κττand 3.33 mm for non-randomized studies (Appendix Figure 10; $p< 0.001$; 95%CI=2.36-4.29).

Sensitivity analysis and publication bias

The results of sensitivity analyses showed that excluding retrospective and prospective non-randomized studies did not substantially change the estimates of effect to the extent that affect the study conclusions (Appendix 1). The results of publication bias assessment are presented in the Appendix.

Discussion

The present study evaluated the long-term outcomes of periodontal regeneration procedures after at least 5 years following the intervention. Several systematic reviews and meta-analyses have assessed the efficacy of periodontal regenerative procedures by including the studies with varying follow-up durations (Trombelli *et al.*, 2002; Wu *et al.*, 2017).

A meta-analysis assessing the long-term efficacy of periodontal regenerative procedures by including studies with a minimum follow-up period of six months (Wu *et al.*, 2017). They found that the CAL gain and PPD reduction achieved after periodontal regenerative procedures can be maintained up to 5–10 years, which supports the findings of the present study. However, they reported that the confidence intervals for these variables increased with the length of follow-up period due to the limited number of included studies with reported long-term results. It should be noted that only 5 out of 52 included studies had at least 5-year follow-up period. All those five studies are also included in the present meta-analysis (Bhutda and Deo, 2013; Nickles *et al.*, 2009; Sculean *et al.*, 2008b; Sculean *et al.*, 2007a; Sculean *et al.*, 2006). Another systematic review published by Trombelli and colleagues in 2002 evaluated the short-term and long-term clinical and patient-centered outcomes of periodontal regenerative therapy for the treatment of intrabony periodontal defects (Trombelli *et al.*, 2002). The long-term outcomes were considered those that measured more than 12 months following

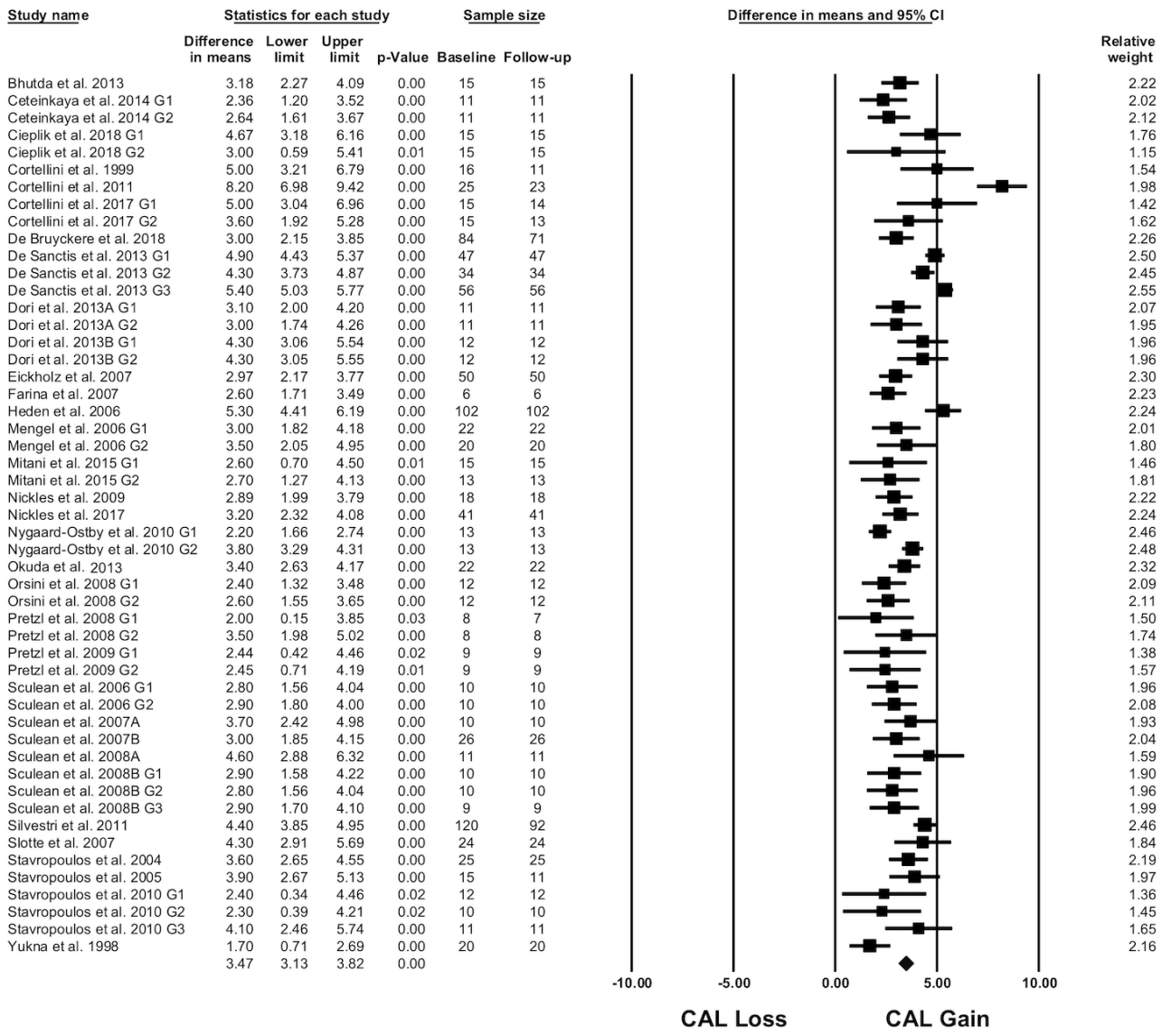

Figure 3. Forest plots for the mean changes in clinical attachment level (primary outcome variable) after at least 5 years following periodontal regenerative procedures

the intervention. Only two studies met their inclusion criteria for the long-term outcomes, both of which had less than five-years of follow-up. Therefore, the authors could not perform any meta-analysis for the long-term outcomes of these procedures. In addition, they found no data on the patient-centered outcomes (Trombelli *et al*., 2002). The present study was performed eighteen years after the above-mentioned systematic review. However, still, no study was found to report data on patient-centered outcomes.

The results of the present systematic review support the long-term efficacy of periodontal regenerative procedures for the treatment of intrabony periodontal defects. The goal of the present study was not to compare the periodontal regenerative therapy to any other treatment modalities. Rather, the goal was to provide clinicians quantitative data of the long-term (≥5 years) efficacy of periodontal regenerative procedures for the treatment of periodontal intrabony defects. This quantitative data can benefit clinicians by having long-term predictability prior to initiating the surgical procedure and enabling them to anticipate the long-term clinical outcomes. We found that on average clinicians can expect a tooth retention rate of 92.8 % after at least 5 years and 87.7% after at least 10 years after performing periodontal regenerative therapy for intrabony defects. In addition, we can expect on average 3.47 mm gain in CAL, 4.06 mm reduction in PPD, and 3.69 mm of radiographic vertical defect fill after a minimum of 5 years following periodontal regenerative therapy.

This information can be valuable for the treatment planning of teeth with periodontal intrabody defects, particularly in the clinical situations where a decision needs to be made regarding saving a tooth with a questionable prognosis with periodontal regenerative therapy or performing tooth extraction and implant therapy. The 5-year and 10-year tooth retention rates that were reported in the present studies are comparable with

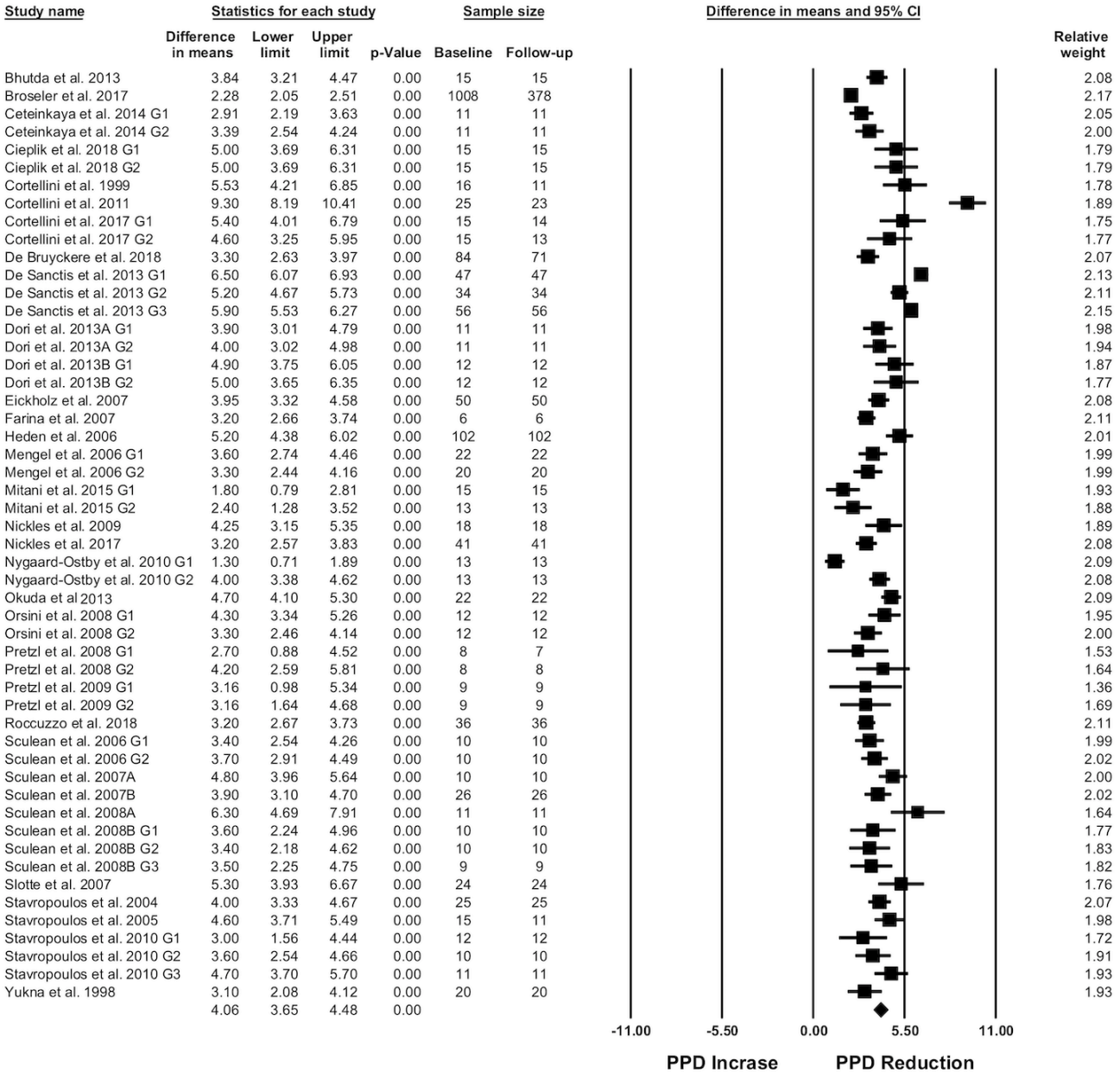

Figure 4A. Forest plots for the mean changes in pocket probing depth after at least 5 years following periodontal regenerative procedures

5-year and 10-year implant survival rates reported in the literature (Da Silva *et al.*, 2014; Karoussis *et al.*, 2003). Hence, preserving the natural dentition with the aid of periodontal regenerative therapy might be a more suitable option in such conditions based on lower number of required surgical interventions, shorter overall treatment course, and the lack of mechanical and biological complications that are associated with the implant therapy. Still, future clinical trials are needed to directly compare the long-term outcomes of periodontal regenerative therapy with those of implant therapy.

It should be also mentioned that all included studies in this systematic review reported that patients received periodontal supportive therapy following periodontal regenerative procedures. Therefore, the imperative role of periodontal maintenance following periodontal regenerative therapy on the treatment outcomes should not be overlooked.

It is important to highlight that all study designs with a comparison from baseline were considered for inclusion in this systematic review. Inclusion of non-randomized studies might be considered as a limitation of the present systematic review. However, the sensitivity analysis demonstrated that exclusion of non-randomized studies did not substantially affect the pooled analyses. Furthermore, other limitations of the present systematic review are the lack of inclusion of gray literature and non-English citations. In addition, the effect of the defect type on the long-term outcomes of periodontal regeneration procedures was not assessed since the quantitative data for each defect type was not reported in the majority of the

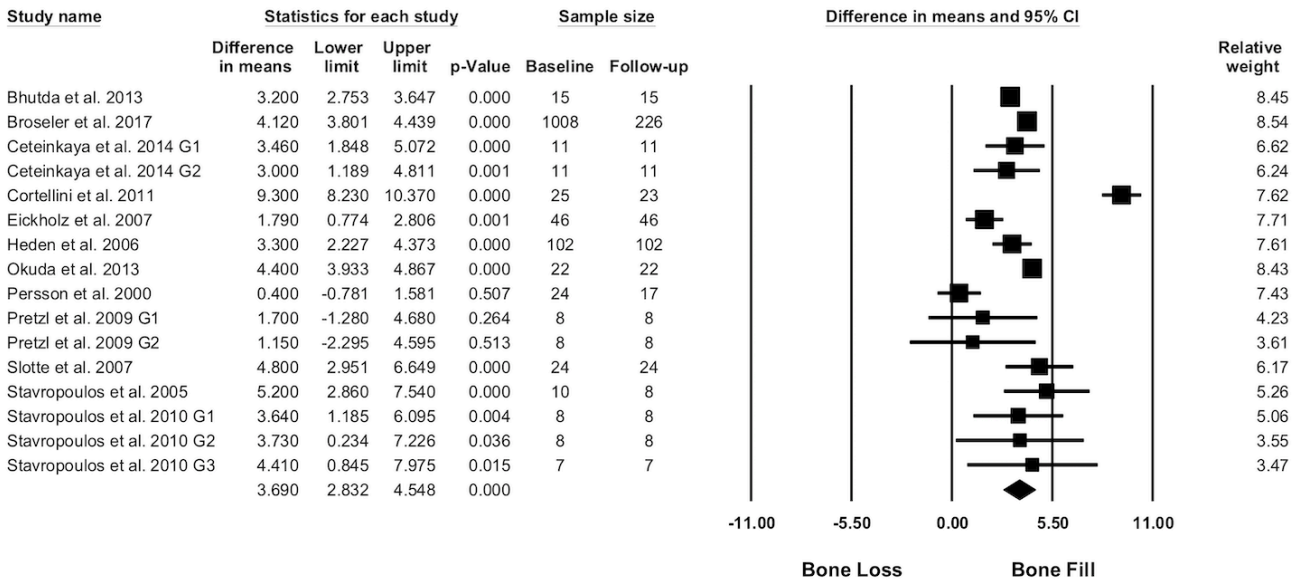

Figure 4B. Forest plots for the mean radiographic vertical defect fill after at least 5 years following periodontal regenerative procedures

included studies. Furthermore, different periodontal regeneration procedures were not compared in the present study because they were performed in different clinical settings. Future network-meta analyses are recommended to compare the long-term outcomes of various periodontal regeneration treatment modalities.

Patient-centered outcomes have become an indispensable component of quality health care. No study was found to report data on long-term patient-centered outcomes for periodontal regenerative procedures. Thus, future studies are required to assess the long-term patient-centered outcomes of periodontal regenerative therapy.

Conclusions

The current evidence supports the long-term clinical efficacy of periodontal regeneration therapy for the treatment of intrabony periodontal defects. The present systematic review and meta-analysis found that periodontal regenerative therapy results in the long-term tooth retention, defect reduction, and lasting improvements in clinical attachment level and pocket probing depth. Future clinical trials are needed to assess the long-term patient-centered outcomes of periodontal regeneration procedures.

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Appendix

Methods

Search strategy

Electronic search was conducted using the following search strategies:

Database	Search Strategy
PubMed	((“Periodontitis”[Mesh] OR “Periodontal Atrophy”[Mesh] OR “Periodontal Ligament”[Mesh] OR “Periodontics”[Mesh] OR “Furcation Defects”[Mesh] OR “Periodontal Diseases”[Mesh] OR “intrabony defect”[tw] OR “periodontal disease”[tw]) AND (“Humans”[Mesh] OR “Adult”[Mesh] OR “Aged”[Mesh] OR “Aged, 80 and over”[Mesh])) AND (“Biological Factors”[Mesh] OR “Bone Transplantation”[Mesh] OR “Bone Regeneration”[Mesh] OR “Bone Substitutes”[Mesh] OR “Autografts”[Mesh] OR “Heterografts”[Mesh] OR “Allografts”[Mesh] OR “Apatites”[Mesh] OR “enamel matrix proteins”[Supplementary Concept] OR “Platelet-Derived Growth Factor”[Mesh] OR “Bone Morphogenetic Proteins”[Mesh] OR “Transforming Growth Factors”[Mesh] OR “Fibroblast Growth Factors”[Mesh] OR “Platelet-Rich Plasma”[Mesh] OR “Platelet-Rich Fibrin”[Mesh] OR “Parathyroid Hormone”[Mesh] OR “Membranes, Artificial”[Mesh] OR “Wound Closure Techniques”[Mesh] OR “Guided Tissue Regeneration”[Mesh] OR “Guided Tissue Regeneration, Periodontal”[Mesh] OR “Surgical Flaps”[Mesh] OR “Tissue Engineering”[Mesh] OR “GEM 21S”[Supplementary Concept] OR “enamel matrix proteins”[tw] OR “GTR”[tw] OR “enamel matrix derivative”[tw])) AND (“Periodontal Pocket”[Mesh] OR “Periodontal Attachment Loss”[Mesh] OR “Alveolar Bone Loss”[Mesh] OR “Periodontal Index”[Mesh] OR “Treatment Outcome”[Mesh] OR “probing depth”[tw] OR “pocket depth”[tw] OR “attachment level”[tw] OR “bone fill”[tw] OR “bone gain”[tw] OR “defect fill”[tw]) AND (“Longitudinal Studies”[Mesh] OR “Prospective Studies”[Mesh] OR “Long Term Adverse Effects”[Mesh] OR “Long-Term Care”[Mesh] OR”Long-Term Care”[Mesh] OR “long term follow up”[tw] OR “long term”[tw] OR “years”[tw]) AND English[lang]
CINAHL	(MH “Furcation Defects” OR MH “Periodontal Diseases” OR MH “Periodontitis” OR MH “Periodontal Atrophy” OR MH “Periodontal Ligament” OR MH “Periodontics” OR TX “intrabony defect” OR TX “periodontal disease”) AND (MH “Human” OR MH “Adult” OR MH “Aged” OR MH “Aged, 80 and over”[Mesh] OR MH “dental care for the aged”) AND MH “Biological Factors” OR MH “Tissue Scaffolds” OR MH “Bone Transplantation” OR MH “Bone Regeneration” OR MH “Bone Substitutes” OR MH “Autografts” OR MH “Allografts” OR MH “Platelet-Derived Growth Factor” OR MH “Bone Morphogenetic Proteins” OR MH “Platelet-Rich Plasma” OR MH “Platelet-Rich Fibrin” OR MH “Parathyroid Hormones” OR MH “Membranes, Artificial” OR MH “Guided Tissue Regeneration” OR MH “Surgical Flaps” OR MH “Tissue Engineering” OR TX “Regenerative Medicine” OR TX “Heterografts” OR TX “Apatites” OR TX “dental enamel proteins” OR TX “enamel matrix proteins” OR TX “Transforming growth factors” OR TX “Fibroblast Growth Factors” OR TX “Wound closure techniques” OR TX “periodontal guided tissue regeneration” OR TX “Gem 21s” OR TX “GTR” OR TX “enamel matrix derivative” AND (MH “Periodontal Pocket” OR MH “Periodontal Attachment Loss” OR MH “Alveolar Bone Loss” OR MH “Treatment Outcomes” OR MH “Outcome Assessment” OR TX “periodontal index” OR TX “probing depth” OR TX “pocket depth” OR TX “attachment level” OR TX “bone fill” OR TX “bone gain” OR TX “defect fill”) AND (Prospective Studies” OR MH “Treatment Complications, Delayed” OR MH “Long Term Care” TX “longitudinal studies” OR TX “longitudinal study” OR TX “long terms adverse effects” OR TX “long term follow up” OR TX “years” OR TX “long term”)

Continued overleaf...

Embase	('periodontitis'/exp OR 'periodontitis' OR 'periodontal ligament'/exp OR 'periodontal ligament' OR 'periodontics'/exp OR 'periodontics' OR 'furcation defects'/exp OR 'furcation defects' OR 'periodontal atrophy'/exp OR 'periodontal atrophy' OR 'intrabony defect' OR 'periodontal disease'/exp OR 'periodontal disease' AND 'human'/exp OR 'adult'/exp OR 'very elderly'/exp OR 'aged'/exp) AND ('biological factor'/exp OR 'tissue scaffold'/exp OR 'regenerative medicine'/exp OR 'bone transplantation'/exp OR 'bone regeneration'/exp OR 'bone prosthesis'/exp OR 'autograft'/exp OR 'xenograft'/exp OR 'allograft'/exp OR 'apatite'/exp OR 'enamel protein'/exp OR 'enamel matrix proteins'/exp OR 'platelet derived growth factor'/exp OR 'bone morphogenetic protein'/exp OR 'transforming growth factor'/exp OR 'fibroblast growth factor'/exp OR 'platelet-rich fibrin'/exp OR 'parathyroid hormone'/exp OR 'artificial membrane'/exp OR 'wound closure'/exp OR 'periodontal guided tissue regeneration'/exp OR 'tissue regeneration'/exp OR 'surgical flaps'/exp OR 'tissue engineering'/exp OR 'enamel matrix derivative'/exp OR 'bone substitutes' OR 'heterografts' OR 'dental enamel proteins' OR 'gem 21s' OR 'gtr') AND ('periodontal pocket'/exp OR 'alveolar bone loss'/exp OR 'periodontal index'/exp OR 'probing depth'/exp OR 'pocket depth'/exp OR 'periodontal attachment loss' OR 'attachment level' OR 'bone fill' OR 'bone gain' OR 'defect fill') AND ('longitudinal study'/exp OR 'prospective study'/exp OR 'long term care'/exp OR 'long term follow up'/exp OR 'long term adverse effects' OR 'years' OR 'long term')
Web of Science	TS=("Furcation Defects" OR "periodontal disease" OR Periodontitis OR "periodontal atrophy" OR "Periodontal Ligament" OR "periodontics" OR "intrabony defect" OR "periodontal disease") AND TS=(human OR adult OR Aged OR Elderly) AND TS=("biological factors" OR "Tissue Scaffolds" OR "Regenerative Medicine" OR "bone transplantation" OR "Bone Regeneration" OR "bone substitutes" OR "Autografts" OR "Heterografts" OR "allografts" OR "Apatites" OR "Dental Enamel Proteins" OR "enamel matrix proteins" OR "Platelet-Derived Growth Factor" OR "Bone Morphogenetic Proteins" OR "Transforming Growth Factors" OR "Fibroblast Growth Factors" OR "Platelet-Rich Plasma" OR "Platelet-Rich Fibrin" OR "Parathyroid Hormone" OR "Membranes, Artificial" OR "Wound Closure Techniques" OR "Guided Tissue Regeneration" OR "periodontal guided tissue regeneration" OR "surgical flaps" OR "tissue engineering" OR "gem 21s" OR "enamel matrix proteins" OR "GTR" OR "enamel matrix derivative") AND TS=("periodontal pocket" OR "Periodontal Attachment Loss" OR "Alveolar Bone Loss" OR "Periodontal Index" OR "Treatment Outcome" OR "outcome assessment" OR "probing depth" OR "pocket depth" OR "attachment level" OR "bone fill" OR "bone gain" OR "defect fill") AND TS=("longitudinal studies" OR "prospective studies" OR "long term adverse effects" OR "long term care" OR "long term follow up" OR "years" OR "long term")

Data Extraction

Two investigators (K.N. and J. Sze) independently reviewed and extracted data from the included studies using a predetermined data extraction table. Any discrepancies between reviewers were resolved by discussion and consensus, and by consulting a third author (S.B.). The data for the following variables were extracted from each included study: A) study characteristics: first author, year of publication, study design, country, setting (private practice vs. academic setting), funding source, length of follow-up, and number of regenerative groups; B) patient characteristics: number of patients in each group, average age of subjects, number of smokers in each group, and number of male and female subjects; C) defect characteristics: number of evaluated teeth at baseline and at follow up in each group, number of extracted teeth and number of drop-outs in each group, location (maxilla, mandible or both), type of teeth (incisors, canines, premolars, or molars), and defect morphology; D) surgical considerations: pre-operative antibiotic intake, use and type of grafting material, use and type of barrier membrane, use and type of biological agent, use of root conditioning, type of soft tissue closure, report of maintenance protocol; and E) outcomes: outcome variables and results.

Results

Quality assessment

Assessment of risk of bias for randomized clinical trials showed that the overall risk of bias was low for 11 studies, and six studies were judged as having "some concerns". For non-randomized studies, the total score ranged between 5-8 stars for the included studies. The variability between studies was found for the Comparability category, and the item 3 in the Outcome category (adequacy of follow up of cohorts). None of the studies received the maximum nine stars. Five studies received eight stars. Six studies scored seven stars, seven studies scored six stars, and three studies scored five stars.

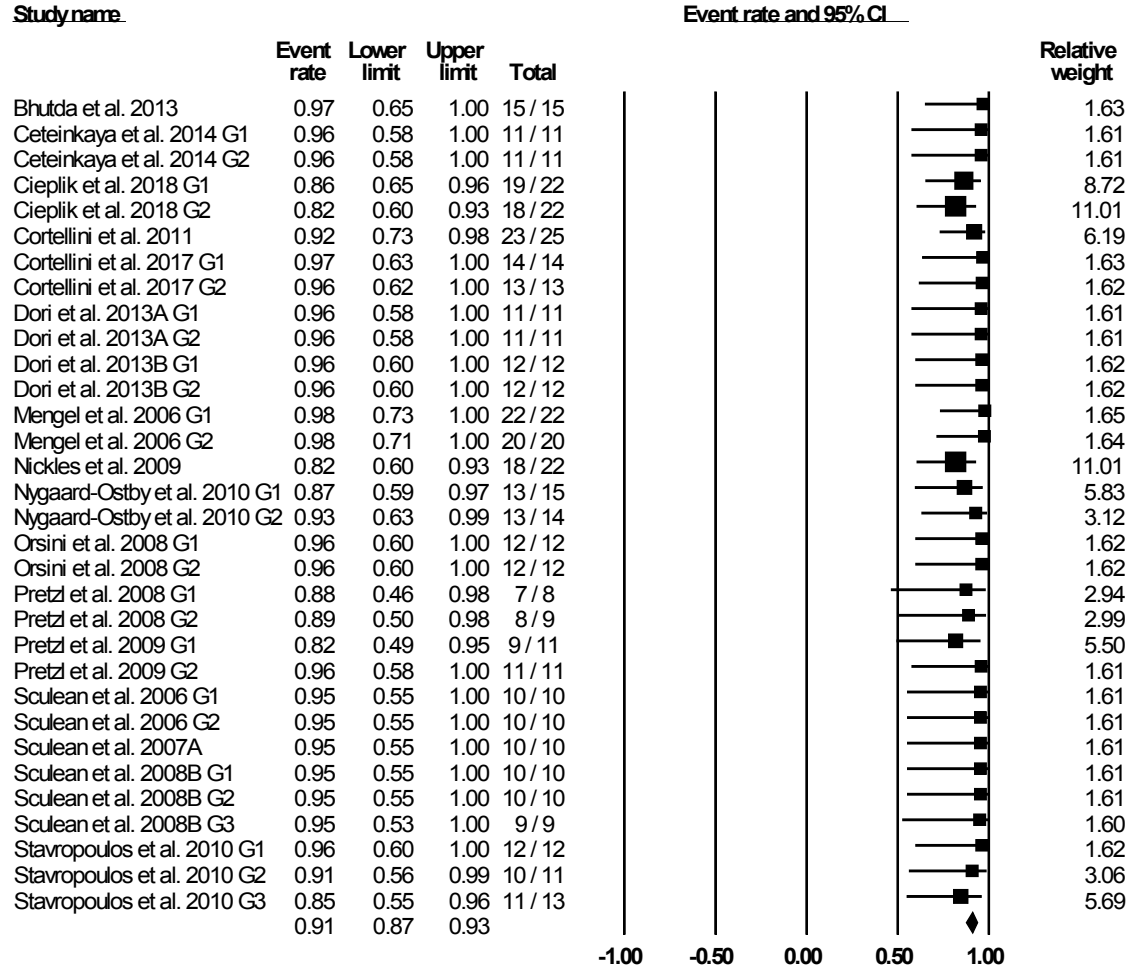
Publication Bias

Funnel plots for the outcome variables are presented in the Appendix Figures 11-15. No obvious asymmetry was observed in the funnel plots analyzing the 5-year tooth retention (Appendix Figure 11), changes in clinical attachment level (Primary outcome variable; Appendix Figure 13), changes in pocket probing depth (Appendix Figure 14), and radiographic vertical defect fill (Appendix Figure 15). Some asymmetry was noted in the funnel plots for the 10-year tooth retention (Appendix Figure 12), indicating potential publication bias for this variable.

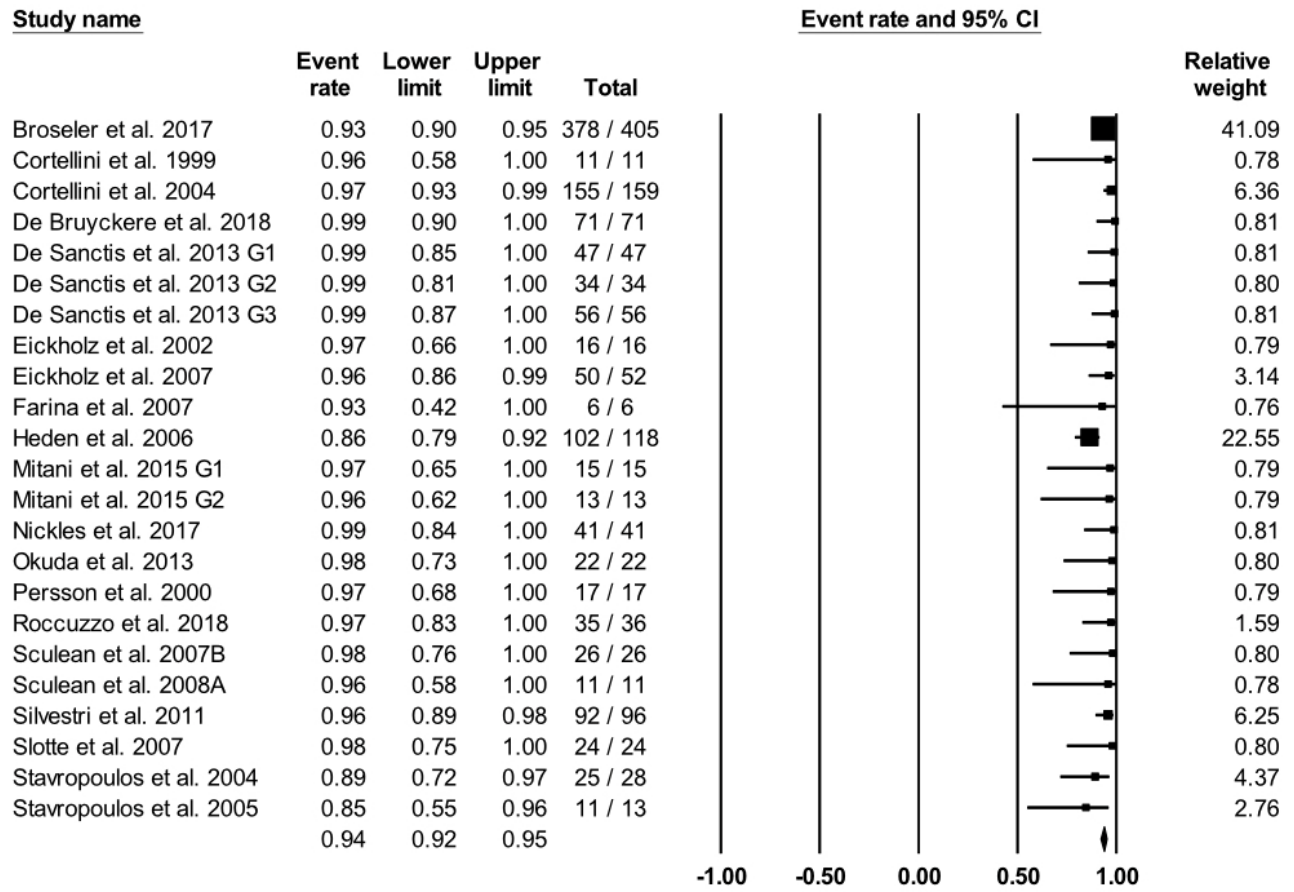
No evidence of publication bias was found by Begg and Mazumdar rank correlation test for 5-year tooth retention ($p = 0.08$, $\tau = -0.13$), changes in clinical attachment level ($p = 0.40$, $\tau = 0.08$), changes in pocket probing depth ($p = 0.30$, $\tau = 0.10$), and radiographic vertical defect fill ($p = 0.53$, $\tau = 0.17$). Begg and Mazumdar rank correlation showed a significant publication bias for 10-year tooth retention variable ($p = 0.004$, $\tau = 0.46$).

Appendix Table 1. Results of the sensitivity analysis after exclusion of retrospective and prospective non-randomized studies

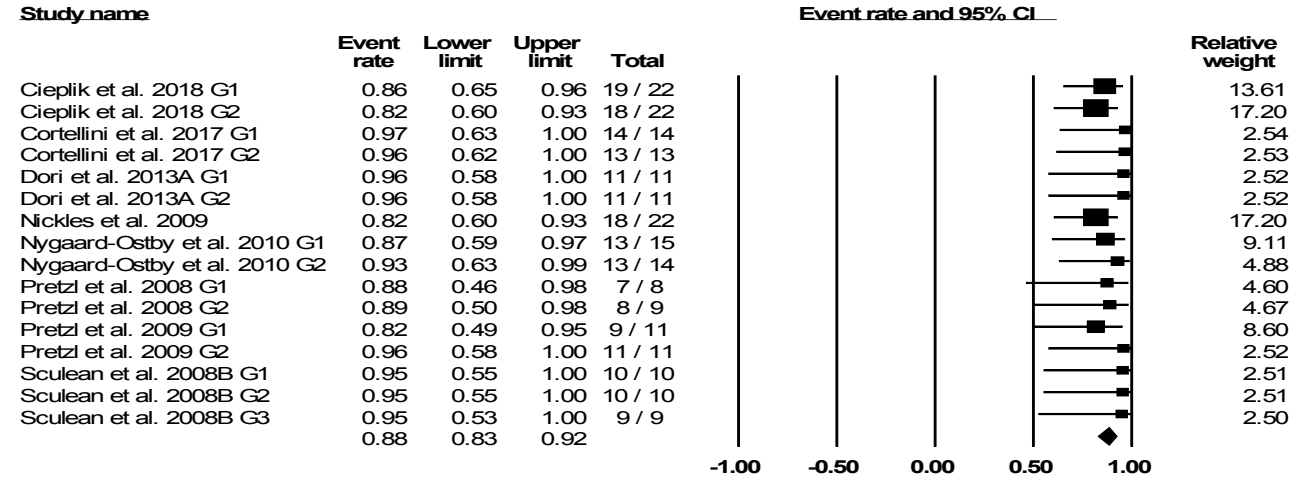
Outcome variable	Number of groups	Effect size (95% CI)	P value	Heterogeneity I2, %	τ	
Tooth retention 5-yr	32	Event rate: 0.908 (0.87-0.93)	p < 0.001	< 0.001	0.001	Fixed effect model
Tooth retention 10-yr	16	Event rate: 0.882 (0.83-0.92)	p < 0.001	< 0.001	0.001	Fixed effect model
Changes in clinical attachment level	32	WMD: 3.28 mm (2.88-3.68)	p < 0.001	72.11	0.94	Random effect model
Changes in pocket probing depth	32	WMD: 4.0 mm (3.54-4.46)	p < 0.001	85.2	1.20	Random effect model
Radiographic vertical defect fill	9	WMD: 3.85 mm (1.83-5.87)	p < 0.001	92.93	2.83	Random effect model



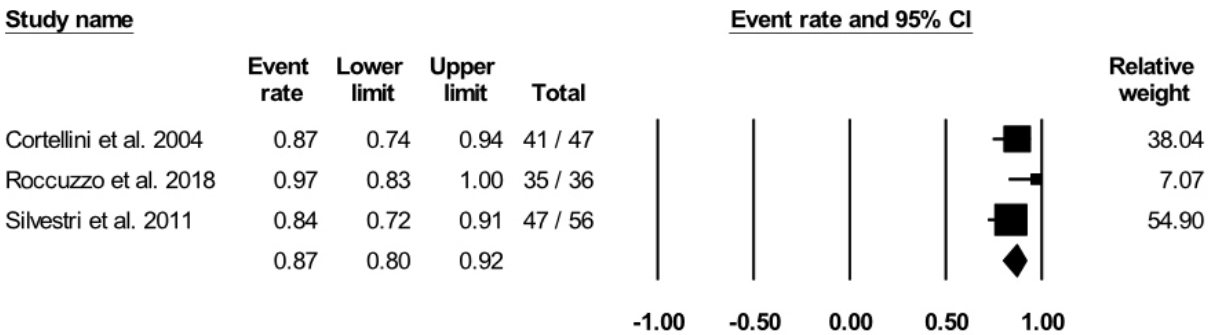
Appendix Figure 1. Forest plots of the tooth retention after at least 5 years following periodontal regenerative procedures for randomized clinical trials



Appendix Figure 2. Forest plots of the tooth retention after at least 5 years following periodontal regenerative procedures for non-randomized studies

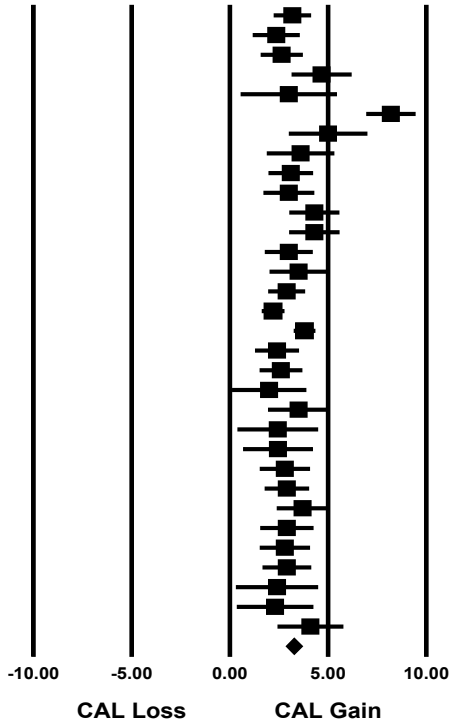


Appendix Figure 3. Forest plots of the tooth retention after at least 10 years following periodontal regenerative procedures for randomized clinical trials



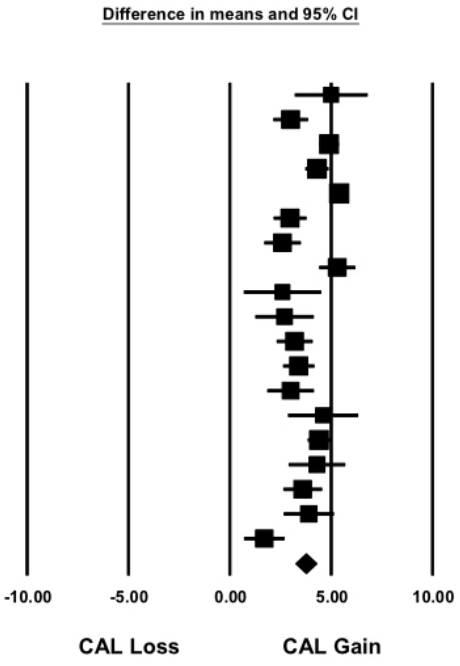
Appendix Figure 4. Forest plots of the tooth retention after at least 10 years following periodontal regenerative procedures for non-randomized studies

Study name	Difference in means	Lower limit	Upper limit	p-Value	Baseline	Follow-up	Relative weight
Bhutda et al. 2013	3.18	2.27	4.09	0.00	15	15	3.83
Ceteinkaya et al. 2014 G1	2.36	1.20	3.52	0.00	11	11	3.42
Ceteinkaya et al. 2014 G2	2.64	1.61	3.67	0.00	11	11	3.63
Cieplik et al. 2018 G1	4.67	3.18	6.16	0.00	15	15	2.88
Cieplik et al. 2018 G2	3.00	0.59	5.41	0.01	15	15	1.76
Cortellini et al. 2011	8.20	6.98	9.42	0.00	25	23	3.32
Cortellini et al. 2017 G1	5.00	3.04	6.96	0.00	15	14	2.24
Cortellini et al. 2017 G2	3.60	1.92	5.28	0.00	15	13	2.60
Dori et al. 2013A G1	3.10	2.00	4.20	0.00	11	11	3.52
Dori et al. 2013A G2	3.00	1.74	4.26	0.00	11	11	3.26
Dori et al. 2013B G1	4.30	3.06	5.54	0.00	12	12	3.28
Dori et al. 2013B G2	4.30	3.05	5.55	0.00	12	12	3.28
Mengel et al. 2006 G1	3.00	1.82	4.18	0.00	22	22	3.38
Mengel et al. 2006 G2	3.50	2.05	4.95	0.00	20	20	2.95
Nickles et al. 2009	2.89	1.99	3.79	0.00	18	18	3.85
Nygaard-Ostby et al. 2010 G1	2.20	1.66	2.74	0.00	13	13	4.39
Nygaard-Ostby et al. 2010 G2	3.80	3.29	4.31	0.00	13	13	4.43
Orsini et al. 2008 G1	2.40	1.32	3.48	0.00	12	12	3.55
Orsini et al. 2008 G2	2.60	1.55	3.65	0.00	12	12	3.60
Pretzl et al. 2008 G1	2.00	0.15	3.85	0.03	8	7	2.38
Pretzl et al. 2008 G2	3.50	1.98	5.02	0.00	8	8	2.84
Pretzl et al. 2009 G1	2.44	0.42	4.46	0.02	9	9	2.17
Pretzl et al. 2009 G2	2.45	0.71	4.19	0.01	9	9	2.52
Sculean et al. 2006 G1	2.80	1.56	4.04	0.00	10	10	3.29
Sculean et al. 2006 G2	2.90	1.80	4.00	0.00	10	10	3.52
Sculean et al. 2007A	3.70	2.42	4.98	0.00	10	10	3.22
Sculean et al. 2008B G1	2.90	1.58	4.22	0.00	10	10	3.16
Sculean et al. 2008B G2	2.80	1.56	4.04	0.00	10	10	3.29
Sculean et al. 2008B G3	2.90	1.70	4.10	0.00	9	9	3.34
Stavropoulos et al. 2010 G1	2.40	0.34	4.46	0.02	12	12	2.13
Stavropoulos et al. 2010 G2	2.30	0.39	4.21	0.02	10	10	2.30
Stavropoulos et al. 2010 G3	4.10	2.46	5.74	0.00	11	11	2.67
	3.28	2.88	3.68	0.00			

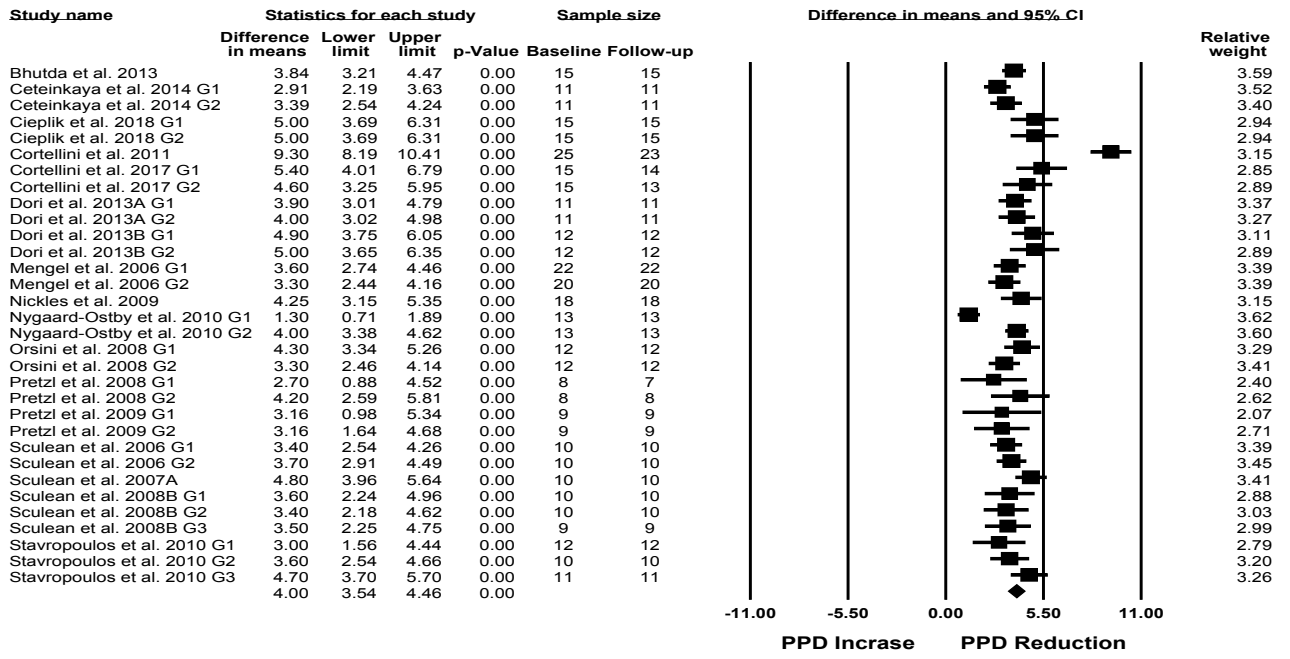


Appendix Figure 5. Forest plots of the mean changes in clinical attachment level (primary outcome variable) after at least 5 years following periodontal regenerative procedures for randomized clinical trials

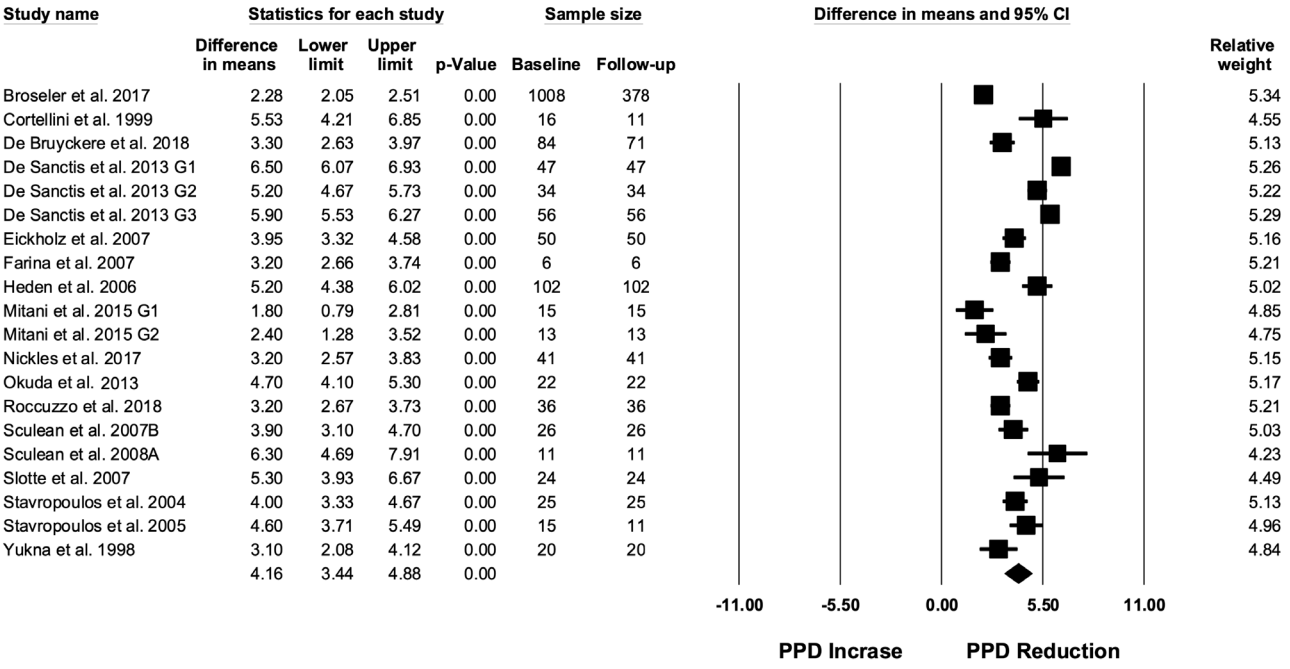
Study name	Difference in means	Lower limit	Upper limit	p-Value	Baseline	Follow-up	Relative weight
Cortellini et al. 1999	5.00	3.21	6.79	0.00	16	11	3.70
De Bruyckere et al. 2018	3.00	2.15	3.85	0.00	84	71	5.67
De Sanctis et al. 2013 G1	4.90	4.43	5.37	0.00	47	47	6.36
De Sanctis et al. 2013 G2	4.30	3.73	4.87	0.00	34	34	6.20
De Sanctis et al. 2013 G3	5.40	5.03	5.77	0.00	56	56	6.48
Eickholz et al. 2007	2.97	2.17	3.77	0.00	50	50	5.77
Farina et al. 2007	2.60	1.71	3.49	0.00	6	6	5.58
Heden et al. 2006	5.30	4.41	6.19	0.00	102	102	5.60
Mitani et al. 2015 G1	2.60	0.70	4.50	0.01	15	15	3.50
Mitani et al. 2015 G2	2.70	1.27	4.13	0.00	13	13	4.41
Nickles et al. 2017	3.20	2.32	4.08	0.00	41	41	5.60
Okuda et al. 2013	3.40	2.63	4.17	0.00	22	22	5.83
Sculean et al. 2007B	3.00	1.85	4.15	0.00	26	26	5.03
Sculean et al. 2008A	4.60	2.88	6.32	0.00	11	11	3.83
Silvestri et al. 2011	4.40	3.85	4.95	0.00	120	92	6.23
Slotte et al. 2007	4.30	2.91	5.69	0.00	24	24	4.51
Stavropoulos et al. 2004	3.60	2.65	4.55	0.00	25	25	5.47
Stavropoulos et al. 2005	3.90	2.67	5.13	0.00	15	11	4.84
Yukna et al. 1998	1.70	0.71	2.69	0.00	20	20	5.37
	3.76	3.24	4.27	0.00			



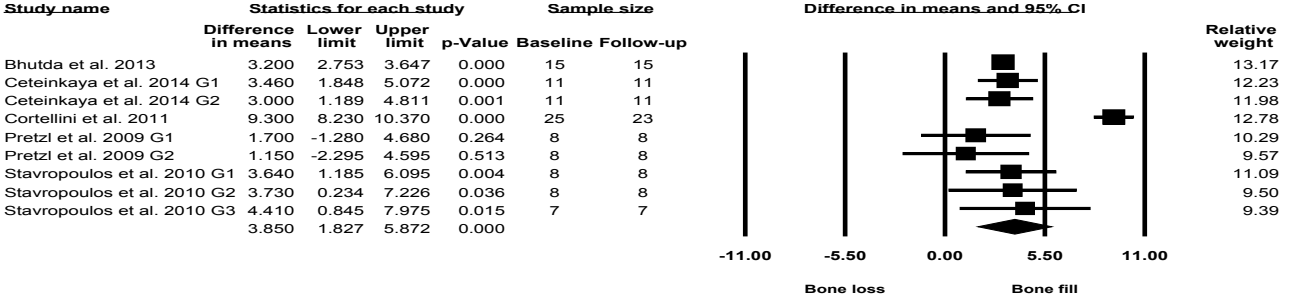
Appendix Figure 6. Forest plots of the mean changes in clinical attachment level (primary outcome variable) after at least 5 years following periodontal regenerative procedures for non-randomized studies.



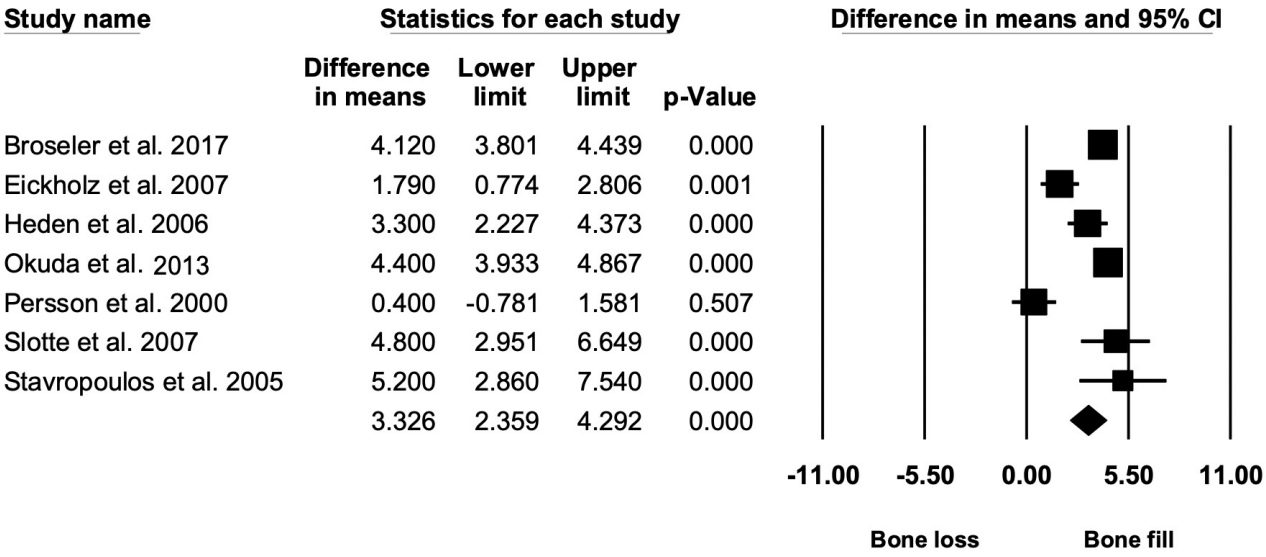
Appendix Figure 7. Forest plots of the mean changes in pocket probing depth after at least 5 years following periodontal regenerative procedures for randomized clinical trials



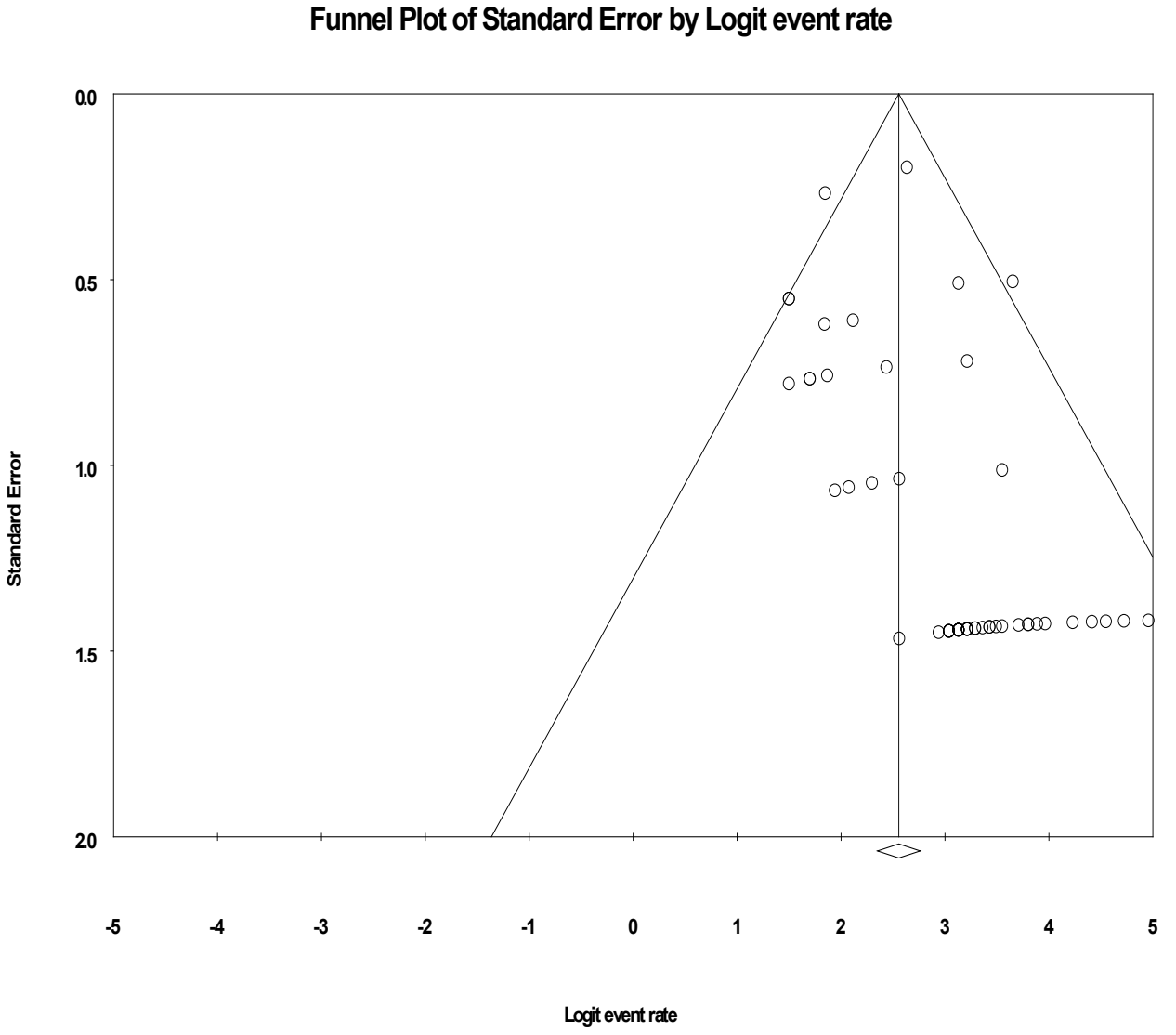
Appendix Figure 8. Forest plots of the mean changes in pocket probing depth after at least 5 years following periodontal regenerative procedures for non-randomized studies



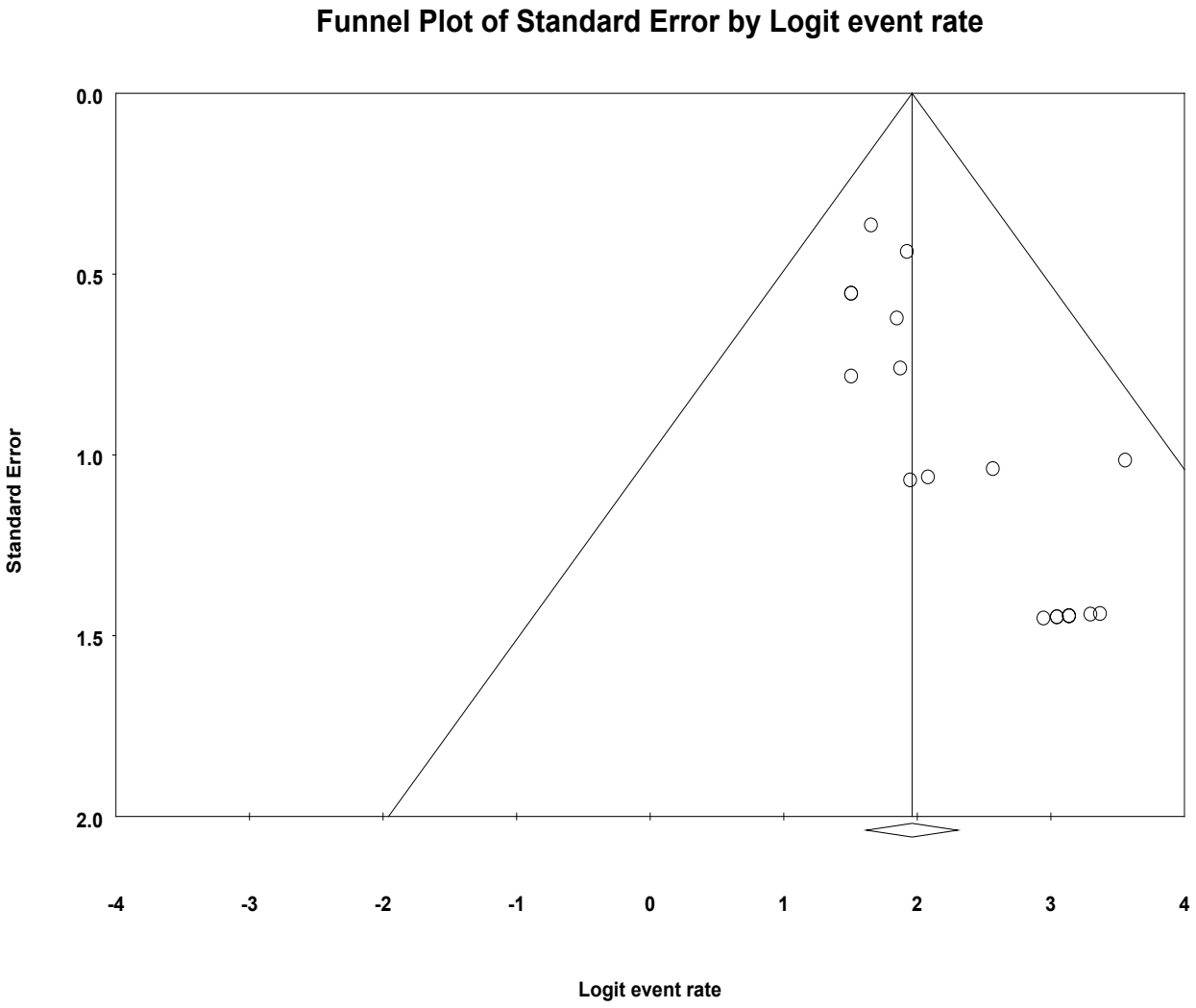
Appendix Figure 9. Forest plots of the mean radiographic vertical defect fill after at least 5 years following periodontal regenerative procedures for randomized clinical trials



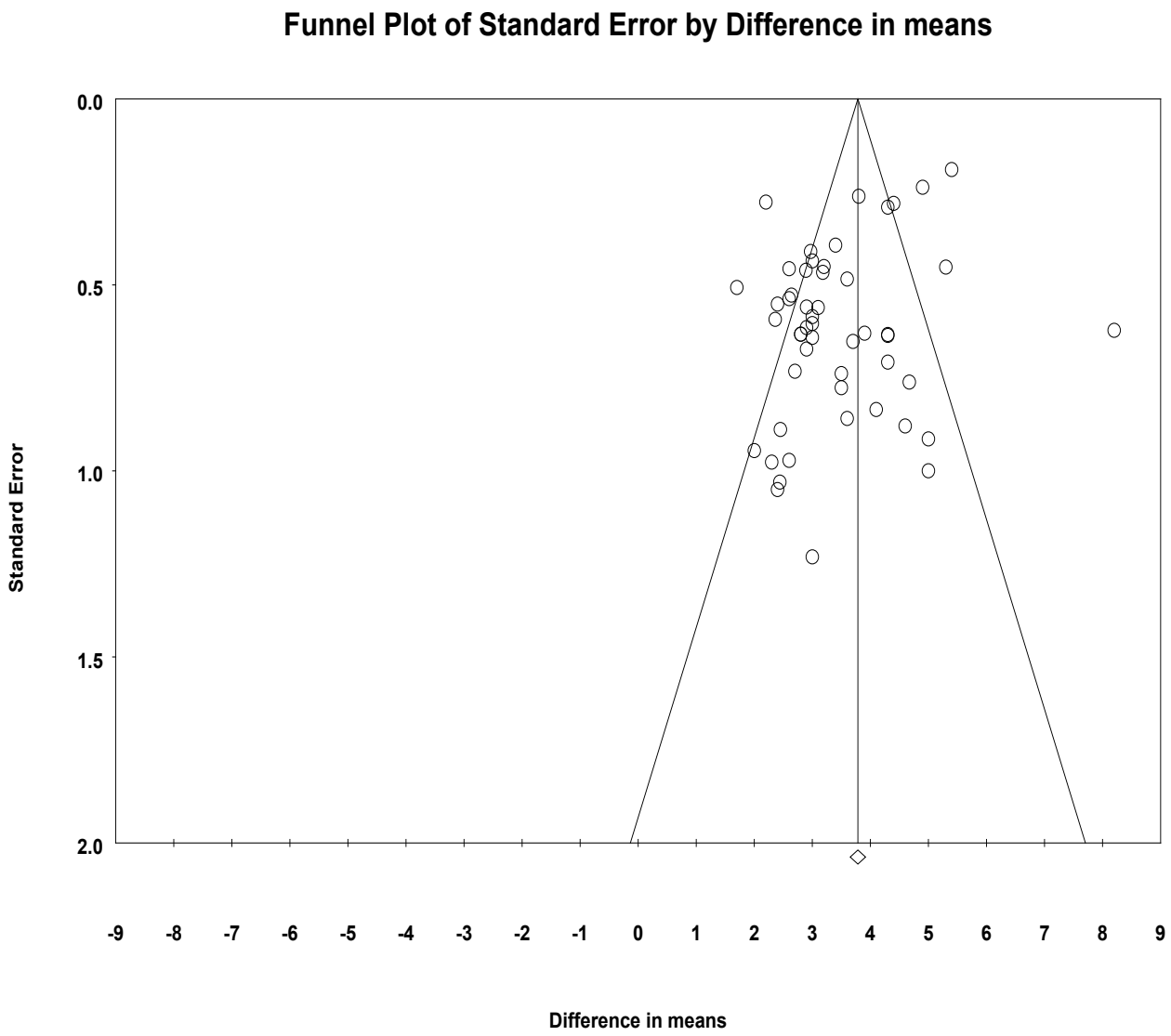
Appendix Figure 10. Forest plots of the mean radiographic vertical defect fill after at least 5 years following periodontal regenerative procedures for non-randomized studies



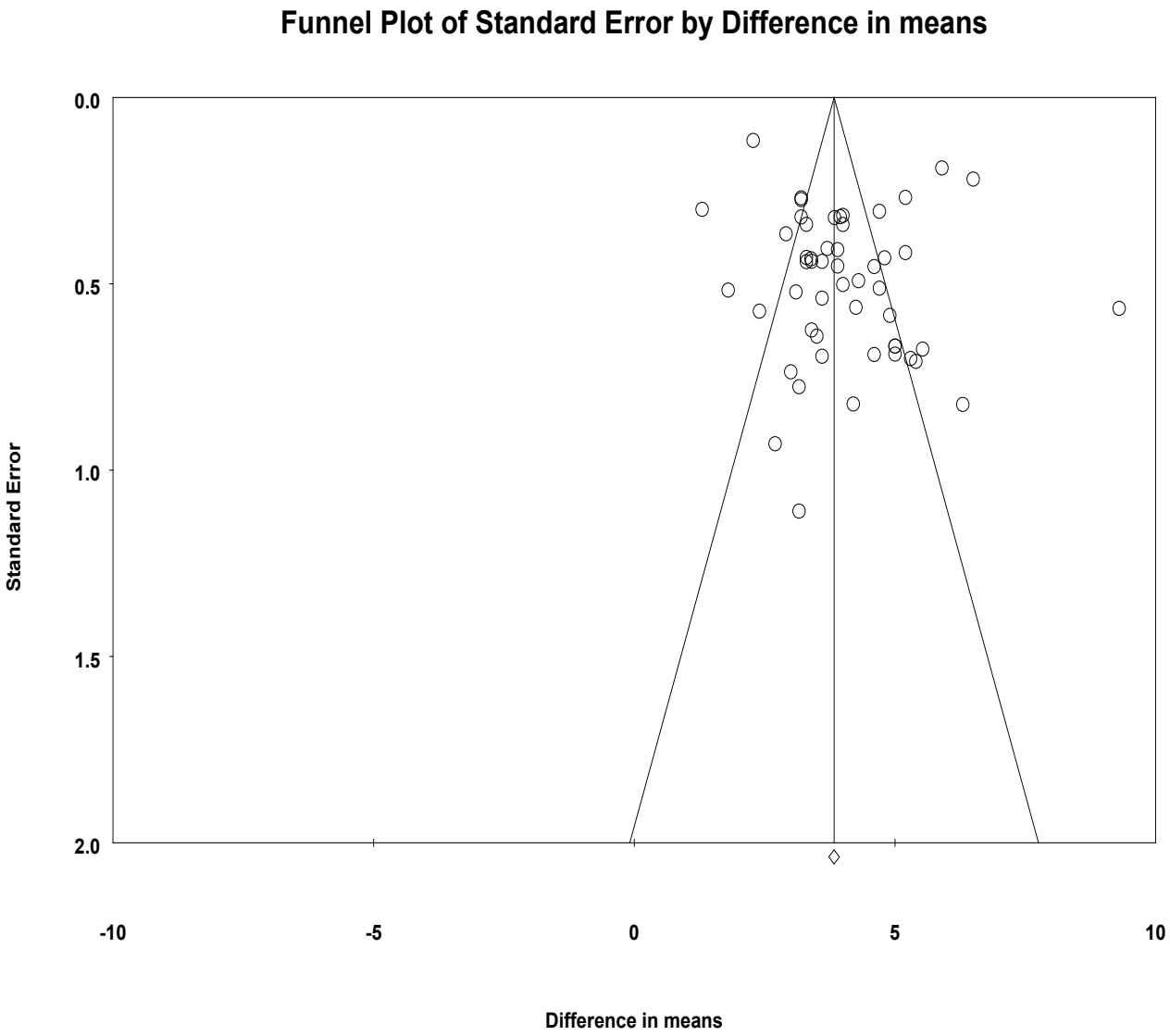
Appendix Figure 11. Funnel plots evaluating potential publication bias for the 5-year tooth retention



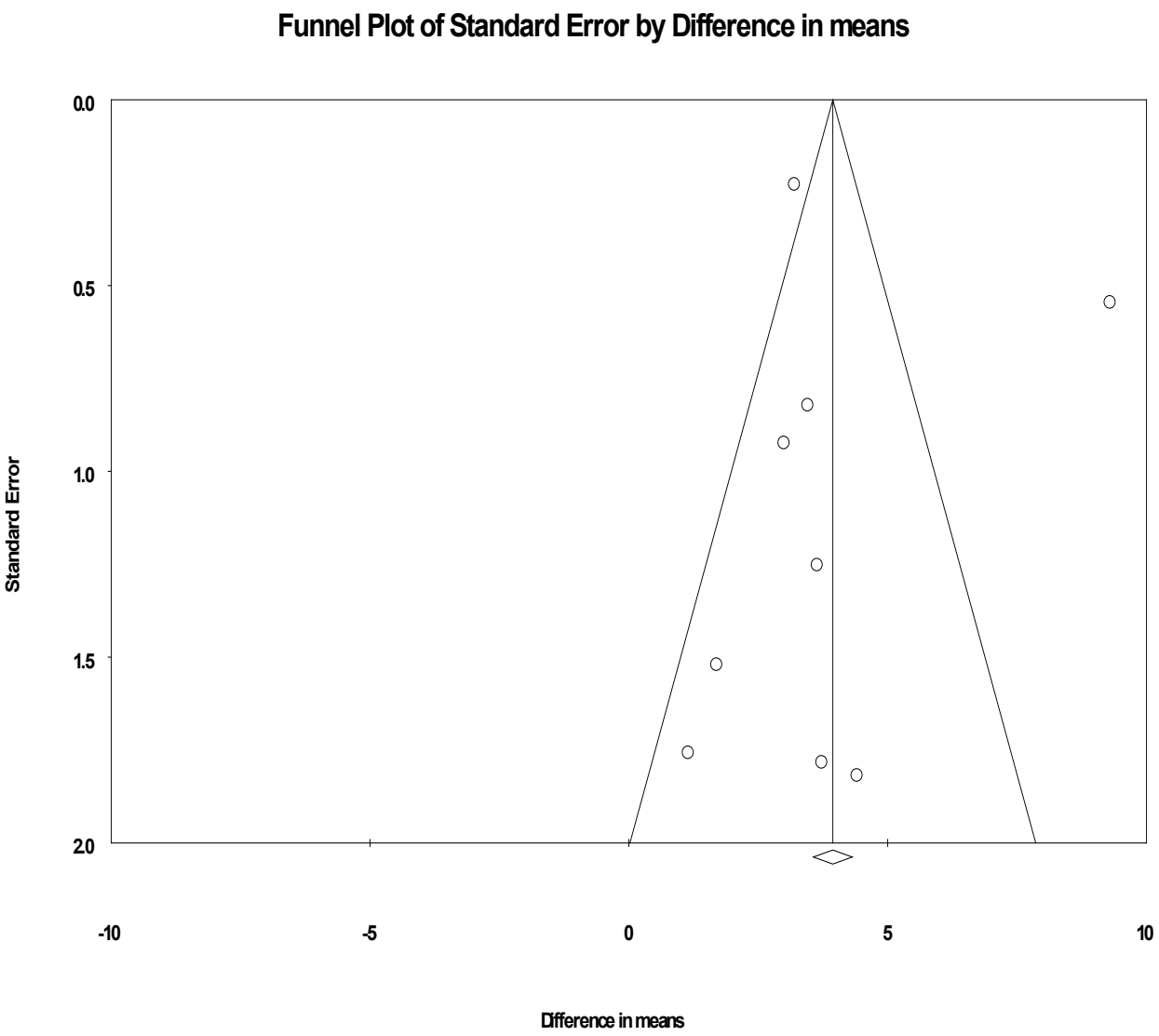
Appendix Figure 12. Funnel plots evaluating potential publication bias for the 10-year tooth retention



Appendix Figure 13. Funnel plots evaluating potential publication bias for the changes in clinical attachment level (Primary outcome variable)



Appendix Figure 14. Funnel plots evaluating potential publication bias for the changes in pocket probing depth



Appendix Figure 15. Funnel plots evaluating potential publication bias for the radiographic vertical defect fill