Supplementary Material S1: PRISMA checklist.

Section	#	Checklist item	Reported on page
TITLE	1	Identify the report as systematic review, meta-analysis or both	1
ABSTRACT	2	Structured summary	2
INRODUCTION	3	Rationale	3
	4	Objectives	3
METHODS	5	Protocol and registration	3,4
	6	Eligibility criteria	4
	7	Information sources	4
	8	Search	4
	9	Study selection	4, 5
	10	Data collection process	5
	11	Data items	5
	12	Risk of bias in individual studies	5
	13	Summary measures	5
	14	Synthesis of results	5
	15	Risk of bias across studies	5
	16	Additional analyses	n/a
RESULTS	17	Study selection	6
	18	Study characteristics	6, Tables
	19	Risk of bias within studies	6, Suppl mat 5
	20	Results of individual studies	Tables
	21	Synthesis of results	6,7,8,9
	22	Risk of bias across studies	6
	23	Additional analysis	n/a
DISCUSSION	24	Summary of evidence	9,10,11,12

	25	Limitations	12
	26	Conclusions	12
FUNDING	27	Sources of funding	1

Supplementary Material S2: Search strategy and study selection.

The searches from two recent systematic reviews (SRs) (Nibali et al. 2020, Jepsen et al. 2020) were used as starting point for this SR. All the studies enclosed in the two SRs were reconsidered according to the PICO criteria for this review.

Intra-Bony Defect

In the review of Nibali et al. 2020, 88 manuscript reporting data for 79 RCTs were included. Eight manuscript reported data on long term follow-up from included RCTs (*Stravopolous 2010; Sculean 2007b; Hoffmann 2016; Sculean 2007a; Moder 2012; Döri 2013a; Döri 2013b; Mengel 2006*). These manuscripts were excluded from this review. The study of Nevins et al. 2013 was excluded as the data were reported on graphs and was not possible to retrieve the data expressed as mean and SD. The manuscript of Tonetti et al. 2004b reported data on post-operative healing and patient discomfort and was excluded also. (For the references see Nibali et al. 2020)

Thus, a total of 78 RCTs from those included in Nibali et al. 2020 were included in this SR.

Then, the list of excluded full-text from Nibali et al. 2020 was checked for additional title. Two articles were added from those excluded (*Abu-Ta'a 2016; Eickholz 2014*).

Finally, the electronic and hand searches used in Nibali et al. 2020 were updated from 31/01/2019 to 20/11/2020.

From the new research update 10 manuscript were selected to be evaluated full text according to the eligibility criteria for this SR:

- Four were excluded (*Corbella 2019* – Not RCT; *Kothiwale 2019* – less than 10 defects per group; *Xu 2019* – Unclear defect definition; *Sànchez 2020* Not RCT)
- Six were included in this systematic review (*Aslan 2020; Lee 2019; Mazzonetto 2020; Paolantonio 2020; Pietruska 2020; Aoki 2020*)

At the end of this process a total of 86 RCTs treating IDs with a regenerative approach were included in this SR.

Furcation Involvement

The 19 RCTs included in Jepsen et al. 2020, were all included in this SR.

The list of excluded full-text from Jepsen et al. 2020 was check but no additional titles were find.

The electronic and hand searches used in Jepsen et al. 2020 were updated from 01/12/2018 to 20/11/2020.

From the new research update 4 manuscript were selected to be evaluated full text according to the eligibility criteria for this SR. However, no manuscripts meet the inclusion criteria for this SR. (*Bevilacqua 2020*; less than 10 patients for group; *Djurkin 2019*, *Courval 2020* and *Shah 2019* less than 12 months follow-up)

At the end of this process a total of 19 RCTs treating FI with a regenerative approach were included in this SR.

1. Bevilacqua, L.; Fonzar, A.; Olivier, S.; De Biasi, M.; Visintin, M.; Angerame, D.; Maglione, M. Out-come of different surgical approaches in the treatment of class II furcation defects in mandibular molars: A randomized clinical trial. *Int. J. Periodontics Restor. Dent.* **2020**, *40*, 693–701.
2. Corbella, S.; Alberti, A.; Calciolari, E.; Taschieri, S.; Francetti, L. Enamel matrix derivative for the treatment of partially contained intrabony defects: 12-month results. Aust. Dent. J. 2019, 64, 27–34. https://doi.org/10.1111/adj.12654.
3. Courval, A.; Harmouche, L.; Mathieu, A.; Petit, C.; Huck, O.; Séverac, F.; Davideau, J.-L. Impact of Molar Furcations on Photodynamic Therapy Outcomes: A 6-Month Split-Mouth Randomized Clinical Trial. Int. J. Environ. Res. Public Health 2020, 17, 4162. https://doi.org/10.3390/ijerph17114162.
4. Djurkin, A.; Toma, S.; Brecx, M.C.; Lasserre, J.F. Treatment of mandibular Class II furcations using bovine-derived bone xenograft with or without a collagen membrane: A randomized controlled trial. Quintessence Int. 2019, 50, 652–660.
5. Kothiwale, S.; Bhimani, R.; Kaderi, M.; Ajbani, J. Comparative study of DFDBA and FDBA block grafts in combination with chorion membrane for the treatment of periodontal intra-bony defects at 12 months post surgery. Cell Tissue Bank. 2019, 1–9. https://doi.org/10.1007/s10561-018-09744-5.
6. Sànchez, N.; Fierravanti, L.; Núñez, J.; Vignoletti, F.; Gonzàlez-Zamora, M.; Santamaria, S.; Sanz, M. Periodontal regeneration using a xenogeneic bone substitute seeded with autologous periodon-tal ligament-derived mesenchymal stem cells: A 12-month quasi-randomized controlled pilot clinical trial. J. Clin. Periodontol. 2020, 47, 1391–1402.
7. Shah, K.K.; Kolte, R.A.; Kolte, A. Evaluation of Demineralized Freeze-Dried Bone Allograft in Combination with Chorion Membrane in the Treatment of Grade II Furcation Defects: A Randomized Controlled Trial. Int. J. Periodontics Restor. Dent. 2019, 39, 659–667. https://doi.org/10.11607/prd.4267.
8. Xu, Y.; Qiu, J.; Sun, Q.; Yan, S.; Wang, W.; Yang, P.; Song, A. One-Year Results Evaluating the Effects of Concentrated Growth Factors on the Healing of Intrabony Defects Treated with or without Bone Sub-stitute in Chronic Periodontitis. Med. Sci. Monit. 2019, 25, 4384–4389.

Supplementary Material S3: full list of included papers.

Intrabony Defect Studies

9. Abu-Ta'A, M. Adjunctive Systemic Antimicrobial Therapy vs Asepsis in Conjunction with Guided Tissue Regeneration: A Randomized, Controlled Clinical Trial. J. Contemp. Dent. Pr. 2016, 17, 3–6. https://doi.org/10.5005/jp-journals-10024-1794.

10. Agarwal, A.; Gupta, N.D. Platelet-rich plasma combined with decalcified freeze-dried bone allograft for the treatment of noncontained human intrabony periodontal defects: A randomized controlled split-mouth study. Int. J. Periodontics Restor. Dent. 2014, 34, 705–711. https://doi.org/10.11607/prd.1766.

11. Agarwal, A.; Gupta, N.D.; Jain, A. Platelet rich fibrin combined with decalcified freeze-dried bone allograft for the treatment of human intrabony periodontal defects: A randomized split mouth clinical trail. Acta Odontol. Scand. 2016, 74, 36–43. https://doi.org/10.3109/00016357.2015.1035672.

12. Al Machot, E.; Hoffmann, T.; Lorenz, K.; Khalili, I.; Noack, B. Clinical Outcomes after Treatment of Periodontal Intrabony Defects with Nanocrystalline Hydroxyapatite (Ostim) or Enamel Matrix Derivatives (Emdogain): A Randomized Controlled Clinical Trial. BioMed Res. Int. 2014, 2014, 1–9. https://doi.org/10.1155/2014/786353.

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19. Christgau, M.; Moder, D.; Wagner, J.; Gläßl, M.; Hiller, K.-A.; Wenzel, A.; Schmalz, G. Influence of autologous platelet concentrate on healing in intra-bony defects following guided tissue regeneration therapy: A randomized prospective clinical split-mouth study. J. Clin. Periodontol. 2006, 33, 908–921. https://doi.org/10.1111/j.1600-051x.2006.00999.x.

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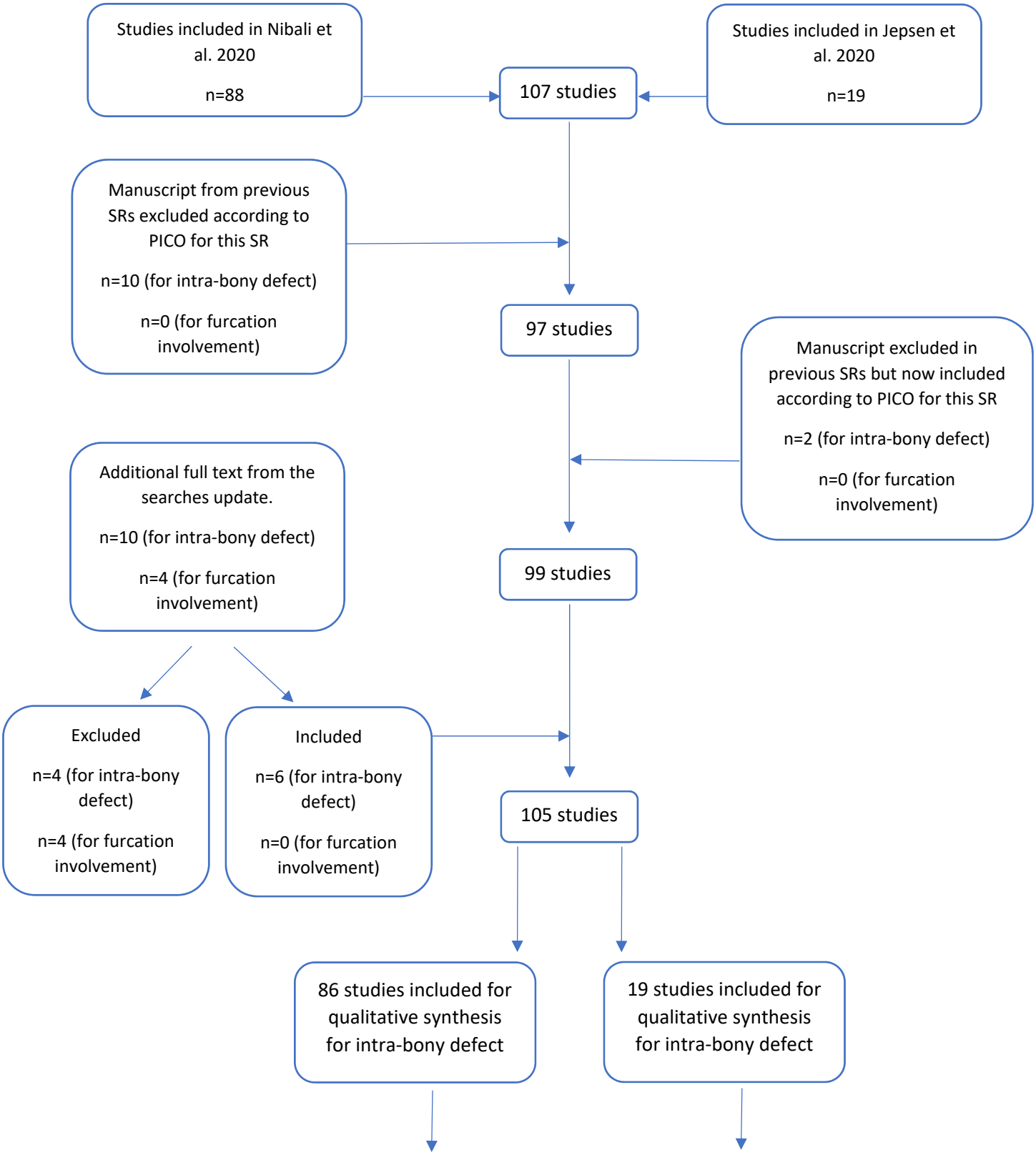
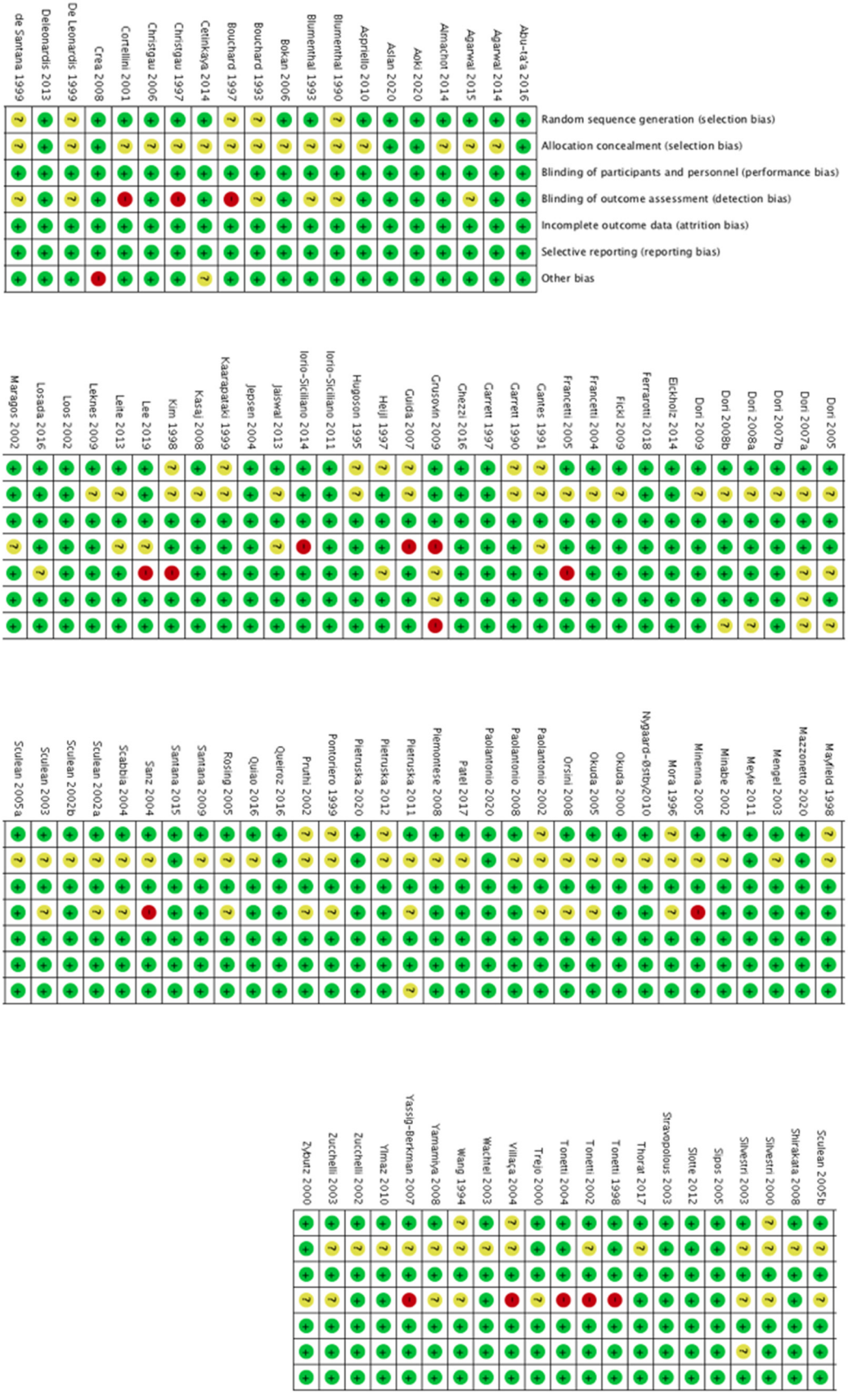
Supplementary Material S4: Flow Chart diagram (modified from PRISMA).



70 studies included for quantitative synthesis

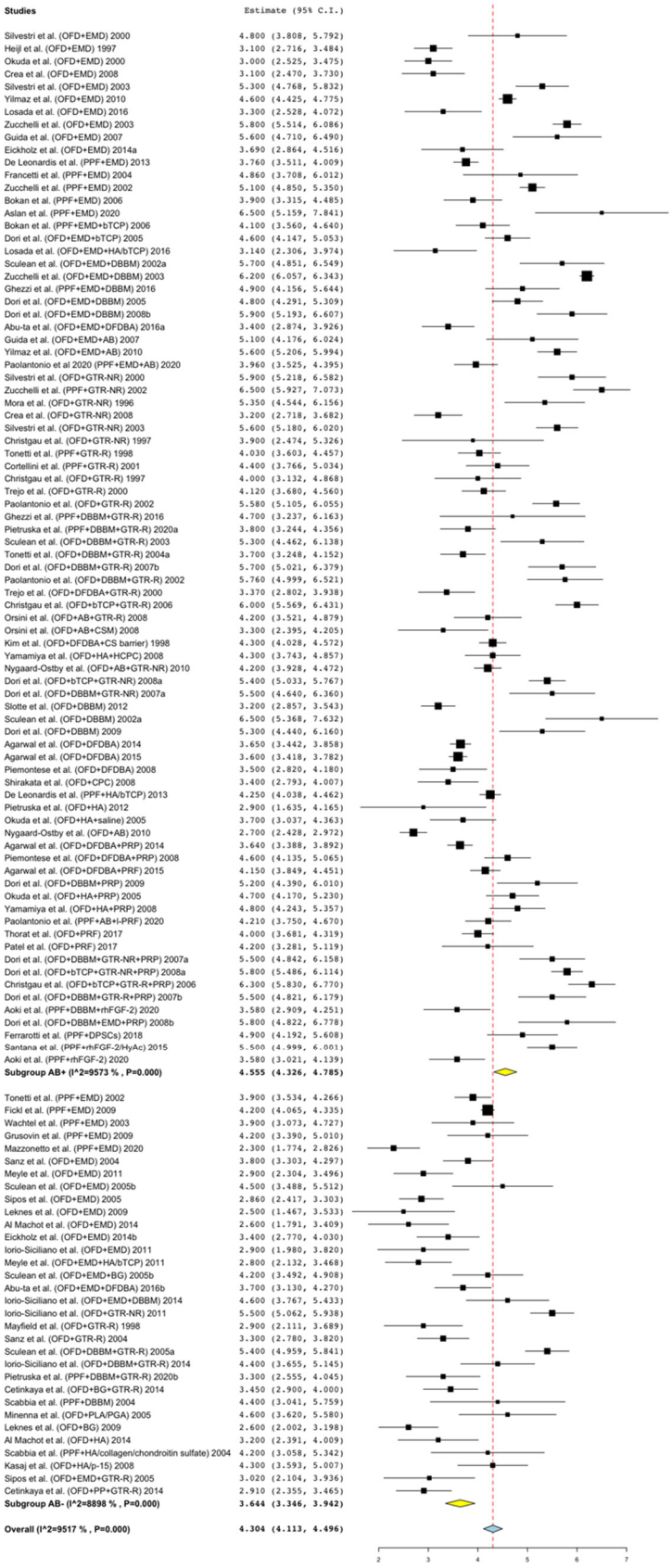
11 studies included for quantitative synthesis

Supplementary Material S5: Risk of bias.



Supplementary Material S6: Forest plots of single-arm meta-analyses and meta-regression models using AB as factor in intrabony defects.

PPD reduction forest plot



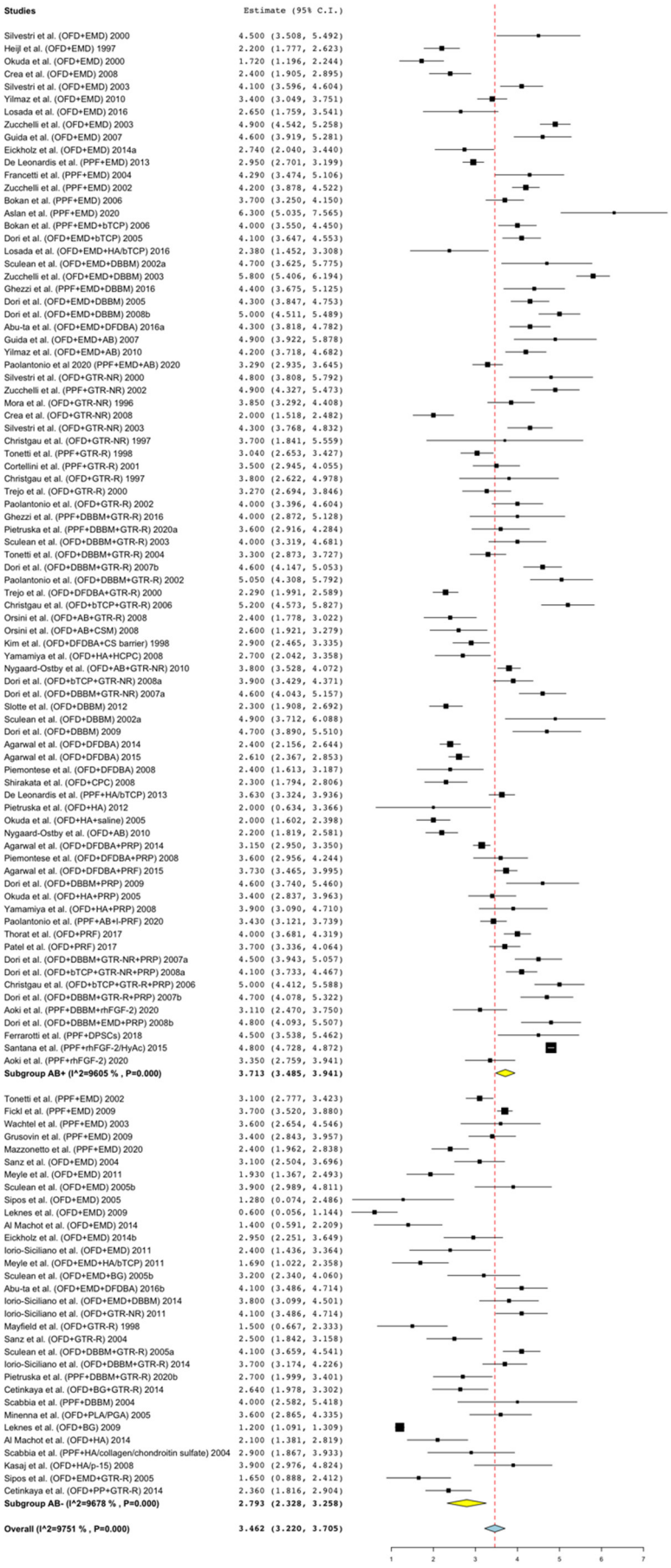
PPD reduction model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			4.553	4.346	4.759	0.105	< 0.001
AB	AB+	82					
	AB-	32	-0.908	-1.302	-0.514	0.201	< 0.001
Omnibus *p*-Value							0.000

PPD reduction adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
AB+	82	4.553	4.346	4.759	0.105
AB-	32	3.644	3.309	3.980	0.171

CAL gain forest plot



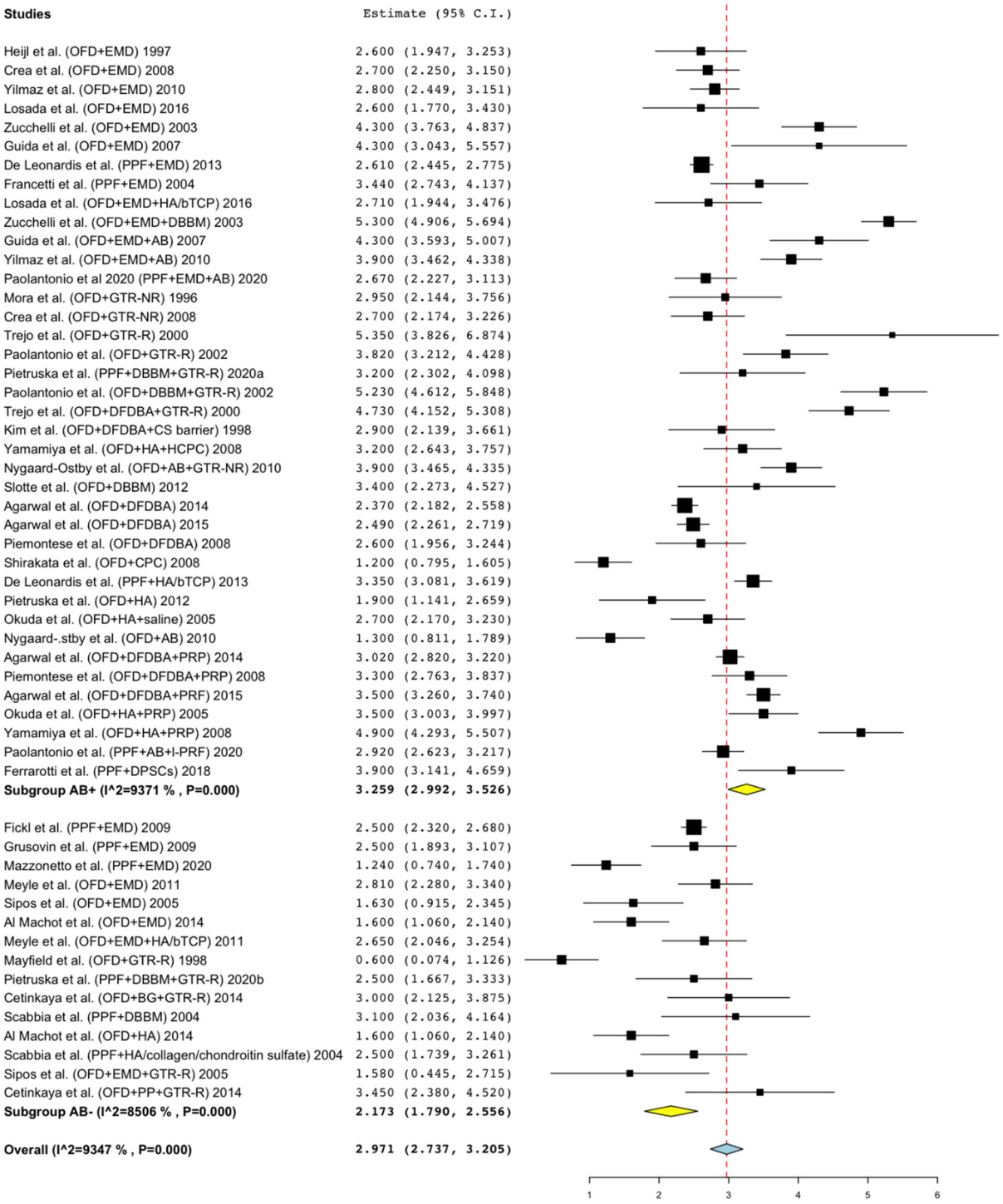
CAL gain model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			3.710	3.499	3.921	0.108	< 0.001
AB	AB+	82					
	AB-	32	-0.919	-1.322	-0.516	0.206	< 0.001
Omnibus *p*-Value							0.000

CAL gain adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
AB+	82	3.710	3.499	3.921	0.108
AB-	32	2.791	2.448	3.135	0.175

Bone gain forest plot



Bone gain model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			3.262	2.976	3.548	0.146	< 0.001
AB	AB+	39					
	AB-	15	-1.076	-1.627	-0.525	0.281	< 0.001
Omnibus *p*-Value							0.000

Bone gain adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
AB+	39	3.262	2.976	3.548	0.146
AB-	15	2.187	1.716	2.657	0.240

Supplementary Material S7: Meta-regression using AB as factor in intrabony defects for the EMD subgroup.

PPD reduction model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			4.372	3.919	4.825	0.231	< 0.001
AB	AB+	15					
	AB-	13	-0.984	-1.650	-0.318	0.340	0.004
Omnibus *p*-Value							0.004

PPD reduction adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
AB+	15	4.372	3.919	4.825	0.231
AB-	13	3.388	2.900	3.876	0.249

CAL gain model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			3.593	3.060	4.126	0.272	<0.001
AB	AB+	15					
	AB-	13	-0.980	-1.766	-0.193	0.401	0.015
Omnibus *p*-Value							0.015

CAL gain adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
AB+	15	3.593	3.060	4.126	0.272
AB-	13	2.613	2.035	3.192	0.295

Supplementary Material S8: Meta-regression using AB as factor in intrabony defects for the Graft +/- GTR-R subgroup.

PPD reduction model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			4.189	3.799	4.578	0.199	< 0.001
AB	AB+	23					
	AB-	10	-0.219	-0.941	0.504	0.369	0.553
Omnibus *p*-Value							0.553

PPD reduction adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
AB+	23	4.189	3.799	4.578	0.199
AB-	10	3.970	3.361	4.578	0.310

CAL gain model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			3.192	2.783	3.601	0.209	<0.001
AB	AB+	23					
	AB-	10	-0.154	-0.908	0.599	0.384	0.688
Omnibus *p*-Value							0.688

CAL gain adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
AB+	23	3.192	2.783	3.601	0.209
AB-	10	3.038	2.405	3.671	0.323

Supplementary Material S9: Meta-regression using AB type as factor in intrabony defects.

PPD reduction model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			4.717	4.456	4.978	0.133	< 0.001
AB Type	Penicillin	55					
	Tetracycline	17	-0.252	-0.792	0.288	0.276	0.360
Omnibus *p*-Value							0.360

PPD reduction adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
Penicillin	55	4.717	4.456	4.978	0.133
Tetracycline	17	4.465	3.992	4.937	0.241

CAL gain model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			3.924	3.688	4.161	0.121	<0.001
AB Type	Penicillin	55					
	Tetracycline	17	-0.240	-0.730	0.250	0.250	0.338
Omnibus *p*-Value							0.338

CAL gain adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
Penicillin	55	3.924	3.688	4.161	0.121
Tetracycline	17	3.685	3.255	4.114	0.219

Supplementary Material S10: Meta-regression using AB type as factor in furcation defects.

PPD reduction model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			1.889	1.427	2.350	0.235	< 0.001
AB Type	Penicillin	12					
	Tetracycline	9	0.341	-0.362	1.045	0.359	0.342
Omnibus *p*-Value							0.342

PPD reduction adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
Penicillin	12	1.889	1.427	2.350	0.235
Tetracycline	9	2.230	1.699	2.761	0.271

CAL gain model results

Covariate	Level	Study arms	Coefficients	Lower bound	Upper bound	Std. error	*p*-Value
Intercept			1.304	0.852	1.757	0.231	<0.001
AB Type	Penicillin	10					
	Tetracycline	9	0.313	-0.338	0.964	0.332	0.346
Omnibus *p*-Value							0.346

CAL gain adjusted means

Level	Study arms	Adjusted Means	Lower bound	Upper bound	Std. error
Penicillin	10	1.304	0.852	1.757	0.231
Tetracycline	9	1.617	1.149	2.086	0.239