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Review

Biomimetic Remineralization Strategies on Dentin Bond Stability—Systematic Review and Network Meta-Analysis

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Abstract: This systematic review and network meta-analysis aimed to evaluate the bond strength of artificial caries-affected dentin (ACAD) of permanent human teeth with and without biomimetic remineralization (BR), assessed in in vitro studies. Following PRISMA guidelines, we conducted a systematic search until June 2023, identifying 82 eligible articles for full-text analysis. We assessed the study characteristics, methodological quality, and summary results. Bond strength was examined immediately and after artificial aging using three bond strength tests. We performed meta-regressions (using OpenBUGS software) to explore the relationship between the independent variable's adhesive application technique (Etch-and-Rinse or Self-Etch) and ACAD protocol (chemical or biological) and the dependent variable bond strength. Additionally, we conducted random-effect NMAs (using CINEMA software) to compare the effect of multiple interventions per application technique and ACAD protocol simultaneously. Among the included studies that compared various BR strategies. Most studies (19 out of 22) presented a medium risk of bias. In some comparisons, meta-regression results revealed a significant association between bond strength at 24h and both the adhesive application technique and the ACAD protocol. Our findings indicate the potential of BR to enhance bond strength in human ACAD in in vitro settings.

Keywords: adhesives; biomimetic material; dentin-bonding agents; tooth demineralization; tooth remineralization

1. Introduction

Dentin-bonding procedures pose persistent challenges in Operative Dentistry despite the currently significant successes achieved in enamel bonding [1]. A well-documented issue in the literature is the gradual deterioration of the adhesive systems' bond strength to dentin over time, primarily due to hybrid layer degradation [2]. This compromise in dentin bonding significantly limits the lifespan of adhesive restorations [3].

The ideal dentin-bonding process involves exposing the collagen network and facilitating the penetration of chelating agents or acidic functional monomers to form the crucial hybrid layer [4]. However, a portion of the exposed collagen matrix remains unfilled with resin monomers, rendering it susceptible to hydrolytic degradation over time, thus jeopardizing the longevity of dentin bonding

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due to nanoleakage. The incomplete water removal within hydrophilic resin monomers also creates a weak point in resin-dentin bonds [5,6]. These phenomena have led to the exploration of an innovative approach to improve dentin adhesion: the biomimetic remineralization (BR) of collagen fibrils exposed during biomineralization [7,8].

There are two primary BR strategies: incorporating mineral-promoting agents into adhesives or restorative materials and applying pre-treating solutions before adhesive systems [9,10]. For the first strategy, researchers have developed experimental adhesive systems or restorative materials containing bioactive components like calcium phosphate or other inorganic materials that supply mineral ions to remineralize the resin-dentin interface [11,12]. The second strategy involves solutions containing non-collagenous proteins or template analogs to stimulate intra/extra-fibrillar mineralization [13,14]. These remineralizing agents facilitate the formation of nanometric apatite crystals, which replace excess water, mimicking physiological remineralization [14], thus enhancing the structural integrity of dentin and extending the longevity of the dentin-composite resin bonding interface [7,15,16]. Some studies have also suggested that these agents can inhibit the degradation of exposed collagen by attracting calcium to it [17].

Therefore, it is essential to analyze the challenges posed by dentin-bonding procedures and the potential advantages of BR procedures. This systematic review uses a comprehensive network meta-analysis (NMA) to assess and compare the bond strength of human artificial caries-affected dentin (ACAD) with and without BR evaluated in in vitro studies.

2. Materials and Methods

2.1. Search Strategy

The systematic review was registered in PROSPERO and performed according to the PRISMA statement [41]. On June 2023, PubMed, ISI Web of Science, and SCOPUS were searched to identify potentially relevant studies. In addition to electronic databases, reference lists of included studies and relevant systematic reviews were also searched. Complete search strategies are available in Appendix 1.

2.2. Outcomes

The primary outcome of this systematic review was the mean difference between the bond strength of ACAD with and without BR by different adhesive application techniques —etch-and-rinse (ER) or self-etch (SE)— and ACAD protocols —chemical or biological.

2.3. Eligibility Criteria

The following inclusion criteria were established: experimental or quasi-experimental in vitro studies investigating the influence of any BR procedure on the ACAD-adhesive interface’s bond strength; having a control group (dentin without BR) for comparison; ACAD protocols in which agents were applied immediately prior to bonding; outcomes measured by shear, micro-shear, or micro-tensile bond strength (SBS, μSBS, μTBS) tests. Exclusion criteria included studies with doped materials or modified adhesive systems.

The terms “caries-affected dentin,” “demineralized dentin,” and “artificial eroded dentin” were considered as references to ACAD. ACAD consists of human dentin tissue artificially demineralized to mimic the characteristics of dentin affected by carious changes. It is created by exposing dentin tissue to acidic or demineralizing solutions to remove mineral content, leading to softening and structural alterations like those observed in natural caries-affected dentin. [46,53,54] This demineralization process is performed in a laboratory setting to replicate the conditions and properties of carious dentin.

The BR procedures considered included any technique aimed at restoring and strengthening damaged or demineralized dentin in a way that mimicked the tooth’s natural remineralization process.[3,52]

2.4. Data Extraction and Collection

Firstly, two authors (RC and JP) independently reviewed titles and abstracts to select articles for further assessment per their consensus. Disagreements were resolved by discussion until a consensus was reached. Full texts of the selected articles were retrieved, and the same two authors further evaluated and independently extracted data from them. The reference lists of included full texts were also screened and cross-referred.

In case of missing/unclear items (e.g., missing bond strength measurements, missing standard deviation values, uncertain number of samples used) or inconsistent data within or between sources (e.g., differences in data between text and figures, bond strength measurements only in figures), authors of the respective studies were contacted via e-mail. Two follow-up e-mails were sent with a one-week interval.

Search results from online databases were imported to Endnote20 (Clarivate, Philadelphia, USA), where duplicates were removed. The Rayyan app[55] was used to keep records and assist in abstract screening, full-text review, and data extraction. Data for the systematic review and NMA were extracted using a custom-made Excel worksheet.

The following items were extracted from each source: authors; year of publication; study randomization; risk of bias; means and standard deviations; number of samples; ACAD protocol (chemical or biological); BR procedure; adhesive type used (ER, SE, or universal) and adhesive application technique; method of bond strength assessment; outcome measurement time point (24h or after artificial aging method).

The authors classified and grouped the treatments by active substance into nine groups: fluorine, calcium phosphate, peptide, silica, hydroxyapatite, flavonoids, calcium, and 2-hydroxyethyl methacrylate/ethylene glycol dimethacrylate (HEMA/EDGMA).

2.5. Risk of Bias Assessment

Two authors (RC and JP) independently assessed the risk of bias in the included in vitro studies according to the QUIN tool [56]. Disagreements were resolved by discussion until a consensus was reached. Each study was graded accordingly as having high, medium, or low risk based on the final score of the tool: low risk of bias if >70%, medium risk of bias if 50–70%, and high risk of bias if <50%.

2.6. Data Synthesis and Statistical Analysis

2.6.1. Qualitative Synthesis

Qualitative evidence synthesis was performed by descriptive analysis of the studies' characteristics, methodologic quality, and summary results, using a narrative description and summary tables providing a clear overview of the individual study characteristics, main findings, and methodological assessments.

2.6.2. Quantitative Synthesis

Quantitative syntheses were performed by random-effects NMA of the mean difference between the intervention and control groups. NMAs were conducted using the CINEMA software, based on R software packages meta an netmeta [57,58], by adhesive application technique and ACAD protocol and included all possible pair-wise comparisons based on direct and indirect evidence. In accordance with Cochrane guidelines [59], when trials had more than two arms, we combined interventions into a single group if they belonged to the same intervention category. When more than one independent treatment-comparator pair existed in each study, we treated them as if they pertained to independent studies. Following Cochrane guidelines[59] standard deviations were imputed from other included studies in cases where they were not available in the manuscript and could not be obtained upon contact with the authors.

The rating of confidence in the results was assessed following the CINEMA approach by evaluating the domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. The minimal clinically important difference was established by consensus of the authors as 7 megapascals (MPa).

In addition, since it has been reported that the adhesive application technique (ER vs. SE) [8,25–27] and the ACAD protocol (chemical vs. biological) [7,28] might influence BR treatment's effect, we explored effects of these two covariates in NMA effects estimates by random-effects Bayesian meta-regressions using the OpenBUGS software (Code in Appendix 1). Within a random-effects Bayesian framework, the OpenBUGS software [60] was also used to estimate each intervention's posterior median ranks and probability to be the best.

Finally, to assess the robustness of the results obtained from NMAs, as assumptions change, we conducted the following two sensitivity analyses:

1. Random selection of one treatment intervention: Instead of combining interventions belonging to the same intervention category, as in the main analysis, we randomly selected only one.
2. Removal of SBS test results: Instead of including all bond strength tests, as in the main analysis, we included only results from µSBS and µTBS tests.

3. Results and Discussion

3.1. Search Results

In the electronic search, 1874 records were identified after eliminating duplicates. Only 82 were selected for full-text screening. Reasons for the exclusion of screened full texts are shown in Appendix Table 1. After critical appraisal, 23 remaining articles were included in our systematic review and 22 in the NMA. A PRISMA flow diagram of the complete process is illustrated in Figure 1.

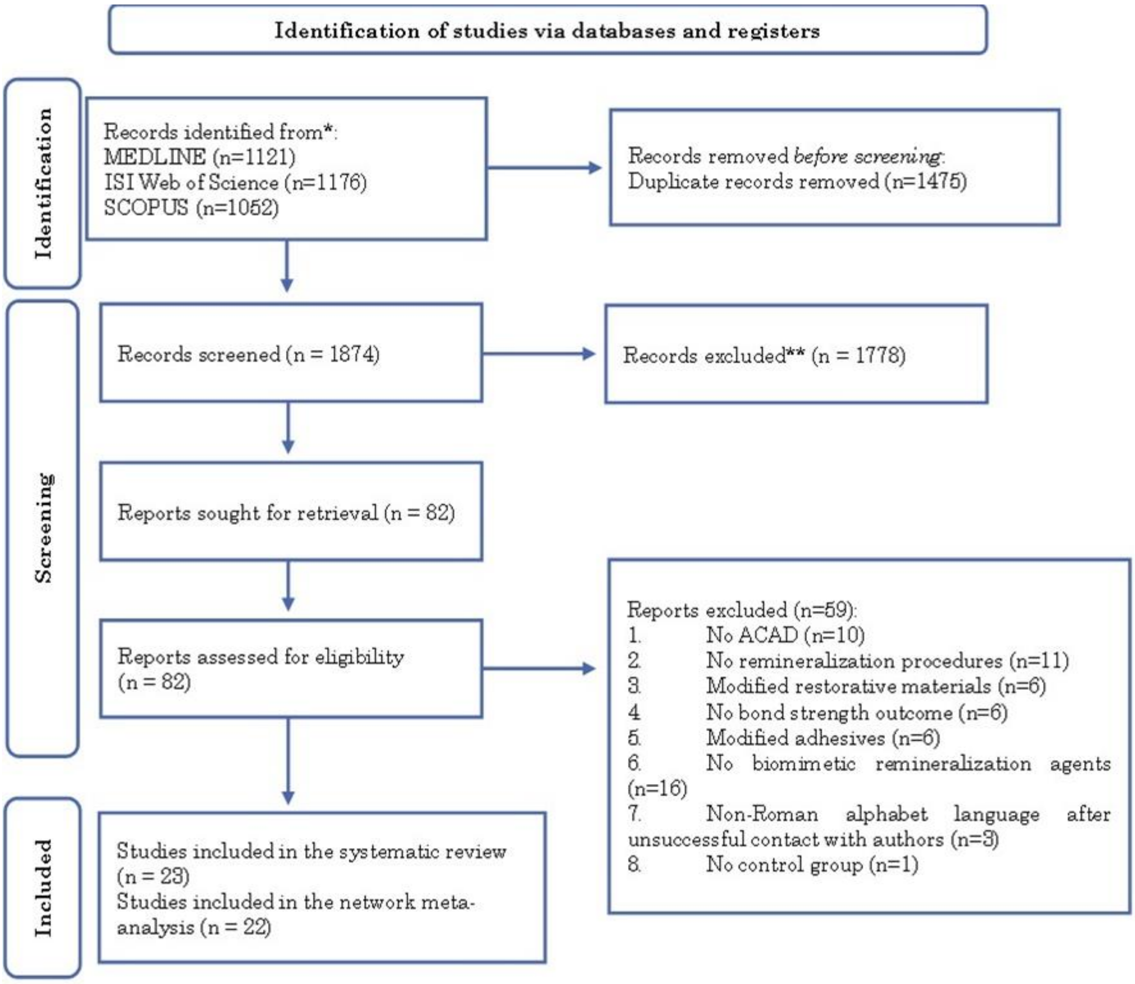


Figure 1. PRISMA 2020 flow diagram of literature search for new systematic reviews[41].

3.2. Characteristics of Included Studies

Table 1 displays the characteristics of the included studies, interventions, and outcomes. Of the 23 studies in the systematic review, 16 were experimental [8,15,18–31] and seven were quasi-experimental [7,14,32–36]. One study was excluded from the NMA because it lacked reporting data, which could not be obtained upon direct contact with the authors. (Appendix Table A2)

All 22 studies in the NMA performed immediate (24h) bond strength measurements. Of those studies, 13 investigated the ER technique associated with the chemical ACAD protocol [7,8,18–20,22,23,27,29,31,35,37], five the ER with the biological ACAD [7,15,21,28,33], 13 the SE with the chemical ACAD [8,14,20,22,23,25,26,32,34,36–39], and only one the SE with the biological ACAD [28]; the latter was insufficient to perform an NMA. In turn, 11 studies measured bond strength after artificial aging of the specimens: four used thermocycling [14,21,25,40], and seven stored them in a fluid solution for months [15,18,29,31–33,36].

Overall, both immediate and aged bond strength in the ACAD benefited from BR. The artificial aging method globally diminished bond strength values, and thermocycling caused the lowest bond strength.

Table 1. Characteristics of the included studies, interventions, and outcomes.

	Study/Year	RoB (score)	Study type	ACAD	BRP	Groups	N (teeth)	Mean (SD)	AT	OM Test
24-hour measurement										
ER + C	Altinci et al. 2018 [31]	M(50)	Exp.	32% phosphoric acid	Control	Control	9	35.27 (4.63)[a]	ER	µTBS
					F	NaF + 6mM F		34.7 (4.63) [a]		
						NaF + 24mM F		54.66 (4.63) [a]		
						NaF+179mM F		47.11 (4.63) [a]		
						KF + 6mM F		51.8 (4.63) [a]		
						KF + 24mM F		48.56 (4.63) [a]		
						KF + 179mM F		47.58 (4.63) [a]		
						CaF2 + 6mM F		36.34 (4.63) [a]		
						CaF2+24mM F		39.49 (4.63) [a]		
						CaF2+179mM F		48.47 (4.63) [a]		
						Excite F		48.84 (4.63) [a]		
	Barbosa-Martins et al. (A) 2018[8]	M(54)	Exp.	6% CMC	Control	Control	6	26.38 (8.64)	ER	µTBS
					F	NaF		33.43 (10.41)		
					CaP	CPP-ACP		45.25 (8.82)		
					Pept.	P11-4		46.42 (12.03)		

Barbosa-Martins et al. (B) 2018[7]	M(54)	Quasi-Exp.	6% CMC	Control	Control	6	21.96 (5.92)	ER	µTBS
				F	NaF		33.43 (10.42)		
				CaP	CPP-ACP		45.25 (8.83)		
				Pept.	P11-4		46.42 (12.03)		
Bauer et al. 2018[18]	M(50)	Exp.	35% phosphoric acid	Control	Control	13	17 (4.1)	ER	SBS
				CaP	5% NbG		17.9 (5)		
					10%NbG		15.8 (6.4)		
					20%NbG		16.6 (4.4)		
					40%NbG		15.8 (4.1)		
Cardenas et al. 2021[19]	M(63)	Exp.	pH cycling	Control	Control	5	33.74 (3.6)	Univ.	µTBS
				F	SDF 12%		38.03 (3.5)		
					SDF 38%		39.68 (2.7)		
					SDF 38% without KI		39.38 (2.5)		
				Control	Control		34.9 (3.3)		
				F	SDF 12%		42.45 (2.9)		
					SDF 38%		40.47 (4.2)		
					SDF 38% without KI		41.3 (2.5)		
Chen et al. 2020[14]	M(54)	Quasi-Exp.	pH cycling	Control	Control	4	13.8 (3.35) [a]	Univ.	µTBS
				CaP	Ca/P-PILP		23.8 (3.35) [a]		
				Pept.	PAA-PASP		14 (3.35) [a]		
				CaP	Ca/P		11.9 (3.35) [a]		
Cifuentes-Jimenez et al. 2021[20]	M(50)	Exp.	pH cycling	Control	Control	5	31.4 (4.63) [a]	ER	µTBS
				F	Cariestop		15.1 (4.63) [a]		
					RivaStar1		10.1 (4.63) [a]		
					RivaStar2		7.5 (4.63) [a]		
					Saforide		23.2 (4.63) [a]		
Gungormus et al. 2021[22]	M(50)	Exp.	37% phosphoric acid	Control	Control	10	15.38 (1.3)	ER	SBS
				CaP	NPR 60min		15.85 (1.44)		
				Pept.	PR 10 min		20.81 (1.74)		
					PR 30 min		20 (1.68)		
					PR 60 min		16.21 (1.1)		
Krithi et al. 2020[23]	M(54)	Exp.	0.5% citric acid	Control	Control	15	11.83 (0.43)	ER	µSBS

				F	NaF		11.56 (0.15)		
				CaP	CPP-ACP		12.12 (0.57)		
					Novamin		11.66 (0.28)		
				Ca	Non-Fidated		11.94 (0.27)		
Meng et al. 2021[24]	M(50)	Exp.	1% citric acid	Control	Control	8	46.8^{b} (4.63)^{a}	Univ.	µTBS
				Hap	Biorepair		50.72^{b} (4.63)^{a}		
					Dontodent Sensitive		50.71^{b} (4.63)^{a}		
					nHAp		51.24^{b} (4.63)^{a}		
				Control	Control		50.41^{b} (4.63)^{a}		
				Hap	Biorepair		53.38^{b} (4.63)^{a}		
					Dontodent Sensitive		54.5^{b} (4.63)^{a}		
					nHAp		55.63^{b} (4.63)^{a}		
				Control	Control		46.85^{b} (4.63)^{a}		
				Hap	Biorepair		50.77^{b} (4.63)^{a}		
					Dontodent Sensitive		53.82^{b} (4.63)^{a}		
					nHAp		55^{b} (4.63)^{a}		
Pulidindi et al. 2021[40]	M(63)	Exp.	37% phosphoric acid	Control	Control	15	48.84 (4.63)^{a}	ER	µTBS
				Pept.	P11-4		38.66 (4.63)^{a}		
				CaP	CPP-ACP		34.07 (4.63)^{a}		
				Control	Control		22.63 (4.63)^{a}		
				Pept.	P11-4		25.37 (4.63)^{a}		
				CaP	CPP-ACP		23.62 (4.63)^{a}		
Van Duker et al. 2019[35]	H(46)	Quasi-Exp.	7 days in ADS	Control	Control	10	23.5 (10.7)	Univ.	µTBS
				F	SDF 38%		19.8 (8.4)		
					SDF 38% without KI		7.9 (6.6)		
Yang et al. 2018[29]	M(50)	Exp.	1% citric acid	Control	Control	10	46.5^{b} (4.63)^{a}	ER	µTBS

					CaP	CPP-ACP		42.6 ^{b} (4.63) ^{a}		
						Novamin		43.3 ^{b} (4.63) ^{a}		
					Control	Control		22.3 ^{b} (4.63) ^{a}		
					CaP	CPP-ACP		41.2 ^{b} (4.63) ^{a}		
						Novamin		31.4 ^{b} (4.63) ^{a}		
ER + B	Barbosa-Martins et al. (B) 2018	M(54)	Quasi-Exp.	BHI+ S.Mutans	Control	Control	6	22.89 (2.68)	ER	µTBS
					F	NaF		26.94 (6.7)		
					CaP	CPP-ACP		47.95 (6.69)		
					Pept.	P11-4		42.07 (7.83)		
	Dávila-Sánchez et al. 2020[21]	M(54)	Exp.	Cariogenic+ S. Mutans	Control	Control	7	14.42 (4.43)	Univ.	µTBS
					Fls.	QUE		24.58 (4.9)		
						HES		18.41 (5.3)		
						RUT		26 (5.51)		
						NAR		24.64 (3.7)		
						PRO		20.66 (3.92)		
	de Sousa et al. 2019[33]	M(50)	Quasi-Exp.	Cariogenic+ S. Mutans	Control	Control	8	21.07 (3.24)	ER	µTBS
					Pept.	P11-4		42.07 (7.83)		
	Moreira et al. 2021[15]	M(54)	Exp.	Cariogenic+ S. Mutans	Control	Control	8	25.4 (2.45)	ER	µTBS
					F	NaF		25.47 (4.8)		
					CaP	CPP-ACP		41.79 (5.85)		
					Pept.	P11-4		40.12 (3.62)		
	Siqueira et al. 2020[28]	M(63)	Exp.	Cariogenic+ S. Mutans	Control	Control	5	16.81 (3.5)	Univ.	µTBS
					F	SDF 12%		21.11 (4.1)		
						SDF 38%		24.36 (3.4)		
					Control	Control		19.89 (2.4)		
					F	SDF 12%		24.47 (3.4)		
						SDF 38%		26.32 (2)		
SE + C	Atomura et al. 2018[32]	H(46)	Quasi-Exp.	7 days in ADS	Control	Control	unknown	48.3 (13)	SE	µTBS
					F	NaF		47.7 (8.6)		
						FCP complex		43.9 (14.3)		
	Barbosa-Martins et al. (A) 2018	M(54)	Exp.	48h 6% CMC	Control	Control	6	25.38 (8.58)	SE	µTBS
					F	NaF		35.59 (9.18)		

				CaP	CPP-ACP		48.11 (11.71)		
				Pept.	P11-4		25.7 (8.95)		
Cardenas et al. 2021	M(63)	Exp.	pH cycling	Control	Control	5	33.74 (3.6)	Univ.	µTBS
				F	SDF 12%		39.53 (4.2)		
					SDF 38%		41.31 (2)		
					SDF 38% without KI		40.55 (2.9)		
				Control	Control		36.56 (4.1)		
				F	SDF 12%		39.98 (1.7)		
					SDF 38%		41.08 (3)		
					SDF 38% without KI		41.57 (2.4)		
Chen et al. 2020	M(54)	Quasi-Exp.	pH cycling	Control	Control	4	13.8 (3.35) [a]	Univ.	µTBS
				CaP	Ca/P-PILP		23.8 (3.35) [a]		
				Pept.	PAA-PASP		14 (3.35) [a]		
				CaP	Ca/P		11.9 (3.35) [a]		
				Control	Control		9.2 (3.35) [a]		
				CaP	Ca/P-PILP		15.1 (3.35) [a]		
				Pept.	PAA-PASP		9.3 (3.35) [a]		
				CaP	Ca/P		9.8 (3.35) [a]		
Cifuentes-Jimenez et al. 2021	M(50)	Exp.	pH cycling	Control	Control	5	31.4 (3.35) [a]	SE	µTBS
				F	Cariestop		9.6 (3.35) [a]		
					Saforide		8.03 (3.35) [a]		
Gungormus et al. 2021	M(50)	Exp.	37% phosphoric acid	Control	Control	10	15.38 (1.3)	SE	SBS
				CaP	NPR 60min		15.49 (1.17)		
				Pept.	PR 10 min		18.93 (0.99)		
					PR 30 min		19.62 (0.9)		
					PR 60 min		21.73 (1.57)		
Krithi et al. 2020	M(54)	Exp.	0.5% citric acid	Control	Control	15	11.83 (0.43)	SE	µSBS
				F	NaF		12.4 (0.18)		
				CaP	CPP-ACP		11.97 (0.39)		
					Novamin		11.97 (0.17)		
				Ca	Non-Fidated		10.62 (0.11)		

Meng et al. 2021	M(50)	Exp.	1% citric acid	Control	Control	8	46.8 ^{b} (3.35) ^{a}	Univ.	µTBS
				Hap	Biorepair		47.62 ^{b} (3.35) ^{a}		
					Dontodent Sensitive		51.89 ^{b} (3.35) ^{a}		
					nHAp		51.89 ^{b} (3.35) ^{a}		
				Control	Control		56.3 ^{b} (3.35) ^{a}		
				Hap	Biorepair		51.62 ^{b} (3.35) ^{a}		
					Dontodent Sensitive		57.47 ^{b} (3.35) ^{a}		
					nHAp		58.39 ^{b} (3.35) ^{a}		
				Control	Control		56.8 ^{b} (3.35) ^{a}		
				Hap	Biorepair		52.25 ^{b} (3.35) ^{a}		
					Dontodent Sensitive		50.8 ^{b} (3.35) ^{a}		
					nHAp		56.1 ^{b} (3.35) ^{a}		
Paik et al. 2022[25]	M(50)	Exp.	35% phosphoric acid	Control	Control	4	21.66 (3.35) ^{a}	Univ.	µTBS
				Fls.	ICT		24.4 (3.35) ^{a}		
					FIS		26.81 (3.35) ^{a}		
					SIB		25.65 (3.35) ^{a}		
					CPIC		25.97 (3.35) ^{a}		
					ICT+ C		30.63 (3.35) ^{a}		
					FIS+ C		25.63 (3.35) ^{a}		
					SIB+ C		24.76 (3.35) ^{a}		
Pei et al. 2019[26]	M(50)	Exp.	1% citric acid	Control	Control	4	43.61 (3.35) ^{a}	SE	µTBS
				Hap	Biorepair		33.16 (3.35) ^{a}		
					Dontodent Sensit.		35.41 (3.35) ^{a}		
					nHAp		46.92 (3.35) ^{a}		
				Control	Control		47.47 (3.35) ^{a}		
				Hap	Biorepair		43.47 (3.35) ^{a}		

						Dontodent Sensit.		42.3 (3.35) [a]		
						nHAp		41.24 (3.35) [a]		
	Priya et al. 2020[34]	H(46)	Quasi-Exp.	37% phosphoric acid	Control	Control	13	6.677 (1.254)	Univ.	SBS
					F	VivaSens		3.332 (0.78)		
						MS Coat F		3.127 (0.478)		
					HEMA	GLUMA Desensit.		4.572 (0.718)		
						Systemp		9.697 (1.127)		
	Zang et al. 2018[30]	M(50)	Exp.	37% phosphoric acid	Control	Control	6	19.73 [b] (2.108)	Univ.	SBS
					SiO2	Charged mesoporous		20.57 [b] (2.244)		
	Zumstein et al. 2018[42]	M(50)	Quasi-Exp.	pH cycling	Control	Control	20	24.7 (8.1) [c]	SE	µTBS
					F	SnCl2/ AmF4		23.3 (8.2) [c]		
					Control	Control		23.73 (8) [c]	Univ.	
					F	SnCl2/ AmF4		21.39 (6.8) [c]		
SE + B	Siqueira et al. 2020	M(63)	Exp.	Cariogenic+ S. Mutans	Control	Control	5	16.81 (3.5)	Univ.	µTBS
					F	SDF 12%		20.02 (4.6)		
						SDF 38%		25.21 (3)		
					Control	Control		19.61 (3.3)		
					F	SDF 12%		23.82 (4.4)		
						SDF 38%		27.16 (3.6)		
TMC measurement										
ER + C	Pulidindi et al. 2021	M(63)	Exp.	37% phosphoric acid	Control	Control	15	48.84 (4.63) [a]	ER	µTBS
					Pept.	P11-4		25.37 (4.63) [a]		
					CaP	CPP-ACP		23.62 (4.63) [a]		
ER + B	Dávila-Sánchez et al. 2020	M(54)	Exp.	Cariogenic+ S. Mutans	Control	Control	7	14.42 (4.43)	Univ.	µTBS
					Fls.	QUE		12.02 (5.21)		
						HES		15.73 (6.07)		
						RUT		21.08 (4.75)		
						NAR		22.12 (2.92)		
						PRO		17.2 (2.72)		

SE + C	Chen et al. 2020	M(54)	Quasi-Exp.	pH cycling	Control	Control	4	13.8 (3.35) ^{a}	Univ.	µTBS
					CaP	Ca/P-PILP		15.1 (3.35) ^{a}		
					Pept.	PAA-PASP		9.3 (3.35) ^{a}		
					CaP	Ca/P		9.8 (3.35) ^{a}		
	Paik et al. 2022	M(50)	Exp.	35% phosphoric acid	Control	Control	4	21.66 (3.35) ^{a}	Univ.	µTBS
					Fls.	ICT		20.53 (3.35) ^{a}		
						FIS		19.4 (3.35) ^{a}		
						SIB		22.04 (3.35) ^{a}		
						CPIC		23.43 (3.35) ^{a}		
						ICT+ C		26.74 (3.35) ^{a}		
						FIS+ C		23.42 (3.35) ^{a}		
						SIB+ C		25.17 (3.35) ^{a}		
Storage in a fluid solution for 3-month measurement										
ER + C	Bauer et al. 2018	M(50)	Exp.	35% phosphoric acid	Control	Control	13	17 (4.1)	ER	SBS
					CaP	5% NbG		11.8 (3.7)		
						10%NbG		13.9 (3.2)		
						20%NbG		13.2 (2.7)		
						40%NbG		14.7 (2.9)		
SE + C	Atomura et al. 2018	H(46)	Quasi-Exp.	7 days in ADS	Control	Control	unknown	48.3 (13)	SE	µTBS
					F	NaF		42.6 (12.1)		
						FCP complex		47.4 (9.2)		
Storage in a fluid solution for 6-month measurement										
ER + C	Altinci et al. 2018	M(50)	Exp.	32% phosphoric acid	Control	Control	9	35.27 (4.63) ^{a}	ER	µTBS
					F	NaF + 6mM F		50.31 (4.63) ^{a}		
						NaF + 24mM F		49.28 (4.63) ^{a}		
						NaF+179mM F		47.73 (4.63) ^{a}		
						KF + 6mM F		41.95 (4.63) ^{a}		
						KF + 24mM F		51.53 (4.63) ^{a}		
						KF + 179mM F		54.29 (4.63) ^{a}		
						CaF2 + 6mM F		52.25 (4.63) ^{a}		
						CaF2+24mM F		41.1 (4.63) ^{a}		

						CaF2+179mM F		40.85 (4.63) ^{a}		
						Excite F		46.22 (4.63) ^{a}		
	de Sousa et al. 2019	M(50)	Quasi-Exp.	Cariogenic+ S. Mutans	Control	Control	8	21.07 (3.24)	ER	µTBS
					Pept.	P11-4		31.98 (3.44)		
	Moreira et al. 2021	M(54)	Exp.	Cariogenic+ S. Mutans	Control	Control	8	25.4 (2.45)	ER	µTBS
					F	NaF		18.36 (5.5)		
					CaP	CPP-ACP		36.55 (4.27)		
Storage in a fluid solution for 12-month measurement										
ER+C	Altinci et al. 2018	M(50)	Exp.	32% phosphoric acid	Control	Control	9	35.27 (4.63) ^{a}	ER	µTBS
					F	NaF + 6mM F		51.63 (4.63) ^{a}		
						NaF + 24mM F		45.56 (4.63) ^{a}		
						NaF+179mM F		39.31 (4.63) ^{a}		
						KF + 6mM F		40.01 (4.63) ^{a}		
						KF + 24mM F		51.85 (4.63) ^{a}		
						KF + 179mM F		36.48 (4.63) ^{a}		
						CaF2 + 6mM F		33.06 (4.63) ^{a}		
						CaF2+24mM F		38.24 (4.63) ^{a}		
						CaF2+179mM F		0.88 (4.63) ^{a}		
						Excite F		42.4 (4.63) ^{a}		
	Yang et al. 2018	M(50)	Exp.	1% citric acid	Control	Control	10	46.5 ^{b} (4.63) ^{a}	ER	µTBS
					CaP	CPP-ACP		41.2 ^{b} (4.63) ^{a}		
						Novamin		31.4 ^{b} (4.63) ^{a}		
SE+C	Zumstein et al. 2018	M(50)	Quasi-Exp.	pH cycling	Control	Control	20	24.7 (8.1) ^{c}	SE	µTBS
					F	SnCl2/ AmF4		16.3 (6.36) ^{c}		
					Control	Control		15.43 (6.53) ^{c}	Univ.	
					F	SnCl2/ AmF4		14.12 (7.12) ^{c}		
Storage in a fluid solution for 18-month measurement										
ER+B	Moreira et al. 2021	M(54)	Exp.	Cariogenic+ S. Mutans	Control	Control	8	25.4 (2.45)	ER	µTBS

F	NaF	7.81 (4.48)
CaP	CPP-ACP	26.01 (3.28)
Pept.	P11-4	25.24 (3.98)

a- Input SD Values; b- Information given by authors; c- Information from another meta-analysis.

Legend: B- Biological; C- Chemical; RoB- Risk of bias; ACAD- Artificial caries-affected dentin; BRP- Biomimetic remineralization procedure; SD- Standard deviation; AT- Adhesive technique; OM-Outcome measurement; ADS- Artificial demineralization solution; M- Medium; H- High; Exp.-Experimental; ER- Etch-and-rinse; SE- Self-etch; Univ.- Universal; F- Fluorine; Ca-Calcium; CaP- Calcium phosphate; Pept.- Peptide; FLs- Flavonoids; SiO_2- Silica Hap-Hidroxiapatite; HEMA- 2-hydroxyethyl methacrylate; TMC- Thermocycling; µTBS- microtensile bond strengh; SBS- shear bond strength; µSBS- microshear bond strength.

3.3. Meta-Regressions

3.3.1. Influence of the Adhesive Technique on NMA Effect Estimates

Meta-regression results showed that the ER technique performed better than the SE in four NMA comparisons: control vs. calcium phosphate, control vs. peptide, fluorine vs. calcium phosphate, and fluorine vs. peptide. On the contrary, the SE technique performed better in the NMA comparison peptide vs. hydroxyapatite. In all other comparisons, both techniques demonstrated similar performance (Appendix Table A5).

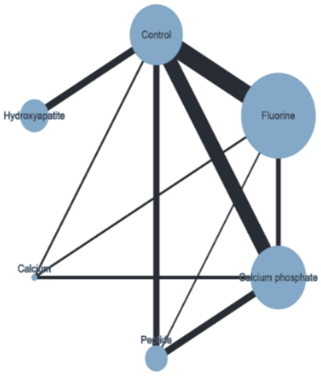
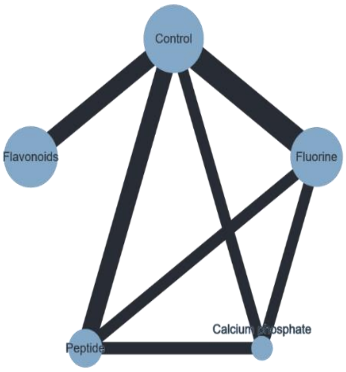
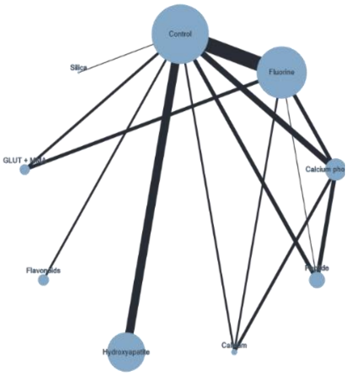
3.3.2. Influence of the ACAD Protocol on NMA Effect Estimates

Regarding the influence of different ACAD protocols on NMA effect estimates, the chemical ACAD protocol resulted in higher bond strength values than the biological ACAD protocol in nine NMA comparisons: control vs. fluorine, control vs. calcium phosphate, control vs. peptide, control vs. HEMA, control vs. flavonoids, control vs. calcium, control vs. hydroxyapatite, fluorine vs. calcium phosphate, and fluorine vs. peptide. In all other comparisons, both protocols performed similarly (Appendix Table A6).

3.4. Network Meta-Analysis

Plots for the three performed NMAs are shown in Table 2.

Table 2. Network meta-analysis plots.

Plot of the NMA **ER + chemical ACAD**	**Plot of the NMA ER + biological ACAD**	**Plot of the NMA SE + chemical ACAD**
		

[1] **Note:** Black lines connect biomimetic remineralization interventions that were compared head-to-head. The size of each node (circle) provides a measure of the sample size. The thickness of the line provides a measure of the number of direct comparisons between two interventions. Legend: ACAD- Artificial caries-affected dentin; ER- Etch-and-Rinse; NMA- Network meta-analysis; SE- Self-etch.

Table 3 shows NMA results from the BR intervention network.

Table 3. Network meta-analysis results from the network of biomimetic remineralization interventions.

NMA	NMA Results									
ER + chemical	Calcium									
	0.596 (-7.289, 8.482)	Calcium Phosphate								
	-0.508 (-8.207, 7.191)	-1.105 (-4.828, 2.619)	Control							
	-0.628 (-8.504, 7.248)	-1.224 (-5.931, 3.482)	-0.120 (-3.783, 3.544)	Fluorine						
	4.333 (-5.240,13.906)	3.736 (-3.063, 0.536)	4.841 (-0.848,10.530)	4.960 (-1.806,11.727)	HAp					
	4.044 (-4.923, 3.011)	3.448 (-1.833, 8.729)	4.553 (-0.635, 9.740)	4.672 (-1.320,10.665)	-0.288 (-7.988, 7.411)	Peptide				
ER + biological	Calcium Phosphate									
	-21.209 (-25.954, -16.463)	Control								
	-12.771 (-20.538, -5.003)	**8.438 (2.289, 14.587)**	Flavonoids							
	-17.012 (-22.103, -11.920)	**4.197 (1.080, 7.314)**	-4.241 (-11.135, 2.652)	Fluorine						
	-2.914 (-8.210, 2.382)	**18.295 (14.418, 22.172)**	**9.857 (2.588, 17.126)**	**14.098 (9.684, 18.512)**	Peptide					
SE + chemical	Calcium									
	2.663 (-2.395, 7.722)	Calcium Phosphate								
	1.124 (-3.670, 5.917)	-1.539 (-4.817, 1.738)	Control							
	5.728 (-2.442,13.897)	3.065 (-4.318, 10.447)	4.604 (-2.011, 11.219)	Flavonoids						
	0.523 (-4.358, 5.404)	-2.140 (-5.787, 1.506)	-0.601 (-2.932, 1.730)	-5.205 (-12.219, 1.809)	Fluorine					
	3.023 (-3.815, 9.861)	0.360 (-5.589, 6.309)	1.899 (-3.210, 7.009)	-2.705 (-11.063, 5.654)	2.500 (-2.603, 7.603)	HEMA				
	-1.792 (-7.415, 3.831)	**-4.455(-8.857, -0.053)**	-2.916 (-5.854, 0.023)	**-7.520(-14.758, -0.281)**	-2.315 (-6.066, 1.436)	-4.815 (-10.709, 1.079)	HAp			
	2.654 (-3.216, 8.524)	-0.009 (-4.076, 4.058)	1.530 (-2.373, 5.434)	-3.074 (-10.755, 4.607)	2.131 (-2.213, 6.475)	-0.369 (-6.728, 5.990)	4.446 (-0.440, 9.332)	Peptide		
	1.964 (-5.802, 9.730)	-0.699 (-7.633, 6.234)	0.840 (-5.270, 6.950)	-3.764 (-12.769, 5.241)	1.441 (-5.099, 7.980)	-1.059 (-9.024, 6.906)	3.756 (-3.024, 10.536)	-0.690 (-7.941, 6.560)	Silica	

* Note: Data in each cell are the mean difference with 95% confidence intervals for the network comparison of row-defining treatment versus column-defining treatment. Negative values favor the intervention in the column. Statistically significant results are in bold and gray. Legend: ER- Etch-and-Rinse; SE- Self-etch; HAp- Hydroxyapatite; HEMA- 2-hydroxyethyl methacrylate.

Contribution tables display Appendix Tables A7–A9.

3.4.1. ER Technique with Chemical ACAD Protocol

The results of this NMA suggested that no statistically significant differences exist between any BR interventions in all the network comparisons

3.4.2. ER Technique with Biological ACAD Protocol

When the ER technique and the biological ACAD protocol were used together, eight of the 10 BR intervention network's comparisons achieved statistically significant results: the calcium phosphate intervention compared to control (MD: -21.209, 95%CI: -25.954, -16.463), flavonoids (MD: -12.771, 95%CI: -20.538, -5.003), and fluorine (MD: -17.012, 95%CI: -22.103, -11.920); the flavonoids intervention compared to control (MD:8.438, 95%CI: 2.289, 14.587); the peptide intervention compared to control (MD:18.295, 95%CI:14.418, 22.172), flavonoids (MD: 9.857, 95%CI: 2.588, 17.126), and fluorine (MD: 14.098, 95%CI: 9.684, 18.512); and the fluorine intervention compared to control (MD:4.197, 95%CI:1.080, 7.314).

3.4.3. SE Technique with Chemical ACAD Protocol

When the SE technique and the chemical ACAD protocol were used together, only two of the 36 BR intervention network's comparisons achieved statistically significant results: the calcium phosphate (MD: -4.455, 95%CI: -8.857, -0.053) and the flavonoids (MD: -7.520, 95%CI: -14.758, -0.281) interventions compared to hydroxyapatite.

3.5. NMA Confidence Ratings

Confidence ratings for each NMA can be found in Appendix Tables A10–A12.

3.5.1. ER Technique with Chemical ACAD Protocol

In this NMA, two direct comparisons (calcium vs. control and control vs. fluorine) and one indirect comparison (hydroxyapatite vs. peptide) presented very low confidence, mainly due to major imprecision, heterogeneity, or incoherence concerns. The remaining indirect and direct comparisons presented a low or moderate confidence rating.

3.5.2. ER Technique with Biological ACAD Protocol

In this NMA, all the direct and indirect comparisons presented a moderate confidence rating.

3.5.3. SE Technique with Chemical ACAD Protocol

A low confidence rating was observed for six direct comparisons (calcium phosphate vs. peptide, calcium vs. fluorine, control vs. HEMA, control vs. SiO2, fluorine vs. HEMA, and fluorine vs. peptide) and two indirect ones (calcium vs. hydroxyapatite and HEMA vs. peptide), mostly due to major concerns in heterogeneity, incoherence, and within-study bias. The remaining comparisons presented a moderate confidence rating.

3.6. Rankings

Treatment rankings and probability to rank best are displayed in Table 4.

Table 4. Treatment rankings and probability of ranking best.

NMA	Ranks and probability of ranking best

		Rank			
		Mean	*Median*	*CrI95%*	*Probability of ranking best (%)*
ER + chemical	*Control*	4.66	5	(3.6)	0.05^{-4}
	Fluorine	4.66	5	(2.6)	0.64
	CaP	3.75	4	(2.6)	1.75
	Peptide	1.92	2	(1.5)	41.55
	Calcium	4.06	4	(1.6)	9.91
	HAp	1.97	2	(1.5)	**46.10**

		Rank			
		Mean	*Median*	*CrI95%*	*Probability of ranking best (%)*
ER + biological	*Control*	4.98	5	(5.5)	0.00
	Fluorine	3.89	4	(4.5)	0.00
	CaP	1.15	1	(1.2)	**85.24**
	Peptide	1.86	2	(1.2)	14.56
	FLs	3.12	3	(3.4)	0.20

		Rank			
		Mean	*Median*	*CrI95%*	*Probability of ranking best (%)*
SE + chemical	*Control*	5.49	6	(3.6)	0.11
	Fluorine	5.96	6	(3.9)	0.32
	CaP	3.28	3	(1.7)	12.41
	Peptide	4.77	4	(1.9)	5.01
	Calcium	6.00	7	(1.9)	4.15
	HAp	7.89	8	(4.9)	0.09
	FLs	2.75	2	(1.9)	**46.36**
	HEMA	4.03	3	(1.9)	17.49
	Silica	4.85	5	(1.9)	14.05

* Note: Interventions ranked best are highlighted in bold. Legend: ER- Etch-and-Rinse; SE- Self-etch; CrI-Credible interval; CaP- Calcium phosphate; FLs- Flavonoids, HAp- Hydroxyapatite; HEMA- 2-hydroxyethyl methacrylate.

3.6.1. ER Technique with Chemical ACAD Protocol

Among all the treatments in the NMA, hydroxyapatite achieved the highest probability of being the best treatment (46.10%), closely followed by peptide (41.55%).

3.6.2. ER Technique with Biological ACAD Protocol

In this NMA, calcium phosphate ranked first, with an 85.24% probability of being the best BR treatment.

3.6.3. SE Technique with Chemical ACAD Protocol

Compared to the other treatments in the NMA, flavonoids achieved the highest probability of being best (46.36%), followed by HEMA (17.49%).

3.7. Sensitivity Analyses

3.7.1. ER Technique with Chemical ACAD Protocol

Both sensitivity analyses showed results like those of the main analysis.

3.7.2. ER Technique with Biological ACAD Protocol

In this NMA, the sensitivity analysis where studies measuring the outcome with SBS tests were excluded was impossible because none used this test to assess the outcome. In the sensitivity analysis where we randomly selected one treatment intervention instead of combining interventions from the same category, the flavonoids vs. peptide comparison result lost statistical significance due to the loss of precision.

3.7.3. SE Technique with Chemical ACAD Protocol

When we excluded studies using SBS tests from the NMA, the flavonoids vs. hydroxyapatite comparison ceased to show differences between the two interventions due to a loss of precision. When we randomly selected one treatment intervention instead of combining interventions from the same category, eight of the 36 NMA comparison conclusions changed from not showing differences between the interventions to favoring one of them.

3.8. Discussion

This systematic review aimed to unravel the intricate interactions among different BR procedures and their influence on bond strength in human ACAD by analyzing and comparing bond strength from various in vitro studies through NMA. NMA allows the integration of data from direct and indirect comparisons, enabling a more precise estimation of treatment effects and a deeper understanding of optimal treatment options. Ultimately, this systematic review and NMA aspires to contribute to the existing knowledge on dentin-bonding procedures and offer valuable insights into the effectiveness of BR. The findings may help clinicians make informed decisions regarding dentin-bonding strategies for improved treatment outcomes [43].

This study’s systematic review and NMA have shed light on the potential benefits of BR for bond strength in human ACAD, measured both immediately and after artificial aging. Its findings indicate that BR protocols are promising in enhancing restorative materials’ bonding performance on demineralized dentin surfaces.

ACAD’s compromised nature negatively affects bond strength, and its surface is more challenging for bonding due to the incomplete infiltration of adhesives into the exposed collagen matrix [44]. Furthermore, the low pH associated with ACAD promotes the activation and activity of proteolytic enzymes, accelerating the breakdown of non-infiltrated collagen and the hybrid layer [28,38].

Our NMA findings highlighted differences between chemical and biological ACAD protocols. Chemical protocols consistently yielded higher bond strength results than biological, agreeing with previous research [45]. This difference may derive from the thicker demineralization layer associated with chemical protocols and the excessive softness of the primary dentine resulting from microbiological approaches [45].

The NMA also revealed variations in bond strength depending on the adhesive application technique. With their additional acid-etching stage, ER techniques proved more efficient in dissolving the smear layer than SE methods, which have a less acidic composition and are more sensitive [46]. Additionally, SE relies on chemical interactions with calcium ions, often found in lower concentrations in ACAD. Consequently, ER techniques yielded significantly higher bond strength values than SE, in line with the existing literature [20,22,44,47]. Moreover, when considering the ACAD surface, ER consistently demonstrated higher bond strength than SE materials [44].

This systematic review’s 23 in vitro studies showed medium heterogeneity, reflecting variations in ACAD protocols, aging methods, and bond strength tests. Thus, random-effects models were employed throughout the NMA investigation. Artificial aging methods, such as thermocycling and months of storage, generally reduce bond strength. Thermocycling promoted the most extreme breakdown of the bond interface and caused the lowest bond strength, even with associated BR, which is consistent with other studies [48]. However, different bond strength tests were used in the included investigations, which could affect the measurement results, and aspects such as specimen preparation and geometry, loading configuration, and material characteristics were not considered [3,49,50].

BR overall increased the bond strength values, even after artificial aging methods [10,51]. Nonetheless, the limited availability of studies reporting BR associated with bond strength restricts the exploration of these relationships [52]. Incorporating these BR methods into dental treatments can potentially enhance the durability and quality of the resin-dentin interface, offering promising avenues for improving clinical outcomes in restorative dentistry. In the NMA on ER with chemical ACAD, hydroxyapatite was the most effective treatment (46.10%), closely followed by peptide (41.55%), despite the low confidence in some comparisons. In the NMA on ER with biological ACAD, calcium phosphate emerged as the top-ranking BR (85.24%), significantly surpassing the control, flavonoids, and fluoride treatments. However, the NMA on SE with chemical ACAD showed low confidence in various comparisons, with flavonoids having the highest probability (46.36%) of being more effective, followed by HEMA (17.49%). These findings highlight the nuanced effectiveness of BR, influenced by different protocols and compositions. Most investigations on BR have shown its ability to remineralize ACAD in a basic manner. However, because they were carried out in vitro, their application in clinical contexts remains unexplored [52].

This study has some limitations. Most notably, in vitro studies lack the complexity of the oral environment, including oral biofluids and microbial interactions [3,44,49,50,52]. The absence of real dental caries development processes in the ACAD models is also a limitation. Future studies should address these shortcomings for a more comprehensive understanding of the clinical applicability of BR.

Another limitation is related to the sensitivity analysis for the NMA on SE with chemical ACAD. In this network, when we randomly selected one treatment intervention instead of combining interventions from the same category, eight out of the 36 NMA comparisons changed their conclusions from not showing differences between the interventions to favoring one of them. Despite this, we are confident that combining multiple arms related to the same intervention yields more reliable estimates because it does not waste useful data and evidence, as outlined and in accordance with the Cochrane recommendations. Moreover, regardless of the strategy used to cope with multiple-arm trials, six of the eight comparisons that had their conclusions changed in the sensitivity analysis were based solely on indirect evidence, which inherently carries less confidence than scenarios where direct evidence is also available.

Despite these limitations, our findings suggest that BR can enhance bond strength in ACAD, offering potential benefits for clinical practice. Dental professionals can use this knowledge to optimize treatment approaches, improve patient outcomes, and extend the longevity of adhesive bonding materials [3,44,49,50,52].

5. Conclusions

In conclusion, through a systematic review and NMAs we showed that bond strength degraded after biological or chemical ACAD protocols. As a result, surface preparation with BR procedures prior to bonding is advised to increase the bonding of ER and SE adhesives.

Supplementary Materials: A supplemental Appendix 1 to this article is available .The following supporting information can be downloaded at: www.mdpi.com/xxx/s1

Author Contributions: Rosário Costa contributed to concepts, design, the definition of intellectual content, literature search, data acquisition, and article preparation. Joana Reis-Pardal contributed to concepts, design, the definition of intellectual content, literature search, data acquisition, statistical analysis, and article preparation. João Cardoso Ferreira contributed to the definition of intellectual content and article preparation. Sofia Arantes-Oliveira contributed to the definition of intellectual content and article preparation. Luís Filipe Azevedo contributed to concepts, design, the definition of intellectual content, statistical analysis and critically revised the manuscript. Paulo Ribeiro de Melo contributed to concepts, design, the definition of intellectual content and critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

Institutional Review Board Statement: The study was approved by local “Comissão de Ética para a Saúde da Faculdade de Medicina Dentária da Universidade do Porto”.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, Rosário Costa, upon reasonable request.

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

Abbreviations

The following abbreviations are used in this manuscript:

NMA	Network Meta-analysis
ACAD	Artificial caries-affected dentin
BR	Biomimetic remineralization

Appendix 1

1. Search Strategies

PubMed: 1121 retrieved records

#1 Light-Curing of Dental Adhesives [MeSH] OR Self-Curing of Dental Resins [MeSH] OR adhesi*[tw] OR (bond*[tw] AND strength[tw])

#2 biomimetic*[tw] OR Biomimetics [MeSH] OR mineraliz*[tw] OR biomineraliz*[tw] OR Biomineralization [MeSH] OR remineraliz*[tw] OR Tooth Remineralization [MeSH] OR ((Dental Caries [MeSH] OR cari*[tw] OR eroded[tw] OR desensitized[tw]) AND (pre-treat*[tw] OR pretreat*[tw] OR treat*[tw] OR therap*[tw]))

#3 Dentin-Bonding Agents [MeSH] OR (dentin[tw] AND bond*[tw])

#1 AND #2 AND #3

ISI Web of Science: 1176 retrieved records

#1 adhesi* OR (bond* AND strength) (All Fields)

#2 biomimetic* OR mineraliz* OR biomineraliz* OR remineraliz* OR ((cari* OR eroded OR desensitized) AND (pre-treat* OR pretreat* OR treat* OR therap*)) (All Fields)

#3 dentin AND bond* (All Fields)

#1 AND #2 AND #3

SCOPUS: 1052 retrieved records

#1 TITLE-ABS-KEY (adhesi* OR (bond* AND strength))

#2 TITLE-ABS-KEY (biomimetic* OR mineraliz* OR biomineraliz* OR remineraliz* OR ((cari* OR eroded OR desensitized) AND (pre-treat* OR pretreat* OR treat* OR therap*)))

#3 TITLE-ABS-KEY (dentin AND bond*)

#1 AND #2 AND #3

Table A1. Reasons for excluding studies after accessing full-texts.

Studies	Reason for exclusion
Doozandeh et al. (2015)[61]	1-Without ACAD
Bergamin et al. (2016)[62]	1-Without ACAD
Ghani et al. (2017)[63]	1-Without ACAD
Komori et al. (2009) [64]	1-Without ACAD
Leal et al. (2017)[65]	1-Without ACAD
Luong et al. (2020)[66]	1-Without ACAD
Meraji et al. (2018)[67]	1-Without ACAD
Prasansuttiporn et al. (2020)[68]	1-Without ACAD
Sajjad et al. (2022)[69]	1-Without ACAD
Yilmaz et al. (2017)[70]	1-Without ACAD
Castellan et al. (2010)[71]	2- Without remineralization procedures
Okuyama et al. (2011)[72]	2- Without remineralization procedures

Wang et al. (2012)[73]	2- Without remineralization procedures
de-Melo et al. (2013)[74]	2- Without remineralization procedures
Carvalho et al. (2016)[75]	2- Without remineralization procedures
Deari et al. (2017)[76]	2- Without remineralization procedures
Giacomini et al. (2017)[77]	2- Without remineralization procedures
Rodrigues et al. (2017)[78]	2- Without remineralization procedures
Imiolczyk et al. (2017)[79]	2- Without remineralization procedures
Stape et al. (2021)[80]	2- Without remineralization procedures
Hartz et al. (2022)[81]	2- Without remineralization procedures
Wang et al. (2016)[82]	3-Modified Materials
Moda et al (2018)[83]	3-Modified Materials
Choi et al. (2020)[84]	3-Modified Materials
Abdelshafi et al. (2021) [85]	3-Modified Materials
Al-Qahtani et al. (2021)[86]	3-Modified Materials
Khor et al. (2022)[87]	3-Modified Materials
Adebayo et al. (2010)[88]	4- Without bond strength measurement
Liu et al. (2011)[89]	4- Without bond strength measurement
Chen et al. (2016)[90]	4- Without bond strength measurement
Bortolotto et al. (2017)[91]	4- Without bond strength measurement
Liang et al. (2017)[92]	4- Without bond strength measurement
Wang et al. (2021)[93]	4- Without bond strength measurement
Zhou et al. (2016) [94]	5- Modified adhesive
Flury et al (2017)[95]	5- Modified adhesive
Ye et al. (2017)[96]	5- Modified adhesive
Liang et al. (2018) [97]	5- Modified adhesive
Cardenas et al. (2021) [38]	5- Modified adhesive
Hasegawa et al. (2021)[98]	5- Modified adhesive
Bridi et al (2012)[99]	6- Not biomimetic remineralization agents
Castellan et al (2013)[100]	6- Not biomimetic remineralization agents
Monteiro et al (2013)[101]	6- Not biomimetic remineralization agents
Abu Nawareg et al (2016)[102]	6- Not biomimetic remineralization agents
Lee et al (2017)[103]	6- Not biomimetic remineralization agents
Prasansuttiporn et al (2017)[104]	6- Not biomimetic remineralization agents
Ramezanian Nik et al (2017)[105]	6- Not biomimetic remineralization agents
Costa et al (2019)[106]	6- Not biomimetic remineralization agents
Fialho et al (2019)[107]	6- Not biomimetic remineralization agents
Landmayer et al (2020) [108]	6- Not biomimetic remineralization agents
Costa et al (2021)[109]	6- Not biomimetic remineralization agents
Giacomini et al (2021)[110]	6- Not biomimetic remineralization agents
Shioya et al (2021)[111]	6- Not biomimetic remineralization agents
Xu et al (2021)[112]	6- Not biomimetic remineralization agents
Atay et al (2022)[113]	6- Not biomimetic remineralization agents
Lemos et al (2022)[114]	6- Not biomimetic remineralization agents
Zhang et al (2015)[115]	7-Non-Roman Alphabet language after unsuccessful contact with authors
Wang et al (2017)[116]	7-Non-Roman Alphabet language after unsuccessful contact with authors
Meng et al (2022)[117]	7-Non-Roman Alphabet language after unsuccessful contact with authors
Kim et al (2020)[13]	8- Missing control group

Table A2. Reasons for excluding studies from Network Meta-Analyses.

Study	Reason for exclusion
Atomura et al (2018)[32]	Standard Deviation and sample size (N) missing and authors didn´t respond to the various emails.

Table A3. Data Information.

Study	Data Information
Zumstein et al. (2018)[42]	Missing data obtained from another Meta-Analysis by Wiegand et al.2021 [50]. Authors didn´t respond to the various emails.

Table A4. Authors providing data via email, upon request.

Study	Data Information
Barbosa-Martins et al. (A) (2018)[8]	Unit of statistical analysis
Barbosa-Martins et al. (B) (2018)[7]	Unit of statistical analysis
de Sousa et al. (2019)[33]	Unit of statistical analysis
Moreira et al. (2021)[15]	Unit of statistical analysis
Meng et al. (2021) [24]	Mean and SD values
Pei et al. (2019)[26]	Unit of statistical analysis
Pulidindi et al. (2021) [40]	Unit of statistical analysis
Yang et al. (2018)[29]	Mean and SD values and Unit of statistical analysis
Zang et al. (2018)[30]	Mean and SD values and Unit of statistical analysis

2. OpenBUGS Code for Random Effects Meta-Regression Model with a Subgroup Indicator Covariate

```
# Normal likelihood, identity link, subgroup
# Random effects model for multi-arm trials

model{                          # *** PROGRAM STARTS

for(i in 1:ns){                # LOOP THROUGH STUDIES
    w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0        # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
    for (k in 1:na[i]) {        # LOOP THROUGH ARMS
         var[i,k] <- pow(se[i,k],2)      # calculate variances
se[i,k] ~ dunif(0,10) # vague prior for SE
         prec[i,k] <- 1/var[i,k]        # set precisions
         y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood

         theta[i,k] <- mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]]) * x[i]# model for linear predictor, covariate effect relative to treat in arm 1

#Deviance contribution
         dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {          # LOOP THROUGH ARMS
```

```
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0     # treatment effect is zero for control arm

beta[1] <- 0 # covariate effect is zero for reference treatment

# vague priors for treatment effects
for (k in 2:nt){ # LOOP THROUGH TREATMENTS
d[k] ~ dnorm(0,.0001) # vague priors for treatment effects
beta[k] <- B # common covariate effect
  }

B ~ dnorm(0,.0001) # vague prior for covariate effect

sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

# treatment effect when covariate = z[j]
for (k in 1:nt){ # LOOP THROUGH TREATMENTS
    for (j in 1:nz) { dz[j,k] <- d[k] + (beta[k]-beta[1])*z[j] }
  }

# All pairwise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
# when covariate is zero
diff[c,k] <- (d[c] - d[k])
#at covariate=z[j]


for (j in 1:nz) {
diff.j[c,k] <- (dz[j,c] - dz[j,k])
}}}

}                             # *** PROGRAM ENDS
```

3. Meta-Regression

Table A5. Meta-Regression results evaluating the influence of Adhesive application type (er vs se) on treatment effects at 24h.

NMA comparison	Mean	95% CrI
CTRL:F	0.8846	(-1.72; 3.52)
CTRL:CaP	**-3.351**	**(-6.664; -0.03009)**
CTRL:Pept.	**-5.384**	**(-9.103; -1.65)**
CTRL:SiO2	-0.8296	(-10.72; 9.049)
CTRL:HEMA	-1.728	(-10.22; 6.768)
CTRL:FLs	-4.982	(-12.35; 2.382)
CTRL:Ca	0.3152	(-5.575; 6.211)
CTRL:HAp	1.223	(-2.536; 4.98)
F:CaP	**-4.236**	**(-7.499; -0.9842)**
F:Pept.	**-6.268**	**(-9.996; -2.552)**
F:SiO2	-1.714	(-11.95; 8.521)
F:HEMA	-2.613	(-11.1; 5.868)
F:FLs	-5.867	(-13.45; 1.726)
F:Ca	-0.5694	(-6.352; 5.196)
F:HAp	0.3381	(-3.942; 4.631)
CaP:Pept.	-2.032	(-5.601; 1.525)
CaP:SiO2	2.522	(-7.906; 12.94)
CaP:HEMA	1.623	(-7.297; 10.54)
CaP:FLs	-1.631	(-9.428; 6.172)
CaP:Ca	3.666	(-2.196; 9.529)
CaP:HAp	4.574	(-0.07638; 9.248)
Pept.:SiO2	4.554	(-6.013; 15.1)
Pept.:HEMA	3.656	(-5.425; 12.76)
Pept.:FLs	0.4015	(-7.578; 8.394)
Pept.:Ca	5.699	(-0.6984; 12.08)
Pept.:HAp	**6.606**	**(1.658; 11.56)**
SiO2:HEMA	-0.8984	(-13.94; 12.13)
SiO2:FLs	-4.153	(-16.46; 8.18)
SiO2:Ca	1.145	(-10.37; 12.64)
SiO2:HAp	2.052	(-8.496; 12.66)
HEMA:FLs	-3.254	(-14.41; 7.904)
HEMA:Ca	2.043	(-8.051; 12.17)
HEMA:HAp	2.951	(-6.264; 12.18)
FLs:Ca	5.297	(-3.932; 14.52)
FLs:HAp	6.205	(-1.944; 14.31)
Ca:HAp	0.9075	(-5.872; 7.675)

[1] Note: Negative mean values favor ER application type. Statistically significant results are highlighted in bold. Legend: Control (CTRL), Fluorine(F), Calcium Phosphate (CaP), Peptide (Pept.), Silica (SiO_2), Flavonoids (FLs), Calcium (Ca), Hydroxyapatite (HAp), Credible Interval (Crl).

Table A6. Meta-Regression results evaluating the influence of acad protocol type (chemical vs biological) on treatment effects at 24h.

NMA comparison	Mean	95% CrI
CTRL:F	**-7.588**	**(-11.3; -3.877)**
CTRL:CaP	**-12.97**	**(-17.32; -8.628)**
CTRL:Pept.	**-14.2**	**(-18.64; -9.77)**
CTRL:SiO2	-10.15	(-20.78; 0.5214)
CTRL:HEMA	**-10.62**	**(-19.71; -1.499)**
CTRL:FLs	**-11.2**	**(-18.69; -3.706)**
CTRL:Ca	**-9.321**	**(-15.94; -2.717)**
CTRL:HAp	**-9.208**	**(-14.65; -3.78)**

F:CaP	**-5.381**	**(-8.621; -2.139)**
F:Pept.	**-6.617**	**(-10.3; -2.935)**
F:SiO2	-2.563	(-12.68; 7.6)
F:HEMA	-3.031	(-11.43; 5.39)
F:FLs	-3.61	(-11.2; 3.981)
F:Ca	-1.734	(-7.48; 3.999)
F:HAp	-1.62	(-5.972; 2.749)
CaP:Pept.	-1.236	(-4.793; 2.332)
CaP:SiO2	2.818	(-7.433; 13.12)
CaP:HEMA	2.35	(-6.401; 11.14)
CaP:FLs	1.77	(-6.08; 9.585)
CaP:Ca	3.647	(-2.149; 9.428)
CaP:HAp	3.761	(-0.8584; 8.391)
Pept.:SiO2	4.055	(-6.382; 14.52)
Pept.:HEMA	3.586	(-5.386; 12.55)
Pept.:FLs	3.007	(-4.964; 10.97)
Pept.:Ca	4.884	(-1.454; 11.21)
Pept.:HAp	4.997	(-0.001725; 10.01)
SiO2 :HEMA	-0.4682	(-13.38; 12.48)
SiO2:FLs	-1.048	(-13.4; 11.32)
SiO2:Ca	0.829	(-10.56; 12.18)
SiO2:HAp	0.9427	(-9.562; 11.42)
HEMA:FLs	-0.5796	(-11.75; 10.58)
HEMA:Ca	1.297	(-8.708; 11.3)
HEMA:HAp	1.411	(-7.759; 10.56)
FLs:Ca	1.877	(-7.369; 11.12)
FLs:HAp	1.991	(-6.31; 10.31)
Ca:HAp	0.1137	(-6.606; 6.846)

[1] Note: Negative mean values favor Chem ACAD protocol type. Statistically significant results are highlighted in bold.. Legend: Control (CTRL), Fluorine(F), Calcium Phosphate (CaP), Peptide (Pept.), Silica (SiO_2), Flavonoids (FLs), Calcium (Ca), Hydroxyapatite (HAp), Credible Interval (Crl).

4. Contribution Tables

Table A7. Per-comparison contribution matrix for the ER with Chemical Network.

NMA treatment effect/ comparisons	Ca:CaP	Ca:CTRL	Ca:F	CaP:CTRL	CaP:F	CaP:Pept.	CTRL:F	CTRL:HAp	CTRL:Pept.	F:Pept.
Mixed estimates										
CaP:CTRL	2.935	2.375	0.56	**63.32**	7.4	7.4783	8.4533	0	6.985	0.4933
CaP:F	4.195	0.0675	4.2625	22.975	**31.11**	6.1242	25.1317	0	2.2242	3.9
CaP:Pept.	1.1317	0.6967	0.435	16.795	5.04	**52.39**	0.535	0	18.0267	4.94
Ca:CaP	**38.27**	15.92	11.94	17.4467	7.655	2.7583	3.2517	0	1.725	1.0333
Ca:CTRL	15.095	**36.58**	15.3917	13.445	0.125	1.775	14.73	0	2.3117	0.5367
Ca:F	12.5817	15.78	**38.56**	3.1633	7.905	1.5133	18.9033	0	0.04	1.5533
CTRL:F	0.5775	2.515	3.0925	8.505	8.155	0.2275	**70.38**	0	3.3875	3.16
CTRL:HAp	0	0	0	0	0	0	0	**100**	0	0
CTRL:Pept.	0.8633	0.8783	0.015	14.86	1.5317	17.255	7.2017	0	**51.7**	5.685
F:Pept.	1.5167	0.5925	2.1092	3.9225	10.465	15.9042	25.565	0	22.235	**17.69**
Indirect estimates										
CaP:HAp	2.0033	1.5833	0.42	31.66	4.9333	5.0267	5.7233	43.6233	4.6567	0.37
Ca:HAp	10.2008	18.29	10.3225	8.9633	0.1	1.3375	9.82	38.8133	1.74	0.4025
Ca:Pept.	17.22	16.965	12.4708	0.7075	1.7067	19.6342	4.2742	0	20.5317	6.49

F:HAp	0.4445	1.6767	2.1212	5.6992	5.4367	0.182	35.19	44.8545	2.2887	2.1067
HAp:Pept.	0.6475	0.6595	0.012	9.9067	1.1495	11.7037	4.9275	41.3437	25.85	3.79

* Note: Columns refer to comparisons with direct data and rows to NMA treatment effects. Data in each cell show how much (in %) each direct comparison contributes to the NMA treatment effects. Values in bold and grey identifies the percentage each direct comparison contributes to the corresponding NMA comparison treatment effect. Legend: Control (CTRL), Fluorine(F), Calcium Phosphate (CaP), Peptide (Pept.), Calcium (Ca), Hidroxiapatite (HAp).

Table A8. Per-comparison contribution matrix for the ER with Biological Network.

NMA treatment effect/ comparisons	CaP:CTRL	CaP:F	CaP:Pept.	CTRL:FLs	CTRL:F	CTRL:Pept.	F:Pept.
Mixed estimates							
CaP:CTRL	**47.08**	13.7	12.3317	0	14.5567	11.475	0.8567
CaP:F	17.525	**40.42**	11.1833	0	19.6783	2.1533	9.03
CaP:Pept.	16.035	11.5217	**43.84**	0	1.0367	17.0717	10.485
CTRL:FLs	0	0	0	**100**	0	0	0
CTRL:F	6.015	6.345	0.33	0	**71.49**	8.075	7.745
CTRL:Pept.	7.505	1.1033	8.6083	0	12.8783	**58.13**	11.775
F:Pept.	0.9933	8.17	9.1633	0	21.8183	20.825	**39.04**
Indirect estimates							
CaP:FLs	23.54	9.1333	8.2925	40.9658	9.7758	7.65	0.6425
FLs:F	4.01	4.2575	0.2475	45.1658	35.745	5.4108	5.1633
FLs:Pept.	5.0033	0.8275	5.8308	42.7458	8.6775	29.065	7.85

* Note: Columns refer to comparisons with direct data and rows to NMA treatment effects. Data in each cell show how much (in %) each direct comparison contributes to the NMA treatment effects. Values in bold and grey identifies the percentage each direct comparison contributes to the corresponding NMA comparison treatment effect. Legend: Control (CTRL), Fluorine(F), Calcium Phosphate (CaP), Peptide (Pept.), Calcium (Ca), Flavonoids (FLs).

Table A9. Per-comparison contribution matrix for the SE with Chemical Network.

NMA treatment effect/ comparisons	Ca:CaP	Ca:CTRL	Ca:F	CaP:CTRL	CaP:F	CaP:Pept.	CTRL: FLS	CTRL: F	CTRL: HEMA	CTRL :HAp	CTRL:Pept.	CTRL:SiO2	F:HEMA	F:Pept.
Mixed estimates														
CaP:CTRL	5.215	3.955	1.26	**51.94**	9.345	8.4575	0	10.425	0.4725	0	8.165	0	0.4725	0.2925
CaP:F	6.4433	0.7333	5.71	20.78	**29.56**	5.3175	0	23.9333	1.1025	0	3.5225	0	1.1025	1.795
CaP:Pept.	1.9783	1.3433	0.635	14.09	4.5933	**54.07**	0	2.3683	0.13	0	17.932	0	0.13	2.73
Ca:CaP	**41.85**	14.96	11.2705	15.37	8.04	2.8205	0	2.5325	0.168	0	2.2905	0	0.168	0.53
Ca:CTRL	13.2408	**37.83**	16.005	10.395	0.6525	2.1933	0	15.825	0.6925	0	2.3333	0	0.6925	0.14
Ca:F	11.2397	16.065	**39.64**	3.365	6.74	1.1347	0	19.125	0.773	0	0.468	0	0.773	0.6667
CTRL:FLs	0	0	0	0	0	0	**100**	0	0	0	0	0	0	0
CTRL:F	0.4375	2.85	3.2875	5.19	5.3533	0.6008	0	**72.96**	3.15	0	1.8108	0	3.15	1.21
CTRL:HEMA	0.174	0.9567	1.1307	1.74	1.8025	0.2365	0	18.35	**52.86**	0	0.6432	0	21.6898	0.4067
CTRL:HAp	0	0	0	0	0	0	0	0	0	**100**	0	0	0	0
CTRL:Pept.	1.553	1.29	0.263	11.88	2.5467	15.9797	0	5.8717	0.248	0	**56.8**	0	0.248	3.31

CTRL:SiO2	0	0	0	0	0	0	0	0	0	0	0	**100**	0	0
F:HEMA	0.174	0.9433	1.1173	1.72	1.78	0.234	0	18.125	21.4223	0	0.634	0	**53.44**	0.4
F:Pept.	2.31	0.455	2.765	3.8833	9.255	15.4483	0	28.2333	1.265	0	26.07	0	1.265	**9.05**
Indirect estimates														
CaP:FLs	3.5907	2.6367	0.954	25.97	6.23	5.6773	41.468	7.04	0.378	0	5.4433	0	0.378	0.234
CaP:HEMA	4.1842	1.6142	2.57	23.36	12.08	4.2917	0	3.6925	24.7767	0	3.495	0	19.1392	0.7967
CaP:HAp	3.5907	2.6367	0.954	25.97	6.23	5.6773	0	7.04	0.378	41.468	5.4433	0	0.378	0.234
CaP:SiO2	3.5907	2.6367	0.954	25.97	6.23	5.6773	0	7.04	0.378	0	5.4433	41.468	0.378	0.234
Ca:FLs	9.097	18.915	10.685	6.93	0.522	1.645	38.697	10.55	0.552	0	1.75	0	0.552	0.105
Ca:HEMA	8.9795	17.48	17.97	5.1542	2.6933	1.132	0	1.0295	22.5367	0	0.932	0	21.8928	0.2
Ca:HAp	9.097	18.915	10.685	6.93	0.522	1.645	0	10.55	0.552	38.697	1.75	0	0.552	0.105
Ca:Pept.	17.575	16.975	11.148	0.668	1.6767	19.9197	0	5.6533	0.298	0	22.258	0	0.298	3.52
Ca:SiO2	9.097	18.915	10.685	6.93	0.522	1.645	0	10.55	0.552	0	1.75	38.697	0.552	0.105
FLs:F	0.35	1.9	2.25	3.46	3.5825	0.4725	45.2192	36.48	2.1	0	1.2792	0	2.1	0.8067
FLs:HEMA	0.145	0.7175	0.8625	1.305	1.355	0.195	41.1858	12.2333	26.43	0	0.5	0	14.7558	0.305
FLs:HAp	0	0	0	0	0	0	50	0	0	50	0	0	0	0
FLs:Pept.	1.1862	0.9675	0.2187	7.92	1.91	11.0162	41.6228	4.1287	0.2067	0	28.4	0	0.2067	2.2067
FLs:SiO2	0	0	0	0	0	0	50	0	0	0	0	50	0	0
F:HAp	0.35	1.9	2.25	3.46	3.5825	0.4725	0	36.48	2.1	45.2192	1.2792	0	2.1	0.8067
F:SiO2	0.35	1.9	2.25	3.46	3.5825	0.4725	0	36.48	2.1	0	1.2792	45.2192	2.1	0.8067
HEMA:HAp	0.145	0.7175	0.8625	1.305	1.355	0.195	0	12.2333	26.43	41.1858	0.5	0	14.7558	0.305
HEMA:Pept.	1.4625	0.2	1.2625	4.635	4.37	10.4675	0	5.7817	25.81	0	26.757	0	15.3342	3.92
HEMA:SiO2	0.145	0.7175	0.8625	1.305	1.355	0.195	0	12.2333	26.43	0	0.5	41.1858	14.7558	0.305
HAp:Pept.	1.1862	0.9675	0.2187	7.92	1.91	11.0162	0	4.1287	0.2067	41.623	28.4	0	0.2067	2.2067
HAp:SiO2	0	0	0	0	0	0	0	0	0	50	0	50	0	0
Pept.:SiO2	1.1862	0.9675	0.2187	7.92	1.91	11.0162	0	4.1287	0.2067	0	28.4	41.6228	0.2067	2.2067

* Note: Columns refer to comparisons with direct data and rows to NMA treatment effects. Data in each cell show how much (in %) each direct comparison contributes to the NMA treatment effects. Values in bold and grey identifies the percentage each direct comparison contributes to the corresponding NMA comparison treatment effect. Legend: Control (CTRL), Fluorine(F), Calcium Phosphate (CaP), Peptide (Pept.), Calcium (Ca), Flavonoids (FLs), Hidroxiapatite (HAp), Silica (SiO_2),.

5. Confidence Ratings Output of CINeMA Software

Table A10. Confidence ratings Table for the ER with Chem network meta-analysis.

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed estimates								

CaP:CTRL	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
CaP:F	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
CaP:Pept.	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Ca:CaP	7	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
Ca:CTRL	3	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
Ca:F	4	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
CTRL:F	8	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
CTRL:HAp	3	Some concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Low
CTRL:Pept.	4	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
F:Pept.	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
Indirect estimates								
CaP:HAp	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Low
Ca:HAp	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Low
Ca:Pept.	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Low
F:HAp	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Low
HAp:Pept.	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low

* Legend: Control (CTRL), Fluorine(F), Calcium Phosphate (CaP), Peptide (Pept.), Calcium (Ca), Hidroxiapatite (HAp).

Table A11. Confidence ratings Table for the ER with Biol network meta-analysis.

ER with Biological								
Comparison	**Number of studies**	**Within-study bias**	**Reporting bias**	**Indirectness**	**Imprecision**	**Heterogeneity**	**Incoherence**	**Confidence rating**
Mixed estimates								
CaP:CTRL	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
CaP:F	2	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
CaP:Pept.	2	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
CTRL:FLs	1	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
CTRL:F	4	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
CTRL:Pept.	3	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate

F:Pept.	2	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
Indirect estimates								
CaP:FLs	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
FLs:F	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
FLs:Pept.	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate

* Legend: Control (CTRL), Fluorine(F), Calcium Phosphate (CaP), Peptide (Pept.), Flavonoids (FLs).

Table A12. Confidence ratings Table for the SE with Chem network meta-analysis.

SE with Chemical								
Comparison	**Number of studies**	**Within-study bias**	**Reporting bias**	**Indirectness**	**Imprecision**	**Heterogeneity**	**Incoherence**	**Confidence rating**
Mixed estimates								
CaP:CTRL	1	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
CaP:F	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
CaP:Pept.	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
Ca:CaP	4	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
Ca:CTRL	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Ca:F	3	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
CTRL:FLs	1	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
CTRL:F	8	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
CTRL:HEMA	1	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low
CTRL:HAp	5	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
CTRL:Pept.	3	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
CTRL:SiO2	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
F:HEMA	1	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low
F:Pept.	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Low
Indirect estimates								
CaP:FLs	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
CaP:HEMA	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
CaP:HAp	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate

CaP:SiO2	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
Ca:FLs	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Ca:HEMA	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Ca:HAp	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
Ca:Pept.	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
Ca:SiO2	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
FLs:F	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
FLs:HEMA	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
FLs:HAp	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
FLs:Pept.	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
FLs:SiO2	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
F:HAp	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Moderate
F:SiO2	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
HEMA:HAp	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
HEMA:Pept.	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Low
HEMA:SiO2	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Moderate
HAp:Pept.	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate
HAp:SiO2	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Moderate

* Legend: Control (CTRL), Fluorine(F), Calcium Phosphate (CaP), Peptide (Pept.), Silica (SiO_2), Flavonoids (FLs), Calcium (Ca), Hidroxiapatite (HAp).

6. *Sensitivity Analyses*

Table A13. Results of Sensitivity analysis for ER with Chemical network meta-analysis.

RANDOM	**Calcium**				
	1.106 (-7.711, 9.922)	**CaP**			
	-0.123 (-8.738, 8.491)	**-1.229 (-5.371, 2.913)**	**Control**		
	-1.291 (-10.094, 7.512)	**-2.397 (-7.595, 2.802)**	**-1.168 (-5.227, 2.892)**	**Fluorine**	
	5.813 (-4.953, 16.580)	**4.707 (-2.965, 12.380)**	**5.937 (-0.522, 12.395)**	**7.104 (-0.524, 14.733)**	**HAp**

	5.028 (-4.929, 14.984)	**3.922 (-1.860, 9.704)**	**5.151 (-0.520, 10.822)**	**6.319 (-0.223, 12.860)**	**-0.786 (-9.381, 7.809)**	**Peptide**
WITHOUT SB	Calcium					
	1.849 (-10.377, 14.074)	CaP				
	-1.065 (-12.941, 10.810)	-2.914 (-9.377, 3.549)	Control			
	-1.323 (-13.357, 10.710)	-3.172 (-10.460, 4.116)	-0.258 (-5.532, 5.016)	Fluorine		
	3.777 (-10.759, 18.313)	1.928 (-8.656, 12.513)	4.842 (-3.540, 13.225)	5.100 (-4.804, 15.004)	HAp	
	5.947 (-8.203, 20.096)	4.098 (-4.949, 13.145)	7.012 (-1.747, 15.771)	7.270 (-2.143, 16.683)	2.170 (-9.954, 14.293)	Peptide

[1] **Note:** Data in each cell are Mean Difference (MD) with 95% confidence intervals (CI) for the network comparison of row-defining treatment versus column-defining treatment. Negative values favour the intervention in the column. Legend: Calcium Phosphate (CaP), Hydroxyapatite (HAp).

Table A14. Results of Sensitivity analysis for ER with Biological network meta-analysis.

RANDOM	**Calcium phosphate**				
	-21.320 (-26.341, -16.299)	**Control**			
	-11.160 (-20.061, -2.258)	**10.160 (2.810, 17.510)**	**Flavonoids**		
	-17.063 (-22.451, -11.675)	**4.257 (0.806, 7.708)**	**-5.903 (-14.023, 2.217)**	**Fluorine**	
	-2.924 (-8.500, 2.652)	**18.396 (14.256, 22.535)**	**8.236 (-0.200, 16.672)**	**14.139 (9.408, 18.870)**	**Peptide**

[1] **Note:** Data in each cell are Mean Difference (MD) with 95% confidence intervals (CI) for the network comparison of row-defining treatment versus column-defining treatment. Negative values favour the intervention in the column. In blue results reaching a different conclusion from the main analysis.

Table A15. Results of Sensitivity analysis for SE with Chemical network meta-analysis.

RANDOM	**Calcium**				
	1.938 (-2.927, 6.803)	**CaP**			
	1.437 (-3.182, 6.057)	**-0.500 (-3.617, 2.616)**	**Control**		
	10.407 (1.928, 18.887)	**8.470 (0.706, 16.233)**	**8.970 (1.859, 16.081)**	**FLs**	
	0.937 (-3.774, 5.649)	**-1.000 (-4.507, 2.507)**	**-0.500 (-2.804, 1.804)**	**-9.470 (-16.945, -1.995)**	**Fluorine**

	0.768 (-5.753, 7.290)	**-1.169 (-6.806, 4.467)**	**-0.669 (-5.510, 4.172)**	**-9.639 (-18.241, -1.036)**	**-0.169 (-5.004, 4.667)**	**HEMA**			
	-3.124 (-8.605, 2.357)	**-5.061 (-9.352, -0.771)**	**-4.561 (-7.511, -1.611)**	**-13.531 (-21.230, -5.832)**	**-4.061 (-7.804, -0.318)**	**-3.892 (-9.561, 1.776)**	**HAp**		
	4.256 (-1.421, 9.932)	**2.318 (-1.565, 6.201)**	**2.818 (-0.994, 6.632)**	**-6.152 (-14.220, 1.917)**	**3.318 (-0.931, 7.568)**	**3.487 (-2.601, 9.576)**	**7.380 (2.559, 12.200)**	**Peptide**	
	2.277 (-5.235, 9.789)	**0.340 (-6.354, 7.033)**	**0.840 (-5.084, 6.764)**	**-8.130 (-17.385, 1.125)**	**1.340 (-5.016, 7.696)**	**.509 (-6.141, 9.159)**	**5.401 (-1.217, 12.019)**	**-1.978 (-9.024, 5.066)**	**Silica**

WITHOUT SB	Calcium						
	3.937 (-3.398, 11.273)	CaP					
	0.117 (-6.760, 6.994)	-3.820 (-9.111, 1.471)	Control				
	4.721 (-6.357, 15.800)	0.784 (-9.386, 10.954)	4.604 (-4.082, 13.290)	FLs			
	0.254 (-6.695, 7.203)	-3.684 (-9.251, 1.884)	0.137 (-3.243, 3.516)	-4.467 (-13.787, 4.853)	Fluorine		
	-2.875 (-10.771, 5.021)	-6.812 (-13.373, -0.252)	-2.992 (-6.871, 0.887)	-7.596 (-17.108, 1.916)	-3.129 (-8.273, 2.016)	HAp	
	-2.811 (-11.987, 6.365)	-6.748 (-13.994, 0.498)	-2.928 (-9.722, 3.866)	-7.532 (-18.559, 3.495)	-3.065 (-10.240, 4.111)	0.064 (-7.759, 7.888)	Peptide

[1] **Note:** Data in each cell are Mean Difference (MD) with 95% confidence intervals (CI) for the network comparison of row-defining treatment versus column-defining treatment. Negative values favour the intervention in the column. In blue results reaching a different conclusion from the main analysis Legend: Calcium Phosphate (CaP), Hydroxyapatite (HAp), Flavonoids (FLs).

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