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Systematic Review Effect of Different Application Modalities on the Bonding Performance of Adhesive Systems to Dentin: A Systematic Review and Meta-Analysis

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Abstract: Diverse types of dental adhesives exhibit different cytotoxic outcomes on cells in vitro. Currently, no standard adhesive application technique has so far been decisive for clinicians for better durability of resin-dentin bonds of adhesive systems. The purpose of this study was to systematically review the literature to evaluate the bonding performance of adhesive systems to dentin by using different application modalities. The systematic research strategy was conducted by two reviewers among multiple databases: PubMed, Scopus, Web of Science, Embase, and Scielo. In vitro studies reporting the effects of additional steps for the application of adhesive systems on the bond strength to dentin were selected. Meta-analysis was performed using Review Manager Software version 5.3.5 using the random effects model. The methodological quality of each in vitro study was assessed according to the parameters of a previous systematic review. The electronic research through different databases generated a total of 8318 references. After the examination of titles and abstracts, a total of 106 potentially relevant studies accessed the full-text evaluation phase. After full-text examination, 78 publications were included for the qualitative analysis, and 68 studies were included in the metaanalysis. Regarding the etch-and-rinse adhesive systems, the application modalities that improved the overall bond strength were the application of a hydrophobic resin layer (p = 0.005), an extended application time (p < 0.001), an application assisted by an electric current (p < 0.001), a double-layer application (p = 0.05), the agitation technique (p = 0.02), and the active application of the adhesive (p < 0.001). For self-etch adhesive systems, the techniques that improved the overall bond strength were the application of a hydrophobic resin layer (p < 0.001), an extended application time (p = 0.001), an application assisted by an electric current (p < 0.001), a double-layer application (p < 0.001), the agitation technique (p = 0.01), and the active application of the adhesive (p < 0.001). The in vitro evidence suggests that the application of adhesive systems using alternative techniques or additional strategies may be beneficial for improving their bond strength to dentin. The application modalities



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that favored the overall bond strength to dentin were an extended application time, a double-layer application, an application assisted by an electric current, the active application of the adhesive, and the application of a hydrophobic resin layer. Worth mentioning is that some techniques are intended to increase the degree of the conversion of the materials, and therefore, improvements in the biocompatibility of the materials can be expected.

Keywords: adhesion; dental adhesive; dental bonding; dentin bonding agent

1. Introduction

Over the years, adhesive systems have been introduced into many fields of modern restorative dentistry; however, there are still some unresolved problems concerning the durability of the resin–dentin bond interface [1]. Adhesion to enamel structures has become a predictable and well-established procedure [2], whereas adhesion to dentin, due to its heterogeneous structure and histology, has been considered defiant [3,4]. In fact, achieving an ideal interdiffusion of the adhesive system within collagen fibrils and the stability of the resin–dentin interface are of key importance [5]. Accordingly, it is fundamental to recognize the mechanism of dentin hybridization, in which an interdiffusion zone, also called the hybrid layer (HL), is created and, consequently, leads to the formation of micromechanical retention of the dental composite restoration [6]. Thus, the HL is a combination of residual hydroxyapatite (HAp), collagen, solvents, and resin monomers, and its strength ultimately relies on the resistance of each constituent to degradation phenomena [7,8].

Through adhesion procedures, the mineral component is partly or completely removed by the acidic monomers of self-etch (SE) or etch-and-rinse (E&R) adhesive systems [9]. A simplification of the conventional view of dental bonding by means of a faster application, a less-sensitive method, and numerous optional applicability is feasible today with the advent of universal adhesives [3,6,9]. These strategies have been used for enamel and dentin bonding to resin-based materials with a number of steps. Strengths have been focused regarding the lessening of the number of steps, the decrease in potential errors, and the reduction in the technique sensitivity related to the bonding procedure [9]. Currently, these dentin bonding agents are comprised of monomers with both hydrophobic and hydrophilic groups, polymerization modulators, and somewhat high concentrations of organic solvents [10]. These solvents help as diluting agents and enhance the spreading, wetting, and penetration of monomers within the microporosities of the exposed, aciddemineralized collagen network [11]. However, it is important to emphasize that the higher the solvent content within the polymer, the lower the resin–dentin bond strength and the mechanical properties of the cured resin [12].

Ideally, any remaining solvent must be evaporated from the dentinal surface by air-drying the applied adhesive prior to photoactivation. The presence of a residual solvent might jeopardize the polymerization of resin monomers, affecting the integrity of the bond, compromising the quality of the polymer inside the HL, and producing undesirable voids within the adhesive interface. These voids may act as defect-initiator sites, providing a pathway for nanoleakage, causing a decrease in bond strength and mechanical properties [13,14]. Solvent evaporation can be achieved by allowing an evaporation time between the application and the curing of the adhesive or by air-drying using an air syringe [15]. All in all, the evaporation of solvents from the adhesive depends on numerous features, such as the type of solvent, the tooth–syringe distance, the type of monomer, operator skills, and the air temperature, which appears to impact the air-drying time of an adhesive system [16].

Furthermore, there are different strategies that can be used to facilitate the removal of solvents and enhance the durability of adhesive systems, such as prolonged air-drying, using a warm-air stream on the primer or the adhesive system [7], a prolonged application

time, active bonding application, multiple adhesive coatings, an extra layer of hydrophobic coat, and increased light-curing exposure [17].

Suitably, a better definition of the gold standard technique for applying adhesive systems to dentin should be of great consideration. Accordingly, many approaches, including active bonding application, multiple-layer application (two layers or more), and the modification of the adhesive application time, might be introduced by clinicians in their daily practice in order to improve the bond strength of adhesive systems to dentin. The issue is that, until now, there has been no ideal protocol for achieving the stable and optimal adhesion of adhesive systems to dentin. Likewise, the improvement in bond strength can be realized by means of several strategies and, thus, has been advocated by various authors [5,7,9,10,17,18].

Another topic to be addressed is related to the fact that as these materials come in close and prolonged contact with vital dentin, biocompatibility is one of the most critical requirements for dental adhesives [19]. Methacrylate monomers (i.e., bis-GMA, UDMA, and HEMA) were reported to induce toxicity via GSH (intracellular glutathione) depletion, cell cycle arrest, apoptosis/necrosis, and even apoptosis of human gingival fibroblast [20,21]. It is a well-known fact that morphological changes in several types of cells, apoptosis, and growth suppression can be generated by HEMA [22,23]. The release of resin monomers has been proposed as one of the possible causes of the adverse effects of dentin adhesives [24], and therefore, the definition of the gold standard technique for applying adhesive systems to dentin must imply a technique that ensures the achievement of the highest possible degree of conversion of the material.

Apart from the above report and to the extent of the researchers' knowledge, no standard adhesive application technique has so far been decisive for clinicians for better durability of resin–dentin bonds of adhesive systems. Therefore, the purpose of this study is to systematically review the literature to evaluate the bonding performance of adhesive systems to dentin by using different application modalities. The null hypothesis to be tested is that different application modalities do not provide similar bond strength to dentin when compared to the application of the adhesive, according to the manufacturer's instructions.

2. Materials and Methods

The present systematic review and meta-analysis was conducted following the guidance of PRISMA (preferred reporting items of systematic reviews and meta-analyses) in order to follow a uniform and transparent methodology [25]. The following PICOS framework was used: population, dentin; intervention, different application modalities; control, application of the adhesive according to the manufacturer's instructions; outcomes, bond strength; and study design, in vitro studies. The research question was: "Does the use of different application modalities improve the bonding performance of adhesive systems to dentin?"

2.1. Literature Search

The systematic research strategy was conducted by two (R.B. and C.E.C.-S.) reviewers among multiple databases: PubMed, Scopus, Web of Science, Embase, and Scielo. The literature search was performed on 2 August 2022. The search strategy used in PubMed is described in the Table 1. The search strategy for the other databases was adapted from that used for PubMed. After the search, all articles were imported into Mendeley Desktop 1.17.11 software (Glyph & Cog, LLC, London, UK) to eliminate duplicates. Table 1. Search strategy used in PubMed.

#1 Deartin OB Dearting
#1 Dentin OR Dentine
#2 Bonding OR Bond OR Bonding efficacy OR Dental bonding OR bond strength OR bonding effectiveness OR Bonding performance OR Bond performance OR adhesive #2 properties OR Micro-tensile strength OR microtensile strength OR Microtensile bond strength OR bonding properties OR microshear bond strength OR shear bond strength OR performance
#3 double-application coat OR double-application time OR Bonding application time OR Time factors, working time OR adhesive dental coating OR rubbing OR agitation OR scrubbing OR application mode OR double application OR single application OR Double-layer application OR adhesive layer OR ultrasonic OR agitation OR vibration OR ultrasonics OR application time OR Double application technique OR adhesive dental coating

#1 AND #2 AND #3

2.2. Study Selection

All the articles were imported into Rayyan online tool [26], and the titles and abstracts were initially screened to identify studies that potentially met the following eligibility criteria: (1) in vitro studies reporting the effect of the use of additional steps for the application of adhesive systems on the bond strength to dentin; (2) evaluating the bond strength of adhesive systems to dentin with a resin-based material as an antagonist; (3) including a control group in which the adhesive system was applied according to manufacturers' instructions; (4) including mean and standard deviation (SD) data in MPa on shear, micro-shear, tensile, and micro-tensile bond tests. Only manuscripts published in the English language were considered. Case series, case reports, pilot studies, and reviews were excluded. Afterwards, full texts were reviewed, and a systematic methodology was used to label all the relevant information for the exclusion or the inclusion of the individual papers. The decision process was performed by two independent reviewers (L.H. and R.B.). In case of disagreement between the reviewers, the final decision was reached through consultation with a third reviewer (C.E.C.-S.), a senior, experienced researcher.

2.3. Data Extraction

The results of the selected studies were extracted using Microsoft Office Excel 2019 (Microsoft Corporation, Redmond, WA, USA). These data comprised the year of publication, the type of adhesive system, strategy evaluated for bonding to dentin, outcomes evaluated, the type of bond strength test evaluated, and storage conditions. Additionally, the mean, SD, and number of specimens from the bond strength test were collected, and these data were then subjected to meta-analysis.

2.4. Quality Assessment

The methodological quality of each in vitro study was assessed by two reviewers (L.H. and R.B.), according to the parameters of a previous systematic review [17]. The risk of bias in each article was evaluated according to the description of the following parameters: specimen randomization, single operator, operator blinded, control group, standardized specimens, failure mode, manufacturers' instructions, and sample size calculation. If the authors reported the parameter, the study received a "YES" for that specific parameter. In the case of missing information, the parameter received a "NO." The risk of bias was classified according to the sum of "YES" answers received: 1 to 3 indicated a high bias, 4 to 6 medium, and 7 to 8 indicated a low risk of bias.

2.5. Statistical Analysis

Meta-analysis was performed using Review Manager Software version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The analysis was carried out using the random-effects model, and pooled-effect estimates were obtained by comparing the standardized mean difference between bond strength values

obtained from the control and experimental groups. The control group was considered when the adhesive system was applied according to the manufacturers' instructions, while the experimental group was considered when the adhesive system was applied using a different approach. In studies where several experimental groups were compared with the same control group, data from the experimental groups (mean, SD, and sample size) were combined for the meta-analysis [27]. E&R and SE adhesives were analyzed separately. Subgroups considering the immediate and long-term bond strength data were used. A *p*-value < 0.05 was considered statistically significant. Statistical heterogeneity of the treatment effect among studies was assessed using the Cochran Q test and the inconsistency I^2 test.

3. Results

The electronic research through three different databases generated a total of 8318 references, which were reduced to 6441 after duplicate removal. After the examination of titles and abstracts, 6335 studies were excluded because of their study design incompatibility with this review. A total of 106 potentially relevant studies accessed the full-text evaluation phase. From these, 19 were excluded because there was no access to the full-text manuscript [28–45], resulting in a final number of 87 publications included for further qualitative assessment (Figure 1). After a full-text review, 9 articles were excluded because the bond strength was not tested [46–54], leaving 78 publications for qualitative analysis. Of these, 10 studies were excluded from the quantitative analysis: 1 study did not present the data in the form of mean and SD [55], 3 studies did not have other studies for making comparisons [43,56,57], 3 studies did not contain a clearly defined control group [58–60], and in 3 articles, complete data could not be extracted [32,61,62]. Thus, 68 studies were included in the meta-analysis.

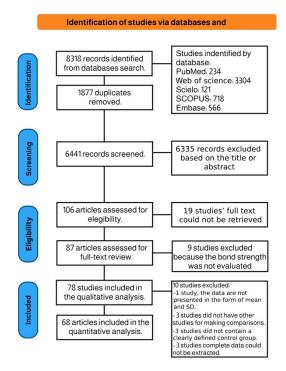


Figure 1. Prisma flowchart according to PRISMA guidelines.

The qualitative synthesis of the studies included in this systematic review are summarized in Table S1. Both E&R and SE adhesives were identified; universal adhesives applied in both adhesive strategies were recognized too. Several strategies were identified, including the active application of the adhesive, multiple-layer application, the application of the adhesive using an electric current, an extended application time, the application of an extra hydrophobic resin layer, the application of the adhesive using an ultrasonic device, and a shortened application time. Most of the studies evaluated the bond strength after 24 h of aging, and for the long-term tests, both distilled water storage and thermocycling were identified.

The results from the meta-analysis are shown in Figures 2–14. Regarding E&R adhesive systems, the application modalities that improved the overall bond strength were the application of a hydrophobic resin layer (p = 0.005), an extended application time (p < 0.001), an application assisted by an electric current (p < 0.001), a double-layer application (p = 0.05), and the active application of the adhesive (p < 0.001). Worth mentioning is that the abovementioned techniques improved, mostly, long-term bond strength. On the other hand, only the use of an ultrasonic device did not improve bond strength (p = 0.43) (Figures 2–7).

	Manufactur	ctions	Hydropho	bic Resin	Layer		Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 Immediate									
Muñoz 2014	32.3	3.7	68	34.6	4.1	47	7.7%	-0.59 [-0.97, -0.21]	
Muñoz 2014	40.8	5	52	36.3	4.4	51	7.7%	0.95 [0.54, 1.36]	
Muñoz 2014	20.5	3.2	62	22.6	4.6	60	7.7%	-0.53 [-0.89, -0.17]	
Perdigão 2014	19.1	0.7	5	17.6	1.2	5	5.1%	1.38 [-0.08, 2.84]	· · · · · · · · · · · · · · · · · · ·
Reis 2010	41.32	10	5	44.13	12	5	5.7%	-0.23 [-1.48, 1.02]	
Sezinando 2015	41.1	4.1	5	35.2	3.8	5	5.2%	1.35 [-0.11, 2.80]	
Sezinando 2015	21.2	4.1	5	20.3	3.4	5	5.7%	0.22 [-1.03, 1.46]	· · · · · · · · · · · · · · · · · · ·
Sezinando 2015	33.1	4.1	5	35.8	4.6	5	5.6%	-0.56 [-1.84, 0.72]	
Silva 2006	29.8	4.4	5	38.4	5.5	5	5.0%	-1.56 [-3.08, -0.04]	
Wang 2021	49.8	7.8	7	48.6	11.2	7	6.2%	0.12 [-0.93, 1.17]	· · · · · · · · · · · · · · · · · · ·
Wang 2021	42.5	6.9	7	52.5	6	7	5.8%	-1.45 [-2.67, -0.22]	
Wang 2021	34.2	4.6	7	54.8	6.4	7	4.3%	-3.46 [-5.30, -1.62]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)			233			209	71.8%	-0.27 [-0.85, 0.31]	-
Test for overall effect 1.1.2 Long-term	L = 0.92 (P =	= 0.36)							
Sezinando 2015	26.8	3.6	5	28.3	3.6	5	5.7%	-0.38 [-1.63, 0.88]	
Sezinando 2015	32.2	4	5	38.4	3.7	5		-1.45 [-2.94, 0.03]	
Sezinando 2015	15.4	2.7	5	22.1	3.8	5		-1.84 [-3.45, -0.22]	
Wang 2021	31.1	3.5	7	37.2	3.6	7	5.7%	-1.61 [-2.87, -0.35]	
Wang 2021	21.9	3.3	7	45	5.5	7	3.3%	-4.77 [-7.10, -2.44]	+
Wang 2021	20.7	2.9	7	46.8	7.7	7	3.7%	-4.20 [-6.31, -2.09]	
Subtotal (95% CI)			36			36	28.2%	-2.14 [-3.32, -0.95]	
Heterogeneity: Tau ² =	= 1.47; Chi ² =	16.39, df	= 5 (P =	0.006 ; $I^2 =$	69%				
Test for overall effect	t: Z = 3.54 (P =	= 0.0004)							
Total (95% CI)			269			245	100.0%	-0.80 [-1.35, -0.24]	•
Heterogeneity: Tau ² =	= 1.00; Chi ² =	105.61, d	f = 17 (P)	< 0.00001);	$l^2 = 84\%$				
Test for overall effect	t: Z = 2.81 (P =	= 0.005)							-4 -2 0 2 4 Hydrophobic Resin Layer Manufacturer instructions
Test for subaroup dif	forences: Chi2	- 7 70 d	f - 1 (P -	0.006) 12 -	87 0%				nyurophobic Resin cayer Manufacturer instructions

Test for subgroup differences: $Chi^2 = 7.70$, df = 1 (P = 0.006), $I^2 = 87.0\%$

Figure 2. Forest plot showing the bond strength values when the adhesive was covered by a hydrophobic resin layer [63–68].

	Manufacturer instructions				pplication	time		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
.7.1 Immediate									
Argolo 2012	7.3	9.1	5	9.5	9.2	5	7.3%	-0.22 [-1.46, 1.03]	
Argolo 2012	7.3	9.1	5	12	5.6	5	7.1%	-0.56 [-1.84, 0.72]	
ashaev 2017	35.3	8.9	5	44.3	15	5	7.0%	-0.66 [-1.95, 0.63]	
ashaev 2017	37.9	1.8	5	46.8	6.7	5	5.7%	-1.64 [-3.18, -0.09]	
ashaev 2017	48.4	5.3	5	51.4	6.7	5	7.2%	-0.45 [-1.71, 0.82]	
aito 2020	18.5	3.5	10	34.7	5.3	10	6.0%	-3.45 [-4.94, -1.97] -	
aito 2020	34.4	4.3	10	34.5	5.9	10	10.1%	-0.02 [-0.90, 0.86]	
aito 2020	29.1	4.8	10	31.6	3.3	10	9.9%	-0.58 [-1.48, 0.32]	
aito 2020	29.6	2.7	10	35.2	4.5	10	9.0%	-1.45 [-2.45, -0.44]	
aito 2020	29.5	3.1	10	33.9	4.5	10	9.5%	-1.09 [-2.04, -0.14]	
ubtotal (95% CI)			75			75	78.9%	-0.93 [-1.47, -0.39]	•
eterogeneity: Tau ² =	= 0.40; Chi ² =	19.91, df	= 9 (P =	0.02 ; $I^2 = 5$	5%				
est for overall effect:	Z = 3.38 (P =	= 0.0007)							
.7.2 Long-term									
ashaev 2017	32.4	1.8	5	32.5	4.9	5	7.4%	-0.02 [-1.26, 1.22]	
ashaev 2017	35.1	2.9	5	42.6	7.2	5	6.3%	-1.23 [-2.66, 0.19]	
ashaev 2017	35.3	4.9	5	35.2	3.6	5	7.4%	0.02 [-1.22, 1.26]	
ubtotal (95% CI)			15			15	21.1%	-0.34 [-1.11, 0.42]	
eterogeneity: Tau ² =	= 0.02; Chi ² =	2.10, df =	= 2 (P = 0	$(0.35); I^2 = 5\%$					
est for overall effect:	Z = 0.88 (P =	= 0.38)							
otal (95% CI)			90			90	100.0%	-0.81 [-1.26, -0.35]	•
eterogeneity: Tau ² =	= 0.34: Chi ² =	23.46. df	= 12 (P)	$= 0.02$; $l^2 =$	49%				
est for overall effect:				/					-4 -2 0 2 4
est for subaroup diff				(0.22) $l^2 = 3$	3 4%				Extended application time Manufacturer instructions

Figure 3. Forest plot showing the bond strength values when the adhesive was applied by extending their application time [69–71].

	Manufactu	er instruc	tions	Double-la	yer applic	ation	:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 Immediate									
Bahari 2021	57.7	18	10	60.4	17.6	10	6.2%	-0.15 [-1.02, 0.73]	
Carvalho 2017	40.8	3	5	63.2	7.1	5	3.1%	-3.71 [-6.14, -1.28]	
D'Arcangelo 2009	33.9	13	4	46.7	13	4	4.8%	-0.86 [-2.36, 0.65]	
Elkassas 2009	35	13	3	21.2	9.4	3	4.1%	0.97 [-0.88, 2.83]	
Lodovici 2009	39.4	15	5	28.3	11	5	5.2%	0.76 [-0.55, 2.07]	
Mandava 2009	16	0.4	10	17.5	0.4	10	4.8%	-3.59 [-5.11, -2.07]	
Pashaev 2017	35.3	8.9	5	33.3	5.6	5	5.4%	0.24 [-1.00, 1.49]	
Pashaev 2017	37.9	1.8	5	39.5	4.4	5	5.3%	-0.43 [-1.69, 0.83]	
Pashaev 2017	48.4	5.3	5	42.4	3.8	5	5.0%	1.18 [-0.23, 2.58]	+
Silva 2006	29.8	4.4	5	21.7	1.9	5	4.3%	2.16 [0.42, 3.89]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)			57			57	48.2%	-0.26 [-1.24, 0.72]	-
Heterogeneity: Tau ² =	1.90; Chi ² =	42.84, df	= 9 (P < 0	0.00001); I ²	= 79%				
Test for overall effect:	Z = 0.52 (P =	= 0.60)							
1.2.2 Long-term									
Bahari 2021	43.9	16.5	10	54.6	14.4	10	6.1%	-0.66 [-1.57, 0.24]	
Felemban 2017	8.8	1.2	5	13.2	0.8	5	3.0%	-3.90 [-6.42, -1.38]	
Felemban 2017	16.6	1.1	5	21.8	1.5	5	3.2%	-3.57 [-5.93, -1.21]	
Lodovici 2009	39.55	1.7	5	46	3.6	5	4.4%	-2.07 [-3.77, -0.37]	
Pashaev 2017	32.4	1.8	5	31.1	3.9	5	5.3%	0.39 [-0.87, 1.65]	
Pashaev 2017	35.1	2.9	5	38.9	3.2	5	5.0%	-1.12 [-2.52, 0.27]	
Pashaev 2017	35.3	4.9	5	34.7	6.6	5	5.4%	0.09 [-1.15, 1.33]	
Platt 2001	12.34	6.3	15	21.39	6.2	15	6.3%	-1.41 [-2.22, -0.60]	
Platt 2001	20.02	2.5	15	19.42	2.4	15	6.5%	0.24 [-0.48, 0.96]	_
Platt 2001	20.13	3.1	15	19.46	3.1	15	6.5%	0.21 [-0.51, 0.93]	
Subtotal (95% CI)			85			85	51.8%	-0.82 [-1.51, -0.13]	◆
Heterogeneity: Tau ² =	0.81; Chi ² =	33.04, df	= 9 (P = 0)	0.0001); I ² :	= 73%				
Test for overall effect:	Z = 2.32 (P =	= 0.02)							
Total (95% CI)			142			142	100.0%	-0.57 [-1.13, -0.00]	
					.2	142	100.0%	-0.57 [-1.15, -0.00]	
Heterogeneity: Tau ² =			= 19 (P <	0.00001);	$1^{\circ} = 75\%$				-4 -2 0 2 4
Test for overall effect:		= 0.05) = 0.83. di							Double-layer application Manufacturer instructions

Figure 4. Forest plot showing the bond strength values when the adhesive was applied in two consecutive layers [63,69,72–79].

	Manufactur	er instruc	tions	Electric-current-	assisted app	lication		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.5.1 Immediate									
Guarda 2020	35.3	8	8	37.6	6.41	56	8.2%	-0.34 [-1.09, 0.40]	
Maciel 2021	32	4.7	57	43.1	5.3	64	12.4%	-2.19 [-2.65, -1.74]	
Maciel 2021	34.9	6.2	62	46.9	5.4	65	12.8%	-2.06 [-2.49, -1.62]	
Mazzoni 2009	38	7.8	152	54.7	7.1	163	15.3%	-2.24 [-2.52, -1.96]	-
Mazzoni 2009	41.1	6.1	147	55.5	7.9	142	15.2%	-2.04 [-2.32, -1.75]	+
Pasquantonio 2007	26.6	5.2	48	38.2	4	68	11.7%	-2.54 [-3.04, -2.04]	
Pasquantonio 2007	28.7	5.1	57	38.8	4.1	51	12.0%	-2.15 [-2.63, -1.68]	
Pasquantonio 2007 Subtotal (95% CI)	29	8.6	52 583	44.2	7.1	63 672	12.5% 100.0%	-1.93 [-2.38, -1.49] -2.01 [-2.30, -1.72]	→
Heterogeneity: Tau ² = Test for overall effect				0.0004); I ² = 73%					
1.5.2 Long-term									
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not ap	pplicable								
Test for overall effect	: Not applicabl	e							
Total (95% CI)			583			672	100.0%	-2.01 [-2.30, -1.72]	◆
Heterogeneity: Tau ² =	= 0.12; Chi ² =	26.31, df	= 7 (P =	0.0004 ; $l^2 = 73\%$					
Test for overall effect	t: Z = 13.71 (P	< 0.0000	1)						-4 -2 0 2 4 Electric-current-assisted application Manufacturer instructions
Test for subgroup dif	fferences: Not a	applicable							Lieune-content-assisted application Manufacturer instructions

Figure 5. Forest plot showing the bond strength values when the adhesive was applied using an electric current [80–83].

	Manufactur	er instruc	tions	Active	applica	tion		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.6.1 Immediate									
Dal-Bianco 2006	9.3	4.1	9	41.3	5.9	9	3.4%	-6.00 [-8.40, -3.60]	←
Dal-Bianco 2006	16.1	8.2	9	34.2	8.4	9			
Gokce 2008	24	3.9	10	30.6	6.7	10	5.2%		
Moritake 2019	36.2	4.6	10	41.5	6.4	10			
Moritake 2019	29.3	5.3	10	32.7	6.6	10			
Moritake 2019	33.5	1.9	10	35.2	4.3	10			
Reis 2007	21.1	4.1	5	43.9	5	5			·
Reis 2007	12.8	2.1	5	42.5	2.3	5		-12.18 [-19.15, -5.21]	
Subtotal (95% CI)		1000	68			68			
Heterogeneity: Tau ² =	= 1.67: Chi ² =	37.05. df	= 7 (P <	0.00001): $I^2 = 8$	1%			
Test for overall effect			10.00		1184 - C.S.				
1.6.2 Long-term									
Moritake 2019	38.6	4.6	10	41.9	4.8	10	5.3%	-0.67 [-1.58, 0.23]	
Moritake 2019	37	4.7	10	30.6	4.8	10	5.2%	1.29 [0.31, 2.27]	
Moritake 2019	41	3.7	10	34	5.6	10	5.2%	1.41 [0.41, 2.42]	
Moritake 2019	38.6	3.7	10	33.5	3.9	10	5.2%		
Moritake 2019	30.4	5.2	10	35.9	7.4	10	5.3%	-0.82 [-1.75, 0.10]	
Moritake 2019	40.2	2.6	10	45.3	2.7	10	5.1%	-1.84 [-2.93, -0.76]	
Moritake 2019	35.1	5.5	10	39.6	3.5	10	5.2%	-0.93 [-1.87, -0.00]	
Moritake 2019	27.8	5.1	10	36.6	6.6	10	5.2%		
Moritake 2019	37.6	3.6	10	47.5	1.8	10			
Moritake 2019	32.1	3.5	10	39.8	5	10	5.1%		
Moritake 2019	15.3	5	10	40	4	10			←
Moritake 2019	34.6	3.9	10	43.8	1.8	10			
Reis 2007	14.9	4.1	5	41.1	6.3	5			<u>←−−−−</u>
Reis 2007	12	5.1	5	24.3	3.4	5	4.0%		
Subtotal (95% CI)	07.75	10.000	130	0.2261025	0.000	130			•
Heterogeneity: $Tau^2 =$	= 2.54: Chi ² =	111.15. df	= 13 (P	< 0.000	01): I ² =	= 88%			
Test for overall effect									
Total (95% CI)			198			198	100.0%	-1.61 [-2.30, -0.92]	•
Heterogeneity: Tau ² =	= 2.13; Chi ² =	150.22, df	= 21 (P	< 0.000	01); I ² =	= 86%			
Test for overall effect									-4 -2 0 2 4
Tast for subgroup dif			1 /0	0 27) 1	00/				Active application Manufacturer instruction

Test for subgroup differences: $Chi^2 = 0.81$, df = 1 (P = 0.37), $I^2 = 0\%$

Figure 6. Forest plot showing the bond strength values when the adhesive was used in an active application [84–87].

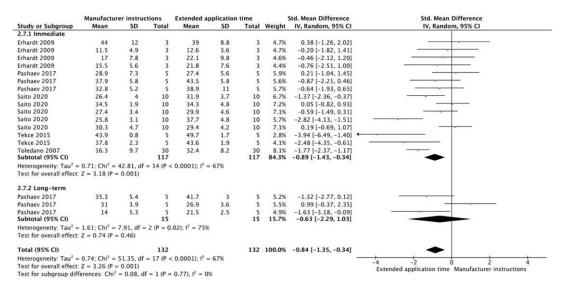
	Manufacture	er instruc	tions	Ultrason	ic applica	ation		Std. Mean Difference	Std. Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	V, Random, 95% CI IV, Random, 95% CI				
1.4.1 Immediate													
Conde 2012	34.04	9.3	10	45.31	8.2	10	27.7%	-1.23 [-2.21, -0.26]					
Fawzy 2019 Subtotal (95% CI)	37.2	6.3	100 110	33.6	7.23	300 310	36.2% 63.8%	0.51 [0.28, 0.74] -0.29 [-2.00, 1.41]	*				
Heterogeneity: Tau ² = Test for overall effect 1.4.2 Long-term			= 1 (P = 0	0.0006); I ²	= 91%								
Fawzy 2019 Subtotal (95% CI)	21.3	7.9	100 100	27.24	8.25	300 300	36.2% 36.2%	-0.73 [-0.96, -0.49] - 0.73 [-0.96, -0.49]	*				
Heterogeneity: Not ap Test for overall effect	•	0.00001)											
Total (95% CI)			210			610	100.0%	-0.42 [-1.45, 0.61]					
Heterogeneity: Tau ² = Test for overall effect Test for subgroup diff	Z = 0.80 (P =	0.43)							-4 -2 0 2 4 Ultrasonic application Manufacturer instructions				

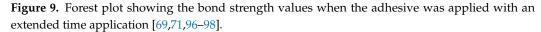
Figure 7. Forest plot showing the bond strength values when the adhesive was applied with an ultrasonic device [88,89].

For the SE adhesive systems, a similar behavior was observed. The techniques that improved the overall bond strength were the application of a hydrophobic resin layer (p < 0.001), an extended application time (p = 0.001), an application assisted by an electric current (p < 0.001), a double-layer application (p < 0.001), and the active application of the adhesive (p = 0.001). Once again, subgroup analysis showed that the statistically significant improvement was observed only for long-term bond strength. On the other hand, the use of an ultrasonic device did not show any improvement (p = 0.39); while the use of reduced application times impaired bond strength (p = 0.008) (Figures 8–14).

101 21 -0 2	Manufactur			Hydrophol				Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
2.1.1 Immediate											
Albuquerque 2008	30	1.2	5	49.8	3.7	5	1.4%	-6.50 [-10.37, -2.64]	·		
Albuquerque 2008	37.1	2.4	5	44.5	3.7	5	2.8%	-2.14 [-3.87, -0.41]			
Albuquerque 2008	18	4.7	5	24.5	4.6	5	3.0%	-1.26 [-2.69, 0.17]			
Albuquerque 2008	24.3	3.1	5	29.5	4.9	5	3.0%	-1.15 [-2.54, 0.25]			
Choi 2008	24.3	7.2	17	29	6.8	19	3.4%	-0.66 [-1.33, 0.02]			
Choi 2008	28.4	4	14	24.9	3.9	14	3.4%	0.86 [0.08, 1.64]			
Choi 2008	30.2	7.5	18	36.6	6.6	17	3.4%	-0.88 [-1.58, -0.19]			
Ermis 2019	32.42	3.5	10	33.76	3.6	10	3.3%	-0.36 [-1.25, 0.52]			
Ermis 2019	34.03	3.7	10	34.46	3.3	10	3.3%	-0.12 [-0.99, 0.76]			
Ito 2005	12.2	7.5	16	62.3	23	16	3.3%	-2.85 [-3.87, -1.84]			
Ito 2005	7.2	6.3	16	27.8	5.9	16	3.2%	-3.29 [-4.40, -2.19]			
Muñoz 2014	34.7	5.8	61	42.7	6.1	68	3.6%	-1.33 [-1.72, -0.95]			
Muñoz 2014	22	5.1	63	48.4	5.9	60	3.4%	-4.77 [-5.47, -4.07]	+		
Muñoz 2014	11.5	3.3	55	22	4.6	55	3.5%	-2.60 [-3.12, -2.09]			
Perdigão 2014	13.4	1.3	5	20.4	1.5	5	2.0%	-4.50 [-7.33, -1.68]	·		
Reis 2008	24.3	3.1	37	29.5	4.9	50	3.5%	-1.22 [-1.68, -0.75]			
Reis 2008	30.2	1.2	33	49.8	3.7	31	3.0%	-7.13 [-8.50, -5.77]	•		
Reis 2008	19.1	2.4	42	37.6	3.4	42	3.2%	-6.23 [-7.28, -5.17]	•		
Reis 2010	42.44	11	5	38.11	13	5	3.1%	0.32 [-0.93, 1.58]			
Serafilm 2018	43.32	7.9	6	35.9	10	6	3.1%	0.76 [-0.43, 1.95]			
Sezinando 2015	35.1	3.4	5	40.2	6.1	5	3.0%	-0.93 [-2.28, 0.41]			
Sezinando 2015	24.1	3.5	5	47.3	4.9	5	1.8%	-4.92 [-7.96, -1.89]	·		
Sezinando 2015	12.1	3.9	5	23.1	5.1	5	2.7%	-2.19 [-3.94, -0.44]			
Subtotal (95% CI)			443			459	69.7%	-2.11 [-2.87, -1.35]	◆		
Heterogeneity: Tau ²				< 0.00001);	$I^2 = 94\%$						
Test for overall effec	t: Z = 5.45 (P <	< 0.00001)									
2.1.2 Long-term											
Ermis 2019	23.72	2.9	10	26.59	2.7	10	3.3%	-0.98 [-1.92, -0.04]			
Ermis 2019	24.81	2.8	10	28.25	3	10	3.3%	-1.14 [-2.10, -0.17]			
Reis 2008	25.2	3.9	22	43.2	4.8	20	3.2%	-4.06 [-5.15, -2.96]	<u>←</u>		
Reis 2008	18.1	4.8	30	28.2	3.1	29	3.4%	-2.46 [-3.14, -1.77]			
Reis 2008	16.9	4.1	23	29.1	3.6	22	3.3%	-3.10 [-3.99, -2.21]			
Serafilm 2018	28.9	11	6	35.4	14	6	3.2%	-0.48 [-1.63, 0.68]			
Serafilm 2018	27.1	13	6	33.4	15	6	3.2%	-0.41 [-1.56, 0.74]			
Sezinando 2015	30.5	4.5	5	36.2	4.5	5	3.0%	-1.14 [-2.54, 0.25]			
Sezinando 2015	23.9	6	5	44.9	5.4	5	2.4%	-3.32 [-5.57, -1.08]	· · · · · · · · · · · · · · · · · · ·		
Sezinando 2015	9.5	2.4	5	24.5	3.7	5	2.0%	-4.34 [-7.09, -1.60]	·		
Subtotal (95% CI)			122			118	30.3%	-2.00 [-2.83, -1.17]	•		
Heterogeneity: Tau ²				0.00001); I ²	= 81%						
Test for overall effect	t: Z = 4.71 (P <	< 0.00001)									
Total (95% CI)			565			577	100.0%	-2.08 [-2.67, -1.48]	-		
Heterogeneity: Tau ²				< 0.00001);	I ^e = 92%				-4 -2 0 2 4		
Test for overall effec									Hydrophobic Resin Layer Manufacturer instructions		
Test for subgroup di	fferences: Chi ²	= 0.04, df	f = 1 (P =	$0.84), I^2 = 0$	0%						

Figure 8. Forest plot showing the bond strength values when the adhesive was covered with a hydrophobic resin layer [64–66,90–95].

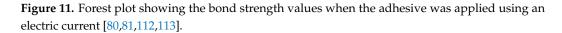




Dependence 2008 18 4-7 5 522 16 5 9.00 -1.85 1-47, -0.23	itudy or Subgroup	Manufactur Mean	er instruct SD	ions Total	Double lay Mean	er-applica SD	tion Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% Cl
Dearter 2020 4, 2, 3 3, 1 5 4, 3 6, 4 5 0, 5 - 3, 77, 14, 23, -1, 11 2021 30, 1 2, 2 6, 0 1 6, 4, 4 4, 4 1 1, 1, 5 - 1, 14, 12, 4 - 4, 4, -4, 4 2021 30, 4 4, 1 1, 1 4, 4 4, 4 1 1, 1, 5 - 1, 44, 14, 4 - 4, 4, -4, 4 2021 30, 4 4, 1 1, 1 3, 1 4, 4 4, 4 1 1, 1, 5 - 1, 44, 14, 4 - 4, 4, -4, 4 2021 30, 4 4, 1 1, 1 3, 1 4, 4 4, 4 1 1, 1, 5 - 1, 44, 14, 4 - 4, 4, -4, 4 10, 10, 10, 2 4, 2 4, 1 4, 1 4, 1 1, 1 1, 1 - 0, 4, 14, 1, 1 4 10, 10, 10, 10, 10, 10, 10, 10, 10, 10,	2.2.1 Immediate									
Descripting 2000 30 12 5 3 3.8 3.4 5 100 -1.35 (2.80.0.11) 2221 23.3 4.3 11 4.46 6 4.4 11 1.58 -1.51 (2.445.4) 2221 23.3 4.3 11 4.46 6 4.4 11 1.58 -1.51 (2.445.4) 2221 23.3 4.3 11 4.46 7 4.5 1 1.58 -1.51 (2.445.4) 2221 23.3 4.3 11 4.46 7 4.5 1 1.58 -1.51 (2.445.4) 2221 23.5 4.4 1 10 3.13 4.1 1.58 -1.51 (2.45.4) 2221 23.5 4.4 1 10 3.13 4.1 1.58 -1.51 (2.45.4) 2221 23.5 4.4 1 10 3.13 4.1 1.58 -1.51 (2.45.4) 2221 23.5 4.4 1 10 3.14 1.58 -1.51 (2.45.4) 2231 23.6 1 2.5 4 4.2 4 4.5 1 1.5 4 4.5 (2.45.4) 2231 23.6 1 2.5 4 4.2 4 4.5 1 1.5 4 4.5 (2.45.4) 2231 23.6 1 2.5 4 4.3 4 4.5 1 1.5 4 4.5 (2.45.4) 2241 23.5 4 4.3 7 5 2.2 7 4.7 5 1.28 -0.46 (1.4.7.6 0.78) 2253 4.3 7 5 2.2 7 4.7 5 1.28 -0.46 (1.4.7.6 0.78) 2253 4.3 7 5 2.2 7 4.7 5 1.28 -0.46 (1.4.7.6 0.78) 2264 1.2 0.2 1 2.5 5 4.7 3 3.6 4.5 1 3 0.08 0 -1.46 (1.4.7.6 0.78) 2253 4.2 7 7 5 3 2.4 7 3 3.6 4.5 1 2.5 7.7 (1.4.1.42.4) Manalyz 2012 23.5 4.7 3 3.6 4.5 1 3 0.08 0 -1.46 (1.4.7.6 0.78) Manalyz 2012 3.5 4.7 3 3.4 4.6 4 3 1.2 8 -0.46 (1.7.7. 0.48) Manalyz 2012 3.5 5 5.6 3 20 7.5 3 0.08 0 -0.5 (1.4.1.1.2.8) Manalyz 2012 3.5 2.4 7 3 3.6 4.5 1 1.5 10.0 0.5 (1.4.1.2.2.4) Manalyz 2012 3.5 2.4 7 3 3.6 4.5 1 2.0 7.7 (1.4.2.2.4) Manalyz 2012 3.5 2.4 7 3 3.4 4.6 4 3 1.2 10 0.08 0.5 (1.4.1.1.2.8) Manalyz 2012 3.5 2.4 7 3 3.4 4.5 1.2 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4	Albuquerque 2008		4.7				5		-1.85 [-3.47, -0.23]	
Dagenergy 20205 37.1 2.24 5 20.6 3.9 5 0.66 4.00 [1.27, 7.47] 2021 2.23 4.3 11 41.4 4.4 11.1 1.51 - 1.44 [2.40, 0.46] 2021 2.23 4.3 11 11 31.3 4.4 11 1.5 1.4 1.4 11 1.55 - 1.44 [2.40, 0.46] 2021 2.23 4.3 11 11 31.3 4.4 11 1.5 1.5 - 1.44 [2.40, 0.46] 2021 2.24 3.9 4.3 11 12 31.3 4.4 11 1.5 1.5 - 1.44 [2.40, 0.46] 10.011 4.4.5 11.5 4.4 30 15 1.2 4.4 30 6 1.3 14 1.5 0.4 0.1 [1.51, 2.4, 0.46] 10.011 4.4.5 11.5 4.4 30 15 1.2 4.4 30 6 4.4 1.5 0.4 4.4 1.5 1.5 0.4 4.1 1.5 0.4 1.5 1.5 1.4 0.4 1.5 0.4 4.4 1.5 1.5 0.4 4.4 1.5 1.5 1.4 0.4 1.5 0.4 4.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 1.4 0.4 1.4 1.5 1.5 1.4 0.4 1.4 1.5 1.4 0.4 1.4 1.5 1.4 0.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1	Albuquerque 2008	24.3	3.1	5	45.3		5			·
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Albuquerque 2008									
2211 36.3 4.3 11 44.6 6.4 11 1.55 -1.51 -2.46 -0.54 20210 23.3 4.1 10 30 1.33 10 1.66 0.58 0.05<	Albuquerque 2008									
2021 2.8.8 4.3 11 31.3 3.4 11 1.5.8 -4.8 [-1.5.0.64] W12011 4.6.3 1.5 1.4 3.0 1.8 1.1 5.0 -4.8 [-1.5.0.64] W12011 4.6.4 1.5 4.4 4.5 4.0 1.5 4.4 4.5 4.0 4.5 1.5 4.4 4.5 4.5 1.6 4.5 1.5 4.4 4.5 4.5 1.6 4.5 1.5 4.4 4.5 4.5 4.5 1.5 4.4 4.5 4.5 4.5 1.5 4.4 4.5 4.5 4.5 1.5 4.5 1.5 4.5 4.5 1.5 4.5 4.5 1.5 4.5 1.5 4.6 4.5 1.5 4.6 4.5 1.5 4.6 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 4.5 1.5 <td< td=""><td>Ali 2021</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></td<>	Ali 2021									
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bar 2021 bar 202 bar 202 bar 202 bar 202 bar 202 bar 202 bar 20 bar 202 bar 20 bar 202 bar 20	Ali 2021								-1.83 [-2.85, -0.80]	
li 2011 48.4 15.5 4 49.6 17 4 1.18 -004 (-1.4), 1.34 - 004 (-1.4), 1.3	Arisu 2009		8.9							
$ \begin{array}{c} 1201 \\ 1$	ahari 2021	43.5	14	10		13.3	10		0.95 [0.01, 1.88]	
li 2011 31.8 12.2 4 30 8.9 4 1.18 0.15 (-1.24, 1.54 wordhur 2019 5.4 12.2 4 30 8.9 4 4 1.18 0.15 (-1.24, 1.54 wordhur 2019 5.4 12.2 4 13 14.3 5 5 6 0.2 1.11 5.4 1.54 wordhur 2019 5.4 12.2 5 6 6.1 14 14.3 5 5 6 0.9 4 - 0.45 (-1.26, 1.51 wordhur 2019 5.4 12.3 5 6 13 0.0 4 - 0.45 (-1.26, 1.51 wordhur 2012 12.5 5 5 1 3 14.7 4 2 5 1.28 - 0.46 (-1.76, 0.78 wordhur 2012 12.5 5 5 1 3 14.7 4 2 5 1.28 - 0.46 (-1.76, 0.78 wordhur 2012 12.5 5 5 1 3 14.7 4 2 5 1.28 - 0.46 (-1.76, 0.78 wordhur 2012 12.5 7 5 1 3 14.7 4 2 5 1.28 - 0.45 (-1.26, 1.51 wordhur 2012 12.5 7 5 1 3 14.7 4 2 5 1.28 - 0.45 (-1.26, 1.51 wordhur 2012 12.5 7 5 1 3 14.7 4 2 5 1.28 - 0.45 (-1.76, 0.68 wordhur 2012 12.5 7 5 1 3 14.7 4 2 5 1.28 - 0.45 (-1.76, 0.68 wordhur 2010 11 5 4 2 3 14.6 7 4 5 1 12.8 - 0.54 (-1.76, 0.68 word 2009 11 5 4 5 3 5 10 15 5 5 12 16 16 18 - 0.48 (-1.67, 0.20 word 2009 10 1 6 6 10 16 3 0 5 10 0.27 - 10.57 (-1.68 word 2009 10 1 6 6 10 16 3 0 5 10 0.27 - 10.57 (-1.68 word 2009 10 1 6 6 10 16 3 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 6 6 10 16 3 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 6 6 10 16 3 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 6 6 10 16 3 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 6 6 10 16 3 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 0.6 13 0 16 3 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 0.6 13 0 16 3 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 0.6 13 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 0.6 13 0 5 10 0.27 - 10.57 (-1.58 word 2009 10 1 0.6 13 0 5 10 0.27 - 0.05 (-1.58 word 2009 10 1 0.6 13 0 5 11 0.2 3 10 0.2 3 - 0.05 (-1.58 word 2009 10 1 0.6 13 0 5 10 0.2 3 - 0.05 (-1.58 word 2009 10 1 0.6 13 0 5 13 0 1 0.2 3 - 0.05 (-1.58 word 2009 10 1 0.6 13 0 5 1 0 0.2 3 - 0.05 (-0.58 , 0.01 word 2009 10 1 0.6 13 0 5 1 0 0.2 3 - 0.05 (-0.58 , 0.01 word 2009 10 1 0.6 13 0 5 1 0 0.2 3 - 0.05 (-0.58 , 0.01 word 2009 10 1 0.6 13 0 5 1 0 0.2 3 - 0.05 (-0.58 , 0.01 word 2009 10 1 1 0.6 13 0 5 1 0 0.2 3 - 0.05 (-0.58 , 0.01 word 2009 0 0 1 1 1 0.6 13 0 5 1 0 0.0 0.0	Belli 2011	48.8	15.5	4	49.6	17	4	1.1%	-0.04 [-1.43, 1.34]	
Seedbary 2019 26 5.2 5 6.4.1 4.3 5 6.2% 7.2.1 [1.1.46, -2.97] Sama 3.000 20.3 8.1 3 5.2.5 5.8 3 0.0% -0.56 [-2.26, 1.1] Sama 3.000 20.3 8.1 3 5.5.5 5.8 3 0.0% -0.56 [-2.26, 1.1] Multally 2012 3.9.1 4.3 4.1.6 4.9 5 1.2% -0.44 [-1.7, 0.61] Multally 2012 3.9.1 4.3 3.4.6 5 1.2% -0.44 [-1.7, 0.61] Mult2 2000 1.3 4.3 8.4.6 2.8 3 0.0% 0.58 [-1.1, 2.43] Mult2 2000 1.3 4.3 8.6.5 5.1 1.5 1.6 4.4.1.7.2.0.81] Mult2 2000 1.3.5 6.1 5.3.1 1.2 1.6 2.9.1.4.0.1.6.2.1.0.1.0.1.0.1.0.1.0.1.0.0.0.0.0.0.0.0	elli 2011	31.8	12.2	4	30	8.9	4	1.1%	0.15 [-1.24, 1.54]	
setter 2019 9 9 9 3.7 5 2.27 4.7 5 1.28 -0.49 1.76 0.75 Manilary 2012 2.83 4.7 5 3.83 5 1.00 -0.08 1.48 -0.24 <td>howdhury 2019</td> <td>50.2</td> <td>3.7</td> <td>5</td> <td>64.1</td> <td>4.3</td> <td>5</td> <td></td> <td>-3.13 [-5.28, -0.98]</td> <td>·</td>	howdhury 2019	50.2	3.7	5	64.1	4.3	5		-3.13 [-5.28, -0.98]	·
setter 2019 9 9 9 3.7 5 2.27 4.7 5 1.28 -0.49 1.76 0.75 Manilary 2012 2.83 4.7 5 3.83 5 1.00 -0.08 1.48 -0.24 <td>howdhury 2019</td> <td>26</td> <td>5.2</td> <td>5</td> <td>64.1</td> <td>4.3</td> <td>5</td> <td>0.2%</td> <td>-7.21 [-11.46, -2.97]</td> <td>·</td>	howdhury 2019	26	5.2	5	64.1	4.3	5	0.2%	-7.21 [-11.46, -2.97]	·
assb. 2009 2 0 25 4 1 3 2 25 5 4 7 5 3 4 6 5 1 5 9 3 0 98 - 0.56 (-226, 1.3) Webling 2012 3 7 4 5 3 5 4 6 7 4 2 5 1 28 - 0.22 (-1.47, 1.02) Webling 2012 3 7 4 5 3 5 4 6 7 4 3 5 1 28 - 0.22 (-1.47, 1.02) Webling 2012 3 7 4 5 3 5 4 6 7 4 3 5 1 28 - 0.22 (-1.47, 1.02) Webling 2012 3 7 4 5 3 5 4 6 7 4 2 3 1 28 - 0.22 (-1.47, 1.02) Webling 2012 1 7 4 3 8 0 20 7 5 3 0 0.8 - 0.34 (-1.23, 0.40) Webling 2020 1 15 5 5 6 3 20 7 5 3 0 0.8 - 0.34 (-1.23, 0.40) Webling 2020 1 15 6 6 6 6 4 1 15 16 1.8 - 0.94 (-1.47, -0.20) Webling 2020 1 15 6 6 6 6 4 5 1 5 1 6 1 18 - 0.94 (-1.47, -0.20) Webling 2020 1 15 6 6 6 16 4 5 1 5 1 6 1 18 - 0.94 (-1.47, -0.20) Webling 2020 1 15 6 6 1 0 10 16 3 5 1 10 0 28 - 0.57 (-1.42, -1.47) Webling 2020 1 10 1 0 6 10 16 3 5 1 10 0 28 - 0.57 (-1.42, -1.47) Webling 2020 1 3 1 6 1 2 16 3 3 1 2 1 6 1 28 - 0.94 (-1.47, -0.20) Webling 2020 1 3 1 6 1 2 16 3 3 1 2 1 6 1 28 - 0.94 (-1.47, -0.20) Webling 2020 1 3 1 6 1 2 16 3 3 2 1 2 6 0 2 1 16 1 28 - 0.94 (-1.47, -0.20) Webling 2020 1 3 1 6 1 0 16 3 0 5 1 10 0 24 -0.57 (-1.12, 1.30) Webling 2020 2 1 4 6 3 2 25 2 6 6 1 3 0 0.8 - 0.34 (-1.47, -1.77) Webling 2020 2 1 4 2 7 2 2 4 29.7 5 7 2 3 1 8 - 2.34 (-1.30, -1.51, 1.70) Webling 2021 4 2 7 2 2 4 29.7 5 7 2 3 1 8 - 2.34 (-1.30, -1.51, 1.70) Webling 2021 4 2 7 2 2 4 29.7 5 7 2 3 1 8 - 2.34 (-1.30, -1.51, 1.70) Webling 2021 4 2 7 2 2 4 29.7 5 7 2 3 1 8 - 2.34 (-1.42, 1.20) Webling 2021 4 2 7 2 2 4 29.7 5 7 7 3 1 8 - 2.34 (-1.42, 1.20) Webling 2021 4 2 7 2 2 4 29.7 5 7 7 3 1 8 - 2.34 (-1.30, -1.51, 1.70) Webling 2021 4 2 3 3 1 7 4 4 3 1 7 1 1 2 1 4 6 2 28 - 0.04 (-0.65, 1.53) Webling 2021 4 2 3 3 1 7 4 4 3 1 7 1 1 2 1 4 6 2 28 - 0.04 (-0.65, 1.53) Webling 2021 4 2 3 3 1 7 4 4 3 1 7 1 1 1 6 - 0.24 (-2.48, 0.44) Webling 2021 3 3 4 7 4 1 1 3 3 4 7 2 3 1 1 1 1 81.24 (-2.48, 0.44) Webling 2037 1 5 3 3 7 7 4 3 3 1 7 4 4 2 2 8 - 0.04 (-0.65, 0.53) Webling 2037 1 5 3 4 6 1 1 1 1 5 4 4 2 3 1 1 1 1 81.24 (-2.48, 0.44) Webling 2037 1 5 3 4 6 1 1 1 1 5 4 4 2 3 1 1 1 1 81.24 (-2.48,	howdhury 2019	50.4	3.7	5	52.7	4.7	5	1.2%	-0.49 [-1.76, 0.78]	
assb. 2009 2015	Ikassas 2009	25.3	9.5	3	26.2	7.8	3	0.9%	-0.08 [-1.69, 1.52]	
Maximity 2012 293 4.3 5 41.6 4.9 5 128 -0.45 [-1.2, 0.81] Maximity 2012 31.4 4.7 5 33.8 5.4 2 5 128 -0.25 [-1.2, 0.81] Maximity 2012 31.4 4.7 5 33.8 5.4 2 5 128 -0.45 [-1.2, 0.81] Maximity 2020 17 7.8 3 9 2.9 3 0.75 3 0.96 0.35 11.11 2.28 Maximity 2020 17 7.8 3 9 2.9 3 0.75 10.9 [-0.43, 1.30] Maximity 2020 17 7.8 3 9 2.9 3 0.75 10.9 [-0.43, 1.30] Maximity 2020 17 7.8 5 30.1 3 5 128 -0.25 [-1.2, 0.81] Maximity 2020 122 7.5 16 13.5 4.2 16 12.8 -0.84 Maximity 2020 13.5 7.6 3 20 7.5 3 0.97 -0.34 [-2.23, 1.14] Maximity 2020 13.5 7.6 3 16 12.6 9.2 16 1.78 -1.99 [-2.76, -1.05] Maximity 2020 13.5 7.8 5 30.1 3 5 12.8 -0.25 [-1.12, 0.81] Maximity 2020 13.5 7.8 5 30.1 3 5 12.8 -0.25 [-1.12, 0.81] Maximity 2020 13.5 7.8 5 30.1 3 5 12.8 -0.25 [-1.12, 0.81] Maximity 2020 13.5 7.8 5 30.1 3 5 12.8 -0.26 [-1.24, 0.95] Maximity 2020 13.5 7.8 5 30.1 3 5 12.8 -0.26 [-1.24, 0.81] Maximity 2017 2.8 7 7.5 7 23 2.8 2 9.9 5 11.2 -0.06 [-1.62, 0.90] Maximity 2020 24.2 7.7 2 5 2.8 2 9.9 5 11.2 -0.06 [-1.62, 0.90] Maximity 2020 24.2 7.2 5 2.8 2 9.9 5 11.2 -0.06 [-1.62, 0.90] Maximity 2021 24.2 7.2 4 2.97 7.7 2.9 1.8 -0.24 [-1.62, 0.90] Maximity 2021 24.2 7.2 4 2.97 7.7 2.9 1.8 -0.24 [-1.62, 0.90] Maximity 2021 24.2 7.2 4 2.97 7.7 2.9 1.8 -0.24 [-1.62, 0.90] Maximity 2021 24.2 7.2 4 2.97 7.7 2.9 1.8 -0.24 [-1.62, 0.90] Maximity 2021 24.2 7.2 4 2.97 7.7 2.9 1.8 -0.24 [-1.62, 0.90] Maximity 2021 24.2 7.1 24 3.9 1.1 4.4 2.2 2.8 -0.43 [-0.45, 0.51] Maximity 2014 4.8 14 5 1.1 4.4 2.2 2.8 -0.43 [-0.45, 0.51] Maximity 2014 4.8 14 5 1.1 4.4 2.2 2.8 -0.45 [-0.45, 0.92] Maximity 2014 4.8 14 5 1.1 4.4 2.2 2.8 -0.45 [-0.45, 0.92] Maximity 2014 4.8 14 5 1.1 14.4 2.2 2.8 -0.45 [-0.45, 0.32] Maximity 2016 14.5 4.9 10 13.4 1.1 10.1 6.6 -0.36 [-1.46, 0.32] Maximity 2017 13.3 7.2 12 9.3 3 10 16 6 -0.76 [-1.46, 0.20] Maximity 2017 13.3 7.2 12 9.3 3 10 16 6 -0.76 [-1.46, 0.20] Maximity 2017 13.3 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9 11 1.5 4.4 9	lkassas 2009	20.5	8.1	3	25.5	5.9	3	0.9%	-0.56 [-2.26, 1.13]	
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$ \begin{aligned} & edan 2007 & 16.3 & 9.7 & 30 & 20.5 & 8 & 30 & 21.8 & -0.47 [-0.98, 0.05] \\ & 2009 & 36.9 & 4.5 & 10 & 40.2 & 6.3 & 10 & 1.66 & -0.58 [-1.48, 0.32] \\ & 2009 & 30 & 3.2 & 10 & 32.2 & 2.8 & 10 & 1.66 & -0.50 [-1.39, 0.39] \\ & 2009 & 30 & 3.2 & 10 & 32.4 & 2.8 & 10 & 1.66 & -0.50 [-1.39, 0.39] \\ & 2016 & 14.5 & 4.9 & 10 & 13 & 4.1 & 10 & 1.66 & -0.32 [-0.57, 1.20] \\ & 10^{-1}\text{Deren 2019} & 6.2 & 111 & 8.8 & 1.7 & 11 & 1.66 & -1.39 [-2.23, -0.36] \\ & 10^{-1}\text{Deren 2019} & 16.3 & 4.6 & 111 & 1.8.6 & 2.4 & 11 & 1.78 & -0.49 [-1.34, 0.36] \\ & 10^{-1}\text{Deren 2019} & 4 & 1.4 & 111 & 10.6 & 3.4 & 11 & 1.38 & -2.44 [-3.60, -1.29] \\ & 10^{-1}\text{Deren 2020} & 16.3 & 4.6 & 111 & 9.3 & 2.5 & 11 & 1.66 & -0.86 [-1.74, 0.02] \\ & 10^{-1}\text{Deren 2020} & 16.3 & 4.6 & 111 & 9.4 & 5.1 & 11.78 & -0.49 [-1.28, 0.42] \\ & 10^{-1}\text{Deren 2020} & 16.3 & 4.6 & 111 & 9.4 & 5.1 & 11.78 & -0.43 [-1.28, 0.42] \\ & 10^{-1}\text{Deren 2020} & 16.3 & 4.6 & 111 & 9.4 & 5.1 & 11.78 & -0.43 [-1.28, 0.42] \\ & 10^{-1}\text{Deren 2020} & 16.3 & 16 & -58 & 0 < 0.00001); 1^{1} & -72xs \\ & stor versal if etcz z = 6.26 & (0 < 0.00001); 1^{1} & -72xs \\ & stor versal if etcz z = 6.26 & (0 < 0.00001); 1^{1} & -72x \\ & stor versal if etcz z = 6.26 & (0 < 0.00001); 1^{1} & -72xs \\ & stor versal if etcz z = 6.26 & (0 < 0.00001); 1^{1} & -72xs \\ & stor versal if etcz z = 6.26 & (0 < 0.00001); 1^{1} & -72xs \\ & store zol1 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.58 & -1.51 [-2.48, -0.54] \\ & -0.21 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.58 & -0.71 [-0.51, 1.26] \\ & -0.21 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.58 & -1.51 [-2.48, -0.54] \\ & -0.21 & 26.1 & 3.3 & 4.4 & 5 & 31.5 & 7.5 & 5 & 1.28 & -0.34 [-0.28, 0.49] \\ & -0.21 & 26.1 & 3.3 & 4.4 & 5 & 31.5 & 7.5 & 5 & 1.28 & -0.71 [-0.51, 0.50] \\ & -0.21 & 25.2 & 2.28 & -0.71 [-0.51, 0.50] \\ & -0.21 & -0.21 & -0.21 & -0.21 & -0.21 \\ & -0.21 & -0.21 & -0.21 & -0.21 & -0.21 \\ & -0.21 & -0.21 & -0.21 & -0.21 & -0.21 & -0.21 \\ & -0.21 & -0.21 & -0.21 & -0.21 & -0.21 & -0.21 \\ & -0.21 & -0.21 & -0.$										
$ \frac{1}{2009} 36.9 4.5 10 40.2 6.3 10 1.6\% -0.58 [-1.48, 0.32] \\ \frac{1}{2009} 30 3.2 10 8.4 2.3 10 1.6\% -0.50 [-1.39, 0.32] \\ \frac{1}{1000} 2.17 2.4 10 8.4 2.3 10 1.6\% -0.50 [-1.30, 0.39] \\ \frac{1}{1000} 2.17 2.4 10 8.4 2.3 10 1.6\% -0.52 [-0.57, 1.20] \\ \frac{1}{1000} 2.11 11 8.8 1.7 11 1.6\% -0.32 [-0.57, 1.20] \\ \frac{1}{1000} 2.11 11 18.6 4.4 11 1.3\% -2.48 [-3.7, -1.40] \\ \frac{1}{1000} 2.2 1 11 11 8.6 4.4 11 1.3\% -2.48 [-3.7, -1.40] \\ \frac{1}{1000} 2.2 1 11 13 9.2 5 11 1.6\% -0.36 [-1.27, 0.38] \\ \frac{1}{1000} 2.2 1 11 13 9.2 5 11 1.6\% -0.68 [-1.27, 0.38] \\ \frac{1}{1000} 2.2 1 11 19.4 4.5 11 1.7\% -0.49 [-1.34, 0.36] \\ \frac{1}{1000} 2.2 1 11 13 9.2 5 11 1.6\% -0.68 [-1.27, 0.02] \\ \frac{1}{1000} 2.2 1 11 19.4 4.5 11 1.7\% -0.66 [-1.52, 0.21] \\ \frac{1}{1000} 2.2 1 11 4.8 10 2.5, 7 4.9 11 1.7\% -0.66 [-1.27, 0.02] \\ \frac{1}{1000} 2.2 1 2.5 1.1 3.1 2.5 11 1.6\% -0.68 [-1.24, 0.02] \\ \frac{1}{1000} 2.2 1 2.5 1.1 3.1 2.5 11 1.1\% -1.51 [-2.48, -0.54] \\ \frac{1}{2021} 2.6 1 7.1 11 3.4 1.3 9 11 1.5\% -1.51 [-2.48, -0.54] \\ \frac{2}{2021} 2.6 1 7.1 11 3.4 1.3 9 11 1.5\% -1.51 [-2.48, -0.54] \\ \frac{2}{2021} 2.6 1 7.1 11 3.4 1.3 9 11 1.5\% -1.51 [-2.48, -0.54] \\ \frac{1}{2021} 2.3 0 14.8 10 2.5, 7 4.9 10 1.6\% 0.37 [-0.51, 1.26] \\ \frac{1}{2021} 3.5 5 4.5 39.3 5.2 5 1.2\% 0.63 [-1.26, 0.62] \\ \frac{1}{3} A4.5 5 17.9 4.6 5 1.2\% 0.63 [-1.36, 0.62] \\ \frac{1}{3} A4.5 5 17.9 4.6 5 1.2\% 0.63 [-1.36, 0.62] \\ \frac{1}{3} A4.5 5 17.9 4.6 5 1.2\% 0.63 [-0.50, 0.19] \\ \frac{1}{3} A4.5 2.2\% 0.55 (-0.94, -0.14] \\ \frac{1}{3} A4.5 10 2.5, 7 4.9 10 1.6\% 0.37 [-0.51, 1.43] \\ \frac{1}{3} A4.5 3 5 17.9 4.6 5 1.2\% 0.63 [-0.50, 0.19] \\ \frac{1}{3} A4.5 3 5 17.9 4.6 5 1.2\% 0.05 [-0.36, -0.18] \\ \frac{1}{3} A4.5 5 11 52 2.2\% 0.55 [-0.36, -0.19] \\ \frac{1}{3} A4.5 5 11 52 2.2\% 0.55 [-0.36, -0.19] \\ \frac{1}{3} A4.5 5 11 52 2.2\% 0.55 [-0.36, -0.19] \\ \frac{1}{3} A4.5 5 11 52 2.2\% 0.55 [-0.36, -0.36] \\ \frac{1}{4} A5.5 11 52 2.2\% 0.55 [-0.36, -0.36] \\ \frac{1}{4} A5.5 11 52 2.2\% 0.55 [-0.36, -0.36] \\ \frac{1}{4} A5.5 11 52 2.2\% 0.55 [-0.36, -0.36] \\ \frac{1}{4} A5.5 11 52 2.2\% 0.55 [-0.36, -0.36] \\ \frac{1}{4} A5.5 11 52 2.2\% 0.55 [-0.36, -0.36] \\ \frac{1}{4} A5.5 11 52 2.2\% 0.55 [-0.$									-0.33 [-1.14, 0.47]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$										
$ \begin{array}{c} 12016 & 7.17 & 2.4 & 10 & 5.4 & 2.3 & 10 & 1.6\% & -0.50 \left[-1.39 \left(0.39 \right] \\ \hline 0.10 = 0.00019 & 6 & 2.4 & 11 & 8.8 & 1.7 & 11 & 1.6\% & -3.21 \left[-0.57 \right] 1.20 \\ \hline 0.10 = 0.00019 & 2.1 & 11 & 11 & 8.1 & 2.9 & 11 & 1.3\% & -2.88 \left[-3.77 - 1.40 \right] \\ \hline 0.10 = 0.00019 & 16.3 & 4.6 & 11 & 18.6 & 4.4 & 11 & 1.7\% & -0.49 \left[-1.34 \right] 0.33 \left[-3.77 - 1.40 \right] \\ \hline 0.10 = 0.00019 & 4 & 1.4 & 11 & 10.6 & 3.4 & 11 & 1.7\% & -0.49 \left[-1.34 \right] 0.33 \left[-3.77 - 1.40 \right] \\ \hline 0.10 = 0.0000 & 2.2 & 1 & 11 & 3.9 & 2.5 & 11 & 1.6\% & -0.85 \left[-1.27 + 0.033 \right] \\ \hline 0.10 = 0.0000 & 2.2 & 1 & 11 & 3.9 & 2.5 & 11 & 1.6\% & -0.86 \left[-1.52 + 0.033 \right] \\ \hline 0.10 = 0.0000 & 2.2 & 1 & 11 & 4.88 & 2.4 & 11 & 1.7\% & -0.66 \left[-1.52 + 0.021 \right] \\ \hline 0.10 = 0.0000 & 16.3 & 4.6 & 11 & 19.4 & 4.5 & 11 & 1.7\% & -0.66 \left[-1.52 + 0.021 \right] \\ \hline 0.10 = 0.0000 & 1 & 4.8 & 11 & 4.88 & 2.4 & 11 & 1.7\% & -0.66 \left[-1.52 + 0.021 \right] \\ \hline 0.10 = 0.0000 & 1 & 4.8 & 10 & 2.5.7 & 4.9 & 11 & 1.5\% & -1.51 \left[-2.48 + 0.54 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.5\% & -1.51 \left[-2.48 + 0.54 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.5\% & -1.51 \left[-2.48 + 0.54 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.5\% & -1.51 \left[-2.48 + 0.54 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.5\% & -1.51 \left[-2.48 + 0.54 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.5\% & -1.51 \left[-2.48 + 0.54 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 12 & 1.2\% & 0.37 \left[-0.51 + 0.24 + 0.54 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 12 & 1.2\% & 0.37 \left[-0.51 + 0.24 + 0.54 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 5.2 & 1.2\% & 0.68 \left[+.38 + 0.62 \right] \\ \hline 0.2021 & 26.1 & 7.1 & 11 & 34.1 & 2.7 & 10 & 1.2\% & 0.37 \left[-0.55 + 0.15 \right] \\ \hline 0.2021 & 25.1 & 2.2\% & 0.57 \left[-0.55 + 0.15 \right] \\ \hline 0.2001 & 33.9 & 5.7 & 5.9 & 5.1 & 2.2\% & 0.57 \left[-0.57 + 0.59 \right] \\ \hline 0.2001 & 1.39 & 2.7 & 10 & 2.11 & 2.8 & 10 & 1.6\% & 0.37 \left[-0.59 + 0.50 \right] \\ \hline 0.20021 & 32.1 & 2.8 & 3.8 & 54 & 9 & 5.4 & 52 & 2.2\% & -0.57 \left[-0.57 + 0.38 \right] \\ \hline 0.20021 & 1.39 & 2.7 & 10 & 1.21 & 2.8 $										
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$\begin{array}{c} \operatorname{cin-Deren} 2020 & 2.2 & 1 & 11 & 3.9 & 2.5 & 11 & 1.6\% & -0.85 (-1.24, 0.02) \\ \operatorname{cin-Deren} 2020 & 16.3 & 4.6 & 11 & 19.4 & 4.5 & 11 & 1.7\% & -0.65 (-1.25, 0.02) \\ \operatorname{cin-Deren} 2020 & 4 & 1.4 & 11 & 4.88 & 2.4 & 11 & 1.7\% & -0.63 (-1.28, 0.42) \\ \operatorname{botal} (955 CI) & 676 & 664 & 78.\% & -0.78 (-1.02, -0.54) \\ \operatorname{teregeneity} Tau' = 0.54; (h')^2 = 204.61, df = 58 (P < 0.00001); l^2 = 72\% \\ \operatorname{st} for overall effect: Z = 6.26 (P < 0.00001) \\ \operatorname{colored} Z = 0.25 (P < 0.00001) \\ \operatorname{colored} Z =$										
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cint-Deren 2020 4 1.4 11 4.88 2.4 11 1.7% -0.43 [-1.28, 0.42]								1.6%	-0.86 [-1.74, 0.02]	
biotal (95% CI) 676 664 76.8% -0.78 [-1.02, -0.54] treogeneity: Tau' = 0.34; Ch' = 204.61, df = 58 ($P < 0.00001$); l' = 72% st for overall effect: Z = 6.26 ($P < 0.00001$); l' = 72% st for overall effect: Z = 6.26 ($P < 0.00001$); l' = 72% 2201 26.1 7.1 11 34.1 3.9 11 1.5% -1.51 [-2.48, -0.54] 2021 26.1 7.1 11 34.1 3.9 11 1.5% -1.34 [-2.29, -0.40] 2021 26.1 7.1 11 34.1 3.9 11 1.5% -1.47 [-2.43, -0.51] bar 2021 30 14.8 10 25.7 4.9 10 1.6% 0.37 [-0.51, 1.26] bar 2021 35.3 5.4 5 39.3 5.2 5 1.2% -0.68 [-1.39, 0.62] bar 2017 35.3 5.4 5 39.3 5.2 5 1.2% -0.68 [-1.39, 0.62] bar 2017 14 5.3 5 17.9 4.6 5 1.2% -0.71 [-2.01, 0.59] bar 2017 14 5.3 5 17.9 4.6 5 1.2% -0.71 [-0.54, -0.14] bar 2017 14 5.3 5 17.9 4.6 5 1.2% -0.71 [-0.54, -0.14] bar 2017 14 5.3 5 17.9 4.6 5 1.2% -0.71 [-0.59] bar 2017 14 5.3 5 17.9 4.6 5 1.2% -0.71 [-0.59] bar 2017 14 5.3 5 17.9 4.6 5 1.2% -0.71 [-0.59] bar 2017 14 5.3 5 17.9 4.6 5 1.2% -0.71 [-0.59] bar 2017 14 5.3 7 1.0 6.14 2.7 10 1.2.1 0.69] bar 2017 14 5.3 2.2% -0.78 [-0.77, -0.20] bar 2014 47.6 12 54 45.5 11 52 2.2% -0.78 [-0.54, -0.14] bar 2017 1.1 4.9 1.1 5 47.6 11 53 2.2% -0.78 [-0.77, -0.20] bar 2014 39 11 55 47.6 11 52 2.2% -0.78 [-0.77, -0.20] bar 2014 39 11 55 47.6 11 6.53 2.2% -0.78 [-0.77, -0.20] bar 2015 20 205 293 2.2% -0.48 [-0.77, -0.20] bar 2016 1.139 2.7 10 12.11 2.8 10 1.6% -0.25 [-1.37, 0.63] bar 2016 1.139 2.7 10 12.11 2.8 10 1.6% -0.25 [-1.37, 0.63] bar 2017 2.3.2 (P = 0.0009) bar 205 295 293 2.2% -0.48 [-0.77, -0.20] bar 206 bar 206 ch' 22 (P < 0.00001); l' = 55% st for overall effect: Z = 0.90 (P < 0.00001); l' = 55% st for overall effect: Z = 0.90 (P < 0.00001); l' = 55% st for overall effect: Z = 0.90 (P < 0.00001); l' = 0.00001; l' = 0.									-0.66 [-1.52, 0.21]	
$ \begin{array}{c} \mbox{teregeneity: Tau' = 0.54; (h')^2 = 204.61, df = 58 (P < 0.00001); l^2 = 72\% \\ \mbox{st for overall effect: Z = 6.26 (P < 0.00001) \\ \mbox{201} & 27.1 & 2.3 & 11 & 23.1 & 4.9 & 11 & 1.5\% & -1.51 [-2.48, -0.54] \\ \mbox{2021} & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.6\% & -1.34 [-2.29, -0.64] \\ \mbox{2021} & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.6\% & -1.34 [-2.43, -0.51] \\ \mbox{2021} & 26.1 & 7.1 & 11 & 34.1 & 3.9 & 11 & 1.6\% & -1.34 [-2.43, -0.51] \\ \mbox{2021} & 30 & 14.8 & 10 & 25.7 & 4.9 & 10 & 1.6\% & 0.37 [-0.51, 1.26] \\ \mbox{2021} & 30 & 14.8 & 10 & 25.7 & 4.9 & 10 & 1.6\% & 0.37 [-0.51, 1.26] \\ \mbox{30ci (2009 33.9 & 4.7 & 5 & 15. 2\% & 51.2\% & 0.48 [-0.94, -0.14] \\ \mbox{31} have 2017 & 31.3 & 5.4 & 5 & 31.52 & 51.2\% & -0.68 [-1.96, -0.14] \\ \mbox{32} have 2017 & 14 & 5.3 & 51.7.9 & 4.6 & 5 & 1.2\% & -0.71 [-2.01, 0.59] \\ \mbox{32} have 2017 & 14 & 5.3 & 51.7.9 & 4.6 & 51.2\% & -0.71 [-2.01, 0.59] \\ \mbox{32} have 2017 & 14 & 5.3 & 51.7.9 & 4.6 & 51.2\% & -0.71 [-2.01, 0.59] \\ \mbox{33} have 2017 & 14 & 5.3 & 51.7.9 & 4.6 & 51.2\% & -0.57 [-0.95, -0.19] \\ \mbox{34} have 2017 & 14 & 5.3 & 51.7 & 52.2\% & -0.68 [-1.96, -0.36] \\ \mbox{35} have 2017 & 14 & 5.3 & 51.7 & 52.2\% & -0.68 [-1.07, -0.38] \\ \mbox{45} have 2017 & 14 & 5.3 & 2.7 & 10 & 12.11 & 2.8 & 10 & 1.6\% & -0.25 [-1.31, 0.63] \\ \mbox{35} have 2014 & 47.6 & 11 & 53 & 2.2\% & -0.48 [-0.77, -0.8] \\ \mbox{45} hotal (95\% CI) & 293 & 23.2\% & -0.48 [-0.77, -0.90, -0.51] \\ \mbox{45} hotal (95\% CI) & 971 & 957 & 100.0\% & -0.70 [-0.90, -0.51] \\ \mbox{45} hotal (95\% CI) & 971 & 957 & 100.0\% & -0.70 [-0.90, -0.51] \\ \mbox{45} hotal (95\% CI) & 971 & 957 & 100.0\% & -0.70 [-0.90, -0.51] \\ \mbox{46} hotal (95\% CI) & 971 & 925.36, df = 72 (P < 0.00001); h^2 = 65\% \\ \mbox{45} hotal (95\% CI) & 971 & 955.5\% \\ \mbox{45} hotal (95\% CI) & 971 & 9$		4	1.4		4.88	2.4			-0.43 [-1.28, 0.42]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	eterogeneity: Tau ² =				< 0.00001);	$I^2 = 72\%$	664	76.8%	-0.78 [-1.02, -0.54]	•
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$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	li 2021									
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tal (95% CI) 971 957 100.0% -0.70 [-0.90, -0.51]	ubtotal (95% CI) leterogeneity: Tau ² =	= 0.13; Chi ² =	28.88, df =	295			10 293	1.6% 23.2%	-0.25 [-1.13, 0.63] -0.48 [-0.77, -0.20]	•
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terogeneity: Tau ² = 0.40; Chi ² = 235.36, df = 72 (P < 0.0001); l ² = 69% st for overall effect: Z = 7.09 (P < 0.0001) Double Jave application Manufacturer instructions	otal (95% CI)						957	100.0%	-0.70 [-0.90, -0.51]	♦
st for overall effect: $Z = 7.09 (P < 0.0001)$		= 0.40; Chi ² =	235.36, df	= 72 (P	< 0.00001);	$I^2 = 69\%$				
				= 1 (P =	0.12), $I^2 = 5$	57.9%				Double-layer application Manufacturer Instructions

Figure 10. Forest plot showing the bond strength values when the adhesive was applied in two consecutive layers [63,69,72,75,77,78,92,93,96–111].

	Manufactur	er instruc	tions	Electric-current-	assisted appl	ication		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD		Weight		IV, Random, 95% CI
2.5.1 Immediate									
Breschi 2006	36.6	8.4	75	48.9	10	69	10.6%	-1.33 [-1.69, -0.97]	
Breschi 2006	25.5	5.9	87	39.3	6.6	76	10.6%	-2.20 [-2.59, -1.81]	
Breschi 2006	22.2	5.7	68	41.5	7	73	10.3%	-3.00 [-3.48, -2.51]	
Chen 2014	42.8	7.1	5	52.6	10.3	30	8.6%	-0.96 [-1.94, 0.02]	
Guarda 2020	41.4	5.2	8	47.2	9.7	56	9.5%	-0.62 [-1.36, 0.13]	
Guarda 2020	24.1	6.3	8	29.2	9.7	56	9.5%	-0.54 [-1.28, 0.21]	
Maciel 2021	38.6	5.1	67	58.3	5.5	59	10.0%	-3.70 [-4.28, -3.12]	
Maciel 2021	36.5	6.4	62	52.6	7.3	55	10.4%	-2.34 [-2.81, -1.87]	
Maciel 2021	41.25	4.5	59	57.26	4.3	60	10.0%	-3.62 [-4.20, -3.03]	
Maciel 2021	39.71	4.8	64	52.89	7.1	61	10.4%		
Subtotal (95% CI)			503			595	100.0%	-2.08 [-2.69, -1.47]	◆
Heterogeneity: Tau ² =	0.89; Chi ² =	122.88, df	f = 9 (P <	0.00001 ; $I^2 = 939$					225°
Test for overall effect	Z = 6.65 (P <	0.00001)							
2.5.2 Long-term									
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not ap	plicable								
Test for overall effect	Not applicabl	e							
Total (95% CI)			503			595	100.0%	-2.08 [-2.69, -1.47]	•
Heterogeneity: Tau ² =	0.89 Chi ² =	122 88 df	F = 9 (P	$0.00001) \cdot 1^2 = 939$					
Test for overall effect				0.00001), 1 = 937					-4 -2 0 2 4
Test for subgroup diff									Electric-current-assisted application Manufacturer instructions



Amaral 2010 16.5 3.4 5 26.3 4.7 5 1.3% $-21.6 [-3.89, -0.2]$ do Amaral 2009 19.6 5.4 5 28.9 5.1 5 1.8% $-1.26 [-2.68, 0.17]$ do Amaral 2009 19.9 6 5 28 5.6 5 1.8% $-1.26 [-2.68, 0.17]$ do Amaral 2009 12.1 7.6 5 30.6 2.8 5 1.7% $-1.47 [-2.96, 0.02]$ do Amaral 2018 21 5.8 6 36.4 6.4 6 1.5% $-2.33 [-3.93, -0.73]$ Irmak 2018 22.5 5.1 6 28.3 6.9 6 2.5% $-0.47 [-1.63, 0.68]$ Jang 2018 22.5 5.1 6 28.3 6.9 6 2.5% $-0.47 [-1.63, 0.68]$ Jang 2018 22.5 5.1 6 28.3 6.9 6 2.5% $-0.47 [-1.63, 0.68]$ Moritake 2019 32.6 4.7 7 5 7.7 10 3.7% $-0.57 [-1.52, 0.28]$ Salkaev 2021 18.9 3.6 6 30.4 11 6 2.1% $-1.30 [-2.59, -0.01]$ Moritake 2019 34.6 3.7 10 37.7 7.1 10 3.5% $-0.62 [-1.52, 0.28]$ Salkaev 2021 18.4 4.5 6 19.8 5 6 2.6% $-0.27 [-1.41, 0.87]$ Salkaev 2021 18.4 4.5 6 19.8 5 6 2.6% $-0.27 [-1.41, 0.87]$ Salkaev 2021 18.4 4.5 6 19.8 5 6 2.6% $-0.27 [-1.41, 0.87]$ Salkaev 2021 18.4 4.5 6 19.8 5 4 2.6 2.6% $-0.27 [-1.41, 0.87]$ Salkaev 2021 18.4 4.5 6 19.8 5 4 2.6 2.6% $-0.27 [-1.41, 0.87]$ Salkaev 2021 18.4 4.5 6 19.8 5 4 2.6 2.6% $-0.27 [-1.41, 0.87]$ Salkaev 2021 18.4 4.5 6 19.8 5 4 2.6 2.6% $-0.27 [-1.41, 0.87]$ Salkaev 2021 24.4 7.2 6 26.1 4.2 6 2.6% $-0.27 [-1.41, 0.87]$ Salkaev 2021 24.4 7.2 6 2.6 1.9 (-2.03) $-0.5 [-1.50, -0.91]$ Zalk 2016 7.17 2.4 10 11.5 10 2.6% $-2.03 [-1.36, -0.91]$ Zalk 2016 7.17 2.4 10 11.5 10 10 2.6% $-2.03 [-1.36, -0.91]$ Zalk 2016 7.17 2.5 2.5 7.7 5 1.8% $-1.23 [-2.66, 0.19]$ Heterogeneity: Tau ² 0.21; Chi ² = 29.26; df = 19 (P = 0.06); i ² = 35% Test for overall effect: $2 = 5.99 (P < 0.00001)$ Zalk 2016 7.17 7.2 2.5 2.5 7.4 5 1.8% $-1.23 [-2.66, 0.19]$ Moritake 2019 3.8 2.6 10 31.8 2.3 5 10 3.6% $-0.75 [-1.67, 0.16]$ Moritake 2019 3.8 2.6 10 34.8 2.5 10 3.6% $-0.75 [-1.67, 0.16]$ Moritake 2019 3.4 2.6 10 34.8 2.3 5 10 3.6% $-0.75 [-1.67, 0.16]$ Moritake 2019 3.4 2.6 10 34.8 2.3 5 10 3.6% $-0.75 [-1.67, 0.16]$ Moritake 2019 3.4 6 10 39.2 2.2 10 3.78 3 10 3.0% $-1.54 [-2.57, -0.51]$ Moritake 2019 3.5 4.5 10 3.88 2.5 10 3.6% $-0.75 [-1.52, -1.06]$ Moritake 2019		Manufactu	rer instruc	tions	Active application				Std. Mean Difference	Std. Mean Difference	
Amaral 2010 17.2 4.2 5 29.9 4.2 5 1.0% -2.73 [-4.71, -0.76] Amaral 2010 16.5 3.4 5 26.3 4.7 5 1.3% -2.16 [-3.80, -0.42] Amaral 2010 19.4 4.5 5 31.8 3.9 5 1.1% -2.26 [-4.60, -0.72] do Amaral 2009 21.3 7.6 5 30.6 2.8 5 1.8% -1.26 [-2.68, 0.17] do Amaral 2009 21.3 7.6 5 30.6 2.8 5 1.7% -1.47 [-0.73, 1.03] do Amaral 2018 21.5 8 6.4 6 1.5% -0.33 [-2.72] -0.74 [-1.63, 0.68] Moritake 2019 37.9 2 10 40.2 2 10 3.3% -1.01 [-2.05, 0.57] Moritake 2019 37.9 2 10 40.2 2 10 3.5% -0.62 [-1.52, 0.28] Salkeev 2021 18.4 4.5 6 1.6 2.1% -0.31 [-1.27], 0.43] -0.31 [-1.27], 0.43] Salkeev 2021 18.4 4.5 6 1.0	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Amaral 2010 16.5 3.4 5 26.3 4.7 5 1.3% $-2.16 (-3.89, -0.42)$ Amaral 2010 19.4 4.5 5 31.8 39 5 1.1% $-2.66 (-4.60, -0.72)$ do Amaral 2009 12.9 6 5 28 5.1 5 1.8% $-1.26 (-2.68, 0.17)$ do Amaral 2009 12.3 7.6 5 30.6 2.8 5 1.7% $-1.47 (-2.96, 0.02)$ do Amaral 2019 21.3 7.6 5 30.6 2.8 5 1.7% $-1.47 (-2.96, 0.02)$ do Amaral 2019 21.3 7.6 6 30.6 2.8 5 1.7% $-0.15 (-0.73, 1.03)$ Irmak 2018 22.5 5.1 6 28.3 6 9 6 2.5% $-0.47 (-1.63, 0.68)$ Iang 2018 22.5 5.1 6 28.3 6 9 6 2.5% $-0.47 (-1.63, 0.68)$ Iang 2018 23.5 4.97 5 27.9 5.7 5 2.1% $-0.74 (-2.05, 0.51)$ Moritake 2019 32.6 4.3 7.1 00 34.1 4.4 10 3.1% $-1.33 (-2.52, -0.43)$ Moritake 2019 34.6 3.7 10 37.7 7.1 10 3.3% $-1.01 (-2.50, -0.51)$ Moritake 2019 34.6 3.7 10 37.7 7.1 00 3.5% $-0.62 (-1.52, 0.28)$ Salkaev 2021 18.9 3.6 6 30.4 11 6 2.1% $-1.30 (-2.59, -0.00)$ Moritake 2019 34.6 4.7 6 19.8 5 6 2.6% $-0.27 (-1.41, 0.87)$ Salkaev 2021 18.4 4.5 6 19.8 5 6 2.6% $-0.27 (-1.41, 0.87)$ Salkaev 2021 18.4 4.5 6 19.8 5 6 2.6% $-0.27 (-1.41, 0.87)$ Salkaev 2021 18.4 4.5 6 19.8 5 1.8% $-1.23 (-2.66, 0.19)$ do Amaral 2009 17.1 7.2 5 20.5 7.7 5 1.8% $-1.26 (-2.47, -0.45)$ Salkaev 2021 24.4 7.2 6 6 5 2.03 5.4 5 1.8% $-1.23 (-2.66, 0.19)$ do Amaral 2009 17.1 7.2 5 2.5 7.7 5 1.8% $-1.23 (-2.66, 0.19)$ Heterogeneity: Tau ² $= 0.21$; Chi ² $= 29.26$, df $= 19 (P = 0.06)$; $t^2 = 35\%$ Test for overall effect: $2 = 5.9 (P < 0.00001)$ 2.62 Long-rem do Amaral 2009 17.1 7.2 5 2.5 7.7 5 1.8% $-1.23 (-2.66, 0.19)$ Moritake 2018 22.41 5.8 6 35.69 7.4 6 1.8% $-1.84 (-3.29, -0.70)$ Moritake 2018 32.3 3.2 0 37.8 3 10 3.0% $-1.46 (-2.47, -0.45)$ Moritake 2019 33.4 2.6 10 34.8 2.3 10 3.0% $-0.75 (-1.67, 0.16)$ Moritake 2019 34.9 4.8 10 38.2 3.5 10 3.5% $-0.75 (-1.67, 0.16)$ Moritake 2019 34.9 4.8 10 38.2 3.5 10 3.5% $-0.75 (-1.67, 0.16)$ Moritake 2019 34.9 4.8 10 38.2 3.5 10 3.5% $-0.75 (-1.67, 0.16)$ Moritake 2019 34.9 4.8 10 37.2 2.0 2.6 10 3.13 3.3 10 2.6% $-0.75 (-1.67, 0.16)$ Moritake 2019 34.9 4.8 10 37.2 2.10 2.2% $-7.79 (-1.66, 0.17)$ Moritake 2019 35.7 3	2.6.1 Immediate										
Amaral 2010 16.5 3.4 5 26.3 4.7 5 1.3% -2.16 [-3.89, -0.42] Amaral 2010 19.4 4.5 5 31.8 39 5 1.1% -2.66 [-4.60, -0.72] do Amaral 2009 19.9 6 5 28 5.1 5 1.8% -1.26 [-2.68, 0.17] do Amaral 2009 12.1 5.6 5 30.6 2.8 5 1.7% -1.47 [-2.69, 0.17] do Amaral 2018 21 5.8 6 36.4 6.4 6 15.5% -0.47 [-1.63, 0.68] Jirmak 2018 22.5 5.1 6 28.3 6 9 6 2.5% -0.47 [-1.63, 0.68] Jang 2018 22.5 5.1 6 28.3 6 9 6 2.5% -0.47 [-1.63, 0.68] Jang 2018 23.5 4.97 5 27.9 5.7 5 2.1% -0.74 [-2.05, 0.51] Moritake 2019 32.6 4 3.7 10 37.7 7 10 33% -1.01 [-2.05, 0.51] Moritake 2019 34.6 3.7 10 37.7 7.7 10 33% -1.02 [-2.59, -0.01] Sakaev 2021 18.9 3.6 6 30.4 11 6 2.1% -1.30 [-2.59, -0.01] Sakaev 2021 18.4 4.5 6 19.8 5 6 2.6% -0.27 [-1.41, 0.87] Sakaev 2021 18.4 4.5 6 19.8 5 6 2.6% -0.27 [-1.41, 0.87] Sakaev 2021 18.4 4.5 6 19.8 5 6 2.6% -0.27 [-1.41, 0.87] Sakaev 2021 18.4 4.5 6 19.8 5 16 2.5% -0.44 [-1.27, 1.24] Thanatvarkorn 2016 6 7.7 2.4 10 11.5 16 10 2.6% -2.03 [-1.36, -0.91] Zaki 2016 7.17 2.4 10 11.5 16 10 2.6% -2.03 [-1.41, 0.87] Sakaev 2021 18.4 4.5 6 19.8 5 18 4 -1.23 [-2.66, 0.19] Heterogeneity: Tau ² = 0.21; Chi ² = 29.26, df = 19 ($P = 0.06$; $l2 = 35\%$ Test for overall effect 2 = 5.9 ($P < 0.00001$) Zaki 2016 7.17 2.2 5 25 7.7 5 1.8% -1.23 [-2.66, 0.19] Heterogeneity: Tau ² = 0.21; Chi ² = 29.26, df = 19 ($P = 0.06$; $l2 = 35\%$ Test for overall effect 2 = 5.9 ($P < 0.00001$) Zaki 2016 14.54 4.9 10 32.0 5.4 5 5 1.8% -1.23 [-2.66, 0.19] Heterogeneity: Tau ² = 0.21; Chi ² = 29.26, df = 19 ($P = 0.06$; $l2 = 35\%$ Test for overall effect 2 = 5.9 ($P < 0.00001$) Zaki 2016 2.24 5.8 6 35.69 7.4 6 1.8% -1.24 [-2.47, 0.45] Moritake 2019 32.9 3.2 10 37.8 3 10 3.0% -1.16 [-1.38, 0.93] Moritake 2019 34.9 4.8 10 38.2 3.5 10 3.5% -0.75 [-1.67, 0.16] Moritake 2019 34.9 4.8 10 38.2 3.5 10 3.5% -0.75 [-1.67, 0.16] Moritake 2019 34.9 4.8 10 38.2 3.5 10 3.5% -0.75 [-1.67, 0.16] Moritake 2019 34.9 4.8 10 37.2 2.0 2.6 00 31.8 3.0 30 Moritake 2019 34.9 4.8 10 37.2 2.0 2.6 00 31.8 3.0 30 Moritake 2019 34.9 4.8 1	Amaral 2010	17.2	4.2	5	29.9	4.2	5	1.0%	-2.73 [-4.71, -0.76]		
Amaral 2010 194 4.5 5 31.8 3.9 5 1.1% $-2.66[-4.60, -0.72]$ do Amaral 2009 21.6 5.4 5 2.8 5.6 5 1.8% $-1.26[-2.66, 0.17]$ do Amaral 2009 21.3 7.6 5 30.6 2.8 5 1.8% $-1.26[-2.66, 0.17]$ do Amaral 2009 21.3 7.6 5 30.6 2.8 5 1.8% $-1.26[-2.66, 0.17]$ do Amaral 2018 21 5.8 6 36.4 6 6 1.5% $-2.33[-3.3], -0.23]$ Irmak 2018 25.2 5.1 6 2.8.3 6.9 6 2.5% $-0.47[-1.63, 0.68]$ Jang 2018 23.5 4.97 5 2.7.9 5.7 5 2.1% $-0.74[-2.25, 0.57]$ Moritake 2019 37.9 2 10 40.2 2 10 3.3% $-1.10[-2.66, 0.15]$ Moritake 2019 34.6 3.7 10 37.7 5.7 10 3.5% $-0.62[-1.52, 0.28]$ Sakaew 2021 18.9 3.6 6 30.4 11 6 2.6% $-0.27[-1.41, 0.87]$ Sakaew 2021 18.4 4.5 6 19.8 5 6 2.6% $-0.27[-1.41, 0.87]$ Sakaew 2021 18.4 4.5 6 19.8 5 6 2.6% $-0.27[-1.41, 0.87]$ Thanatvarakorn 2016 60.2 9.5 5 60.5 9.6 5 2.3% $-0.03[-1.27, 1.21]$ Thanatvarakorn 2016 67.3 9.3 6 66.3 10 5 2.0% $-0.38[-1.24, -0.91]$ Zaki 2016 1.4.54 4.9 10 20.6 31.1 10 2.6% $-2.03[-1.24, -0.91]$ Zaki 2016 1.4.54 4.9 10 20.6 31.1 10 3.6% $-1.46[-1.24, -0.45]$ Subtoal (95% CI) -1.51 $-92.26, df = 19.9 -0.06; t^2 = 35\%Test for overall effect: Z = 5.99 (P < 0.00001)Zal 200 12.5 6 5 2.0.3 5.4 5 1.8% -1.23[-2.66, 0.19]do Amaral 2009 12.5 6 5 2.0.3 5.4 5 1.8% -1.23[-2.66, 0.19]do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -1.05[-1.39, -0.70]4Heterogenety: Tua' -0.21; (-b^2 = 2.9.26, df = 19.9 -0.06; t^2 = 35\%Test for overall effect: Z = 5.99 (P < 0.00001)Zal 200 12.5 6 2.0.3 5.4 5 1.8% -1.23[-2.66, 0.19]do Amaral 2009 13.7 1 7.2 5 25.5 7.7 5 1.9% -1.05[-1.39, -0.70]4Heterogenety: Tua' -0.21; (-b^2 = 2.9.26, df = 19.9 -0.06; t^2 = 35\%Test for overall effect: Z = 5.99 (P < 0.00001)Zal 200 12.5 6 12.5 2.5 7.7 5 1.9% -1.05[-1.39, -0.70]4Heterogenety: Tua' -0.21; (-b^2 = 2.56, df = 10, -2.55, -7.755Heterogenety: Tua' -0.21; (-b^2 = 2.56, df = 10, -2.66, -1.95]Heterogenety: Tua' -0.21; (-b^2 = 2.56, df = 10, -2.55, -7.755Heterogenety: Tua' -0.21; (-b^2 = 2.56, df = 10, -2.55, -7.755Heterogenety: Tua' -$	Amaral 2010	16.5	3.4	5	26.3	4.7	5	1.3%			
do Amaral 2009 19.9 6 5 28 9 5.1 5 1.8% -1.26 [-2.68, 0.17] do Amaral 2009 12.3 7.6 5 30.6 2.8 5 1.7% -1.47 [-2.66, 0.02] Gokre 2008 36 8.3 10 35 3.3 10 3.7% 0.15 [-0.73, 1.03] Irmak 2018 21 5.8 6 36.4 6.4 6 15% -2.33 [-3.93, -0.72] Irmak 2018 252 5.1 6 2.8.3 6.9 6 2.5% -0.47 [-1.63, 0.68] Moritak 2019 37.9 2 10 40.2 2 10 3.3% -1.10 [-2.66, -0.15] Moritak 2019 32.5 4.97 5 2.79 5.7 5 2.1% -0.74 [-2.65, 0.77] Moritak 2019 32.6 6 3.7 10 37.7 7.7 10 3.3% -1.31 [-3.22, -0.34] Moritak 2019 34.6 3.7 10 37.7 7.7 10 3.5% -0.62 [-1.52, 0.28] Moritak 2021 18.9 3.6 6 30.4 11 6 2.1% -1.30 [-2.59, -0.01] Salkew 2021 18.4 4.5 6 19.8 5 6 2.6% -0.27 [-1.41, 0.87] Thanatvarkom 2016 57.3 9.3 5 66.3 10 5 2.0% -0.84 [-2.17, 0.49] Zaki 2016 7.17 2.4 10 11.5 16 10 2.0% -1.08 [-1.27, 1.21] Thanatvarkom 2016 57.3 9.3 5 66.3 10 5 2.0% -0.84 [-2.17, 0.49] Zaki 2016 14.54 4 9 10 20.8 3.1 10 3.0% -1.46 [-2.47, -0.45] Zaki 2016 14.54 4 9 10 20.8 3.1 10 3.0% -1.46 [-2.47, -0.45] Zaki 2016 7.17 7.2 4 10 11.5 16 10 3.0% -1.46 [-2.47, -0.45] Zaki 2016 7.17 7.2 5 25.5 7.7 5 1.8% -1.03 [-3.16, -0.12] Thanatvarkom 2016 60.2 9.5 5 60.5 5 2.5% -0.57 [-1.41, 0.87] Thanatvarkom 2016 7.2 9.9 ($P < 0.00001$) Zaki 2016 7.17 7.2 4 5.5 7.7 5 1.8% -1.23 [-2.66, 0.19] do Amaral 2009 12.5 6 5 20.3 5.4 5 1.8% -1.23 [-2.66, 0.19] do Amaral 2009 12.5 6 19 ($P = 0.066$; $I^2 = 35\%$ Test for overall effect: $Z = 5.90$ ($P < 0.00001$) Zaki 2018 22.41 5.8 6 35.69 7.4 6 1.8% -1.23 [-2.66, 0.19] do Amaral 2009 17.4 7.2 2 25.5 7.7 5 1.8% -1.68 [-3.24, -0.12] Irmak 2018 22.41 5.8 6 35.69 7.4 6 1.8% -1.23 [-2.66, 0.19] do Amaral 2009 17.5 7.8 10 3.7% 3 10 3.0% -1.51 [-2.53, 0.49] Moritak 2019 34.9 4.8 10 38.2 3.5 10 3.5% -0.75 [-1.67, 0.16] Moritak 2019 34.9 4.8 10 38.2 3.5 10 3.5% -0.75 [-1.67, 0.16] Moritak 2019 34.9 4.8 10 38.2 3.5 10 3.5% -0.75 [-1.67, 0.51] Moritak 2019 35.7 3.8 10 41.7 22 10 3.0% -1.54 [-2.52, -0.51] Moritak 2019 35.7 3.8 10 41.7 22 10 3.0% -1.54 [-2.52, -0.51] Moritak 2019 35.7 3.8 10 41.7 22 10 3.0% -1.54 [-2.57,											
do Amaral 2009 do Amaral 2009 19.9 6 6 6 7 8 10 6 10 10 10 10 10 10 10 10 10 10											
do Amaral 2009 21.3 27.6 2009 21.3 2											
$ \begin{array}{c} Gake 2008 & 36 & 8.3 & 10 & 35 & 3.3 & 10 & 3.7 & 0.15 [-0.73, 1.03] \\ Irmak 2018 & 21 & 5.8 & 6 & 36.4 & 6.4 & 6 & 15.8 & -2.38 [-3.33, -0.72] \\ Irmak 2018 & 25.2 & 5.1 & 6 & 28.3 & 6.9 & 6 & 2.58 & -0.47 [-4.50, 0.68] \\ Jang 2018 & 23.5 & 4.97 & 5 & 27.9 & 5.7 & 5 & 2.18 & -0.47 [-4.50, 0.68] \\ Jang 2018 & 23.5 & 4.97 & 5 & 27.9 & 5.7 & 5 & 2.18 & -0.47 [-4.50, 0.51] \\ Moritake 2019 & 36.6 & 3.7 & 10 & 37.7 & 5.7 & 10 & 3.38 & -1.10 [-2.56, -0.51] \\ Moritake 2019 & 36.6 & 3.7 & 10 & 37.7 & 5.7 & 10 & 3.58 & -0.62 [-1.52, 0.28] \\ Satkaew 2021 & 16.9 & 36.6 & 6 & 30.4 & 11 & 6 & 2.18 & -1.30 [-2.59, -0.00] \\ Satkaew 2021 & 18.4 & 4.5 & 6 & 19.8 & 5 & 6 & 2.68 & -0.27 [-1.41, 0.87] \\ Satkaew 2021 & 18.4 & 4.5 & 6 & 19.8 & 5 & 6 & 2.38 & -0.01 [-1.27, 1.21] \\ Thanatvarakom 2016 & 57.3 & 9.3 & 5 & 66.5 & 9.6 & 5 & 2.38 & -0.01 [-1.27, 1.49] \\ Zak 2016 & 7.17 & 2.4 & 10 & 11.5 & 1.6 & 10 & 2.68 & -2.01 [-3.16, -0.91] \\ Zak 2016 & 7.17 & 2.4 & 10 & 11.5 & 1.6 & 10 & 2.68 & -2.01 [-3.16, -0.91] \\ Zak 2016 & 7.17 & 2.4 & 10 & 12.5 & 1.38 & -1.02 [-2.38, 0.35] \\ do Amaral 2009 & 12.5 & 6 & 5 & 20.3 & 5.4 & 5 & 1.88 & -1.23 [-2.66, 0.19] \\ do Amaral 2009 & 12.5 & 6 & 55.69 & 7.4 & 6 & 1.88 & -1.23 [-2.66, 0.19] \\ do Amaral 2009 & 12.5 & 6 & 55.69 & 7.4 & 6 & 1.88 & -1.23 [-2.38, 0.43] \\ Moritake 2019 & 33.2 & 2.5 & 25.4 & 5.1 & 5 & 2.38 & -0.06 [-1.95, 0.64] \\ Moritake 2019 & 34.9 & 4.8 & 10 & 38.2 & 3.5 & 10 & 3.58 & -0.75 [-1.60, 0.70] \\ Horitake 2019 & 34.9 & 4.8 & 10 & 38.2 & 3.5 & 10 & 3.58 & -0.75 [-1.60, 0.16] \\ Moritake 2019 & 35.2 & 10 & 0.38 & 2.5 & 10 & 0.38 & -0.75 [-1.60, 0.16] \\ Moritake 2019 & 35.2 & 10 & 0.38 & 2.5 & 10 & 3.58 & -0.75 [-1.60, 0.61] \\ Moritake 2019 & 35.2 & 10 & 0.38 & 2.5 & 10 & 3.58 & -0.75 [-1.60, 0.61] \\ Moritake 2019 & 35.2 & 10 & 0.38 & 2.5 & 10 & 2.58 & -1.24 [-2.92, -0.66] \\ Moritake 2019 & 35.2 & 1.5 & 10 & 38.8 & 2.5 & 10 & 2.18 & -0.74 [-1.66, 0.16] \\ Moritake 2019 & 35.2 & 4.5 & 10 & 41.2 & 7 & 10 & 3.06 & -0.75 [-1.67, 0.61] \\ Moritake 2019 & 35.2 & 1.5 & 10 & 38.8 & $											
Irmak 2018 21 5.8 6 36.4 6.4 6 1.5% -2.33 [-3.30, -0.72] Irmak 2018 25.2 5.1 6 2.8% -0.47 [-1.63, 0.68] Irmak 2019 25.2 5.1 6 2.8% -0.47 [-1.63, 0.68] Irmak 2019 25.2 4.1 10 34.1 4.4 10 3.3% -1.31 [-2.25, -0.34] Irmak 2019 26.2 4.1 10 37.7 5.7 10 3.3% -0.62 [-1.52, 0.28] Satkew 2021 16.9 3.6 30.4 11 6 2.1% -1.30 [-2.59, -0.00] Satkew 2021 16.9 3.6 6 30.4 11 6 2.1% -1.30 [-2.59, -0.00] Satkew 2021 16.9 3.5 6 0.5 9.6 5 2.3% -0.02 [-1.52, 0.28] Satkew 2021 24.4 7.2 6 26.1 4.2 6 2.6% -0.27 [-1.41, 0.87] Satkew 2021 16 60.2 9.5 5 60.5 9.6 5 2.3% -0.03 [-1.27, 0.49] Irmak 2016 7.3 9.3 5 66.3 10 5 2.6% -0.27 [-1.41, 0.87] Satkew 2021 16 60.2 9.5 5 60.5 9.6 5 2.3% -0.03 [-1.27, 0.49] Irmak 2016 17.3 9.3 5 66.3 10 5 2.0% -0.48 [-2.17, 0.41] Irmak 2016 17.1 2.4 10 11.5 1.6 10 2.6% -2.03 [-3.16, -0.91] Zaki 2016 17.1 7 2.4 10 11.5 1.6 10 2.6% -2.03 [-3.16, -0.91] Zaki 2016 17.1 7 2.4 10 11.5 1.6 10 2.6% -1.05 [-1.39, -0.70] Irmak 2016 17.1 7 2 5 25.5 7.7 5 1.9% -1.02 [-2.38, 0.35] do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -1.02 [-2.38, 0.35] do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -1.02 [-2.38, 0.35] do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -1.02 [-2.38, 0.35] do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -1.02 [-2.38, 0.35] do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -1.02 [-2.38, 0.35] do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -1.02 [-2.38, 0.35] do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -0.66 [-3.24, -0.12] Irmak 2018 22.4 5 8 6 5 6 6 2.5% -0.46 [-1.61, 0.70] Irmak 2018 22.4 5 8 6 5 6 6 2.5% -0.46 [-1.61, 0.70] Irmak 2018 22.4 5 8 6 5 7 4 6 1 8 1.9 (-1.84 [-3.29, -0.60] Irmak 2019 3.3 2.9 10 3.9 3.9 10 3.9 0.7 [-1.66, 0.57] Irmak 2018 22.4 5 8 6 5 1 0 41.8 5.1 10 3.6% -0.90 [-1.83, 0.05] Irmak 2019 3.4 2.6 10 41.2 7.1 0 3.0% -1.54 [-2.57, -0.51] Irmak 2019 3.3 2.9 10 39.9 3.9 10 2.5% -0.54 [-3.24, -0.44] Irmak 2019 3.4 2.6 10 38.2 3.1 0 3.5% -0.74 [-1.66, 0.58] Irmak 2019 3.5. 4 .3 10 41.2 7.1 0 3.0% -0.57 [-1.65, 0.51] Irmak 2019 3.5. 4 .3 10 41.2 7.1 0 3.0% -0.54 [-2.57, -0.51] Irmak 2019 3.5. 4 .3 10 41.2 7.1 0 3.0%											
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Test for overall effect: $Z = 5.99 (P < 0.00001)$ 2.6.2 Long-term do Amaral 2009 12.5 6 5 20.3 5.4 5 1.8% -1.23 [-2.66, 0.19] do Amaral 2009 17.1 7.2 5 25.5 7.7 5 1.9% -1.02 [-2.38, 0.35] do Amaral 2009 18.8 3.7 5 27.2 5.2 5 1.6% -1.68 [-3.24, -0.12] Irmak 2018 26.1 4.2 6 2.8.8 6.5 6 2.5% -0.46 [-1.61, 0.70] Irmak 2018 22.41 5.8 6 35.69 7.4 6 1.8% -1.84 [-3.29, -0.40] Jang 2018 22.3 3.2 5 25.4 5.1 5 2.1% -0.66 [-1.95, 0.64] Moritake 2019 38.2 2.3 10 37.8 3 10 3.0% -1.51 [-2.53, -0.49] Moritake 2019 38.2 2.6 10 41.8 5.1 10 3.4% -0.09 [-1.83, 0.03] Moritake 2019 34.9 4.8 10 38.2 3.5 10 3.5% -0.75 [-1.67, 0.16] Moritake 2019 37.2 2.1 10 43.2 3.3 10 2.6% -2.08 [-3.21, -0.94] Moritake 2019 37.2 2.1 10 43.2 3.3 10 2.6% -0.08 [-3.21, -0.94] Moritake 2019 35.7 3.8 10 41 2.7 10 3.0% -1.54 [-2.57, -0.51] Moritake 2019 35.5 4.3 10 41.7 2.2 10 3.0% -1.54 [-2.57, -0.51] Moritake 2019 35.5 4.3 10 41.7 2.2 10 3.0% -1.54 [-2.57, -0.68] Moritake 2019 35.5 4.3 10 41.7 2.2 10 2.8% -1.74 [-1.66, 0.17] Moritake 2019 35.7 10 16.57 3.4 10 2.1% -2.79 [-4.09, -1.48] Moritake 2019 35.4 4.6 10 39.2 2.2 10 3.0% -1.54 [-2.57, -0.51] Moritake 2019 35.4 4.6 10 39.2 2.2 10 3.0% -1.54 [-2.57, -0.51] Moritake 2019 35.4 4.6 10 39.2 2.2 10 3.0% -1.49 [-2.51, -0.48] Moritake 2019 35.4 4.6 10 39.2 2.2 10 3.0% -1.49 [-2.51, -0.48] Moritake 2019 35.4 4.6 10 39.2 2.2 172 54.4% -1.26 [-1.52, -0.68] Moritake 2019 35.4 4.6 10 39.2 2.2 10 3.0% -1.49 [-2.51, -0.48] Moritake 2019 35.4 4.6 10 39.2 2.2 10 3.0% -1.49 [-2.51, -0.48] Moritake 2019 35.4 4.6 10 39.2 2.2 10 3.0% -1.49 [-2.51, -0.48] Moritake 2019 35.4 4.6 10 39.2 1.2 1.2% Total (95% CI) 172 54.4% -1.26 [-1.52, -1.00] Heterogenetiv: Tau ² = 0.04; Chi ² = 21.61, df = 19 (P = 0.30); l ² = 12% Test for overall effect: $Z = 9.56 (P < 0.00001)$							122	43.0%	-1.05 [-1.59, -0.70]	•	
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$\begin{aligned} \text{Irrmak 2018} & 26.1 & 4.2 & 6 & 28.8 & 6.5 & 6 & 2.5\% & -0.66 [-1.61, 0.70] \\ \text{Irrmak 2018} & 22.41 & 5.8 & 6 & 35.69 & 7.4 & 6 & 1.8\% & -1.84 [-3.29, -0.40] \\ \text{Jang 2018} & 22.3 & 3.2 & 5 & 25.4 & 5.1 & 5 & 2.1\% & -0.66 [-1.95, 0.64] \\ \text{Mortiake 2019} & 38. & 2.6 & 10 & 37.8 & 3 & 10 & 3.0\% & -1.51 [-2.53, -0.49] \\ \text{Mortiake 2019} & 34.9 & 4.8 & 10 & 38.2 & 3.5 & 10 & 3.5\% & -0.75 [-1.67, 0.16] \\ \text{Mortiake 2019} & 33.3 & 2.9 & 10 & 39.9 & 3.9 & 10 & 2.6\% & -1.84 [-3.29, -0.76] \\ \text{Mortiake 2019} & 37.2 & 2.1 & 10 & 43.2 & 3.3 & 10 & 2.6\% & -1.84 [-3.29, -0.76] \\ \text{Mortiake 2019} & 37.2 & 2.1 & 10 & 43.2 & 3.3 & 10 & 2.6\% & -0.74 [-1.66, 0.17] \\ \text{Mortiake 2019} & 38.1 & 2.8 & 10 & 40.2 & 2.6 & 10 & 3.5\% & -0.77 [-1.68, 0.15] \\ \text{Mortiake 2019} & 35.7 & 3.8 & 10 & 41.2 & 7.1 & 0 & 3.0\% & -1.54 [-2.57, -0.51] \\ \text{Mortiake 2019} & 34.5 & 3.4 & 10 & 37 & 2.8 & 10 & 3.5\% & -0.77 [-1.68, 0.15] \\ \text{Mortiake 2019} & 35.5 & 4.3 & 10 & 41.7 & 2.2 & 10 & 2.6\% & -0.48 [-3.21, -0.94] \\ \text{Mortiake 2019} & 35.8 & 1.5 & 10 & 38.8 & 2.5 & 10 & 2.1\% & -2.79 [-4.09, -1.48] \\ \text{Mortiake 2019} & 33.4 & 4.6 & 10 & 39.2 & 2.2 & 10 & 3.0\% & -1.54 [-2.57, -0.51] \\ \text{Mortiake 2019} & 33.4 & 4.6 & 10 & 39.2 & 2.2 & 10 & 3.0\% & -1.47 [-2.80, -0.68] \\ \text{Mortiake 2019} & 33.4 & 4.6 & 10 & 39.2 & 2.2 & 10 & 3.0\% & -1.49 [-2.51, -0.48] \\ \text{Mortiake 2019} & 33.4 & 4.6 & 10 & 39.2 & 2.2 & 10 & 3.0\% & -1.49 [-2.51, -0.48] \\ \text{Mortiake 2019} & 33.4 & 4.6 & 10 & 39.2 & 2.2 & 10 & 3.0\% & -1.49 [-2.51, -0.48] \\ \text{Mortiake 2019} & 33.4 & 4.6 & 10 & 39.2 & 2.2 & 10 & 3.0\% & -1.49 [-2.51, -0.48] \\ \text{Mortiake 2019} & 33.4 & 4.6 & 10 & 39.2 & 2.2 & 10 & 3.0\% & -1.49 [-2.51, -0.48] \\ \text{Mortiake 2019} & 33.4 & 4.6 & 10 & 39.2 & 2.2 & 10 & 3.0\% & -1.49 [-2.51, -0.48] \\ \text{Subtotal (95\% CI)} & 1.7 & 10 & 11.45 & 3.6 & 10 & 3.0\% & -1.49 [-2.51, -0.48] \\ \text{Subtotal (95\% CI)} & -30.6 & (-0.07) \text{ I}^2 = 12\% \\ \text{Test for overall effect: Z = 9.56 (P < 0.00001) \\ \text{Total (95\% CI)} & -102 (-p)^2 - 52.8 & p.6 & f = 30 (P = 0.07) \text{ I}^2 = 78\% \\ Mortiake$											
$\begin{aligned} \text{Irrmak 2018} & 22.41 & 5.8 & 6 & 35.69 & 7.4 & 6 & 1.8\% & -1.84 $											
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Zaki 2016 11.39 2.7 10 16.57 3.4 10 2.9% -1.62 [-2.66, -0.58] Zaki 2016 7.06 1.7 10 11.45 3.6 10 3.0% -1.49 [-2.51, -0.48] Subtotal (95% CI) 172 172 54.4% -1.26 [-1.52 , -1.00] Heterogeneity: Tau ² = 0.04; Chi ² = 21.61, df = 19 (P = 0.30); l ² = 12% Total (95% CI) 307 307 100.0% -1.16 [-1.38 , -0.95] Heterogeneity: Tau ² = 0.12; Chi ² = 52.98, df = 30 (P = 0.07); l ² = 26%											
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Heterogeneity: Tau ² = 0.04; Chi ² = 21.61, df = 19 (P = 0.30); i ² = 12% Test for overall effect: Z = 9.56 (P < 0.00001) Total (95% Cl) 307 307 100.0% -1.16 [-1.38, -0.95] ϕ		7.06	1.7		11.45	3.6					
Total (95% CI) 307 307 100.0% -1.16 [-1.38, -0.95]	Heterogeneity: $Tau^2 = 0$				0.30); l ² =	= 12%	1/2	34.4%	-1.20 [-1.32, -1.00]	•	
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 52.98$, $df = 39.(P = 0.07); l^2 = 26\%$		L = 9.50 (P <	0.00001)								
Heterogeneity: $Tau^2 = 0.12$: $Chi^2 = 52.98$, $df = 39$ (P = 0.07); $l^2 = 26\%$							307	100.0%	-1.16 [-1.38, -0.95]	•	
	Heterogeneity: $Tau^2 = 0$	0.12; Chi ² = 5	2.98, df =	39 (P =)	0.07); l ² :	= 26%			-	-4 -2 0 2	

Figure 12. Forest plot showing the bond strength values when the adhesive was used in an active application [86,87,109,114–119].

	Manufactur	er instruc	tions	Ultrason	ic applica	ation	1	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.4.1 Immediate									
lang 2018	23.5	4.9	5	33.1	5.5	5	7.4%	-1.66 [-3.22, -0.11]	
Mena-Serrano 2014	6.1	3.2	8	4.8	3.6	8	10.6%	0.36 [-0.63, 1.35]	
Mena-Serrano 2014 Subtotal (95% CI)	9.2	4.9	8 21	3	0.9	8 21	9.4% 27.4%	1.66 [0.48, 2.85] 0.19 [-1.48, 1.86]	
Heterogeneity: Tau ²	= 1.77: Chi ² =	11.17. df	= 2 (P = 0)	0.004): $I^2 =$	82%				
Test for overall effect									
2.4.2 Long-term									
Bagis 2008	25.1	8.8	6	35.5	14.1	6	9.3%	-0.82 [-2.02, 0.38]	
agis 2008	25.1	8.8	6	32.6	16.2	6	9.6%	-0.53 [-1.69, 0.63]	
agis 2008	44.3	11.7	6	39.3	14.2	6	9.7%	0.35 [-0.79, 1.50]	
Bagis 2008	35.3	12	6	31.3	13.5	6	9.7%	0.29 [-0.85, 1.43]	
Bagis 2009	35.3	12	6	33.3	11	6	9.7%	0.16 [-0.97, 1.29]	
Bagis 2009	44.3	12	6	49	14	6	9.7%	-0.33 [-1.48, 0.81]	
Bagis 2009	33.5	10	6	51.2	18	6	9.0%	-1.12 [-2.38, 0.14]	
ang 2018	22.3	3.2	5	35.4	6	5	6.0%	-2.46 [-4.32, -0.60]	
Subtotal (95% CI)			47			47	72.6%	-0.41 [-0.94, 0.12]	
Heterogeneity: Tau ² :	= 0.19; Chi ² =	10.51, df	= 7 (P = 0	$(0.16); ^2 =$	33%				
Test for overall effect	t: Z = 1.52 (P =	0.13)							
Total (95% CI)			68			68	100.0%	-0.26 [-0.84, 0.33]	•
Heterogeneity: Tau ² :	= 0.58; Chi ² =	25.23, df	= 10 (P =	0.005); I ²	= 60%				
Test for overall effect	: Z = 0.86 (P =	0.39)							-4 -2 0 2 4 Ultrasonic application Manufacturer instructions
Test for subgroup dif	ferences: Chi ²	= 0.45, df	f = 1 (P =	$0.50), I^2 =$: 0%				on asome appreasion Manufacturer instructions

Figure 13. Forest plot showing the bond strength values when the adhesive was applied with an ultrasonic device [117,120–122].

Study or Subgroup	Manufactur	er instruc	tions	Reduced application time			Std. Mean Difference		Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.3.1 Immediate									
Saikaew 2016	63.3	12	5	61.67	7.9	5	13.5%	0.14 [-1.10, 1.39]	
Saikaew 2016	66.3	10	5	48.6	12	5	10.4%	1.45 [-0.04, 2.93]	
Saikaew 2016	68.9	11	5	68.6	11	5	13.5%	0.02 [-1.22, 1.26]	
Saikaew 2018	30	3	5	26.2	4.8	5	12.2%	0.86 [-0.47, 2.19]	
Saikaew 2018	37.6	4.4	5	27.4	4.6	5	8.4%	2.05 [0.35, 3.74]	
Saikaew 2018 Subtotal (95% CI)	19.1	7.5	5 30	15.3	2.2	5 30	12.8% 70.9%	0.62 [-0.67, 1.91] 0.72 [0.15, 1.30]	•
2.3.2 Long-term									
2.3.2 Long-term									
Saikaew 2018	20.1	4.3	5	13.7	5.3	5	11.2%	1.20 [-0.21, 2.61]	· · · ·
Saikaew 2018	30.3	4.4	5	26.6	5.5	5	12.7%	0.67 [-0.62, 1.97]	
Saikaew 2018 Subtotal (95% CI)	33.4	2.5	5 15	21.9	3.7	5 15	5.2% 29.1%	3.29 [1.06, 5.52] 1.46 [0.16, 2.75]	
Heterogeneity: Tau ² =	= 0.65; Chi ² =	3.99, df =	2(P = 0	.14); $I^2 = 509$	6				
Test for overall effect	: Z = 2.21 (P =	= 0.03)							
Fotal (95% CI)			45			45	100.0%	0.92 [0.38, 1.46]	•
Heterogeneity: Tau ² =	= 0.16; Chi ² =	10.50, df	= 8 (P =	$(0.23); I^2 = 24$	1%				
Test for overall effect									-4 -2 0 2 4 Reduced application time Manufacturer instructions
Test for subgroup dif			f = 1 (P = 1)	$(0,31)$ $I^2 = 2$	6%				Reduced application time Manufacturer Instructions

Figure 14. Forest plot showing the bond strength values when the adhesive was applied with reduced application time [123,124].

According to the parameters for methodological quality assessment, most studies included were classified with medium risk of bias (Table S2). Most of the studies analyzed failed to report the single operator, operator blinded, and sample size calculation parameters.

4. Discussion

A systematic review and meta-analysis were directed concerning the assessment of the bond strength of adhesive systems to dentin depending on distinctive application modalities: an extra hydrophobic resin layer, an extended application time, a doublelayer application, an application assisted by an electric current, the active application of the adhesive, the use of an ultrasonic device, and a reduced application time. Most of the application modalities improved dentin bond strength, while few impaired dentin bond strength. Considering this, the null hypothesis stating that the different application modalities would not provide similar bond strength to dentin when compared to the application of the adhesive according to the manufacturer's instructions was partially rejected.

One of the utmost pertinent conducts to distinguish a commercial dentinal adhesive product is to measure the bond strength [125]. The most popular bond strength testing methods apply tensile or shear force; further, most adhesion strength examinations are executed on enamel or dentinal surfaces [126]. At the beginning of adhesive dentistry, shear and tensile bond strength tests were performed exclusively on specimens with relatively large, bonded areas [127]. Over the years, micro-bond strength tests have been developed claiming that smaller test specimens are "stronger" than larger ones due to the lower probability of the presence of critical sized defects [128]. Additionally, it was claimed that the long-term bond strength evaluation of dental adhesive systems would provide better clinical correlation since, under aging procedures, the resin–tooth interface could be prone to degradation, as occurs in a clinical scenario [1].

Appropriately, numerous methods have been argued to offer noteworthy benefits in enhancing dentinal bond strength, promoting resin infiltration, and solvent evaporation, and they were proposed depending on the application modalities [17]. The purpose of this study is to determine the influence of several changes to the manufacturer's protocol application mode on dentinal bond strength.

The application of an extra bonding layer comprises an application of a supplementary layer of a hydrophobic resin to coat the adhesive [90]. The hydrophilic characteristic of the monomers inside some adhesives makes them permeable to water and compromises dentinal bonding durability. This is due to the affinity of the monomer for generating hydrogen bonds with the hydrophilic portion of acidic monomers existent in the mixture, which changes the formation of the polymer chains [91]. In an attempt to maintain the quality of the adhesive layer, many authors proved that the application of an extra bonding layer results in (1) higher bond strength, (2) higher hydrophobicity, (3) thicker adhesive

layer, (4) better-sealed interface, (5) higher conversion rate, (6) better polymerization efficiency by a reduction in the detrimental effects of polymerization stress of composites resins, (7) better mechanical properties, and (8) less possible hydrolytic degradation of resin and collagen fibrils [49,129,130]. This strategy helps in stabilizing the adhesive interface against water sorption from the outer oral cavity and water ingress by osmosis from the dentin substrate [90,92]. SE adhesives are hydrophilic materials, so additional protection is necessary. Besides this, even E&R adhesives, especially those that are formulated using 2-hydroxyethyl methacrylate (HEMA), are also hydrophilic, so an extra hydrophobic layer can reduce the concentration of retained solvents and unreacted monomers [131]. Hence, to increase the bond strength of the adhesive–dentin interface [132], an extra layer of hydrophobic coat is preferred, as was demonstrated by this meta-analysis.

In the bonding approach to the dentin structure, it is deemed crucial to prolong the application time of adhesive systems for better bond performance and better monomer diffusion, and this is possible by enhancing the chemical interaction between monomers and HAp [93]. This approach increases the saturation of collagen fibrils by resin, as monomers preferably must plug the space between the exposed collagen [133,134]; otherwise, the performance and durability of adhesive systems might be compromised. Further, when a longer application time of the adhesive was achieved, more solvated monomers could evaporate, hereafter authorizing the advance of a stronger polymer within the dentinal surface and superior resin–dentin bond strength [69,135]. This statement is in agreement with this meta-analysis. Further, any recommendation for reducing the application times must be established on an extensive in vivo and in vitro documentation; therefore, it is powerfully logical to follow the manufacturers' directions for adhesive application.

Another bonding application is the use of a multiple-layer application. A previous paper demonstrated that by using this approach, an increase in immediate dentin bond strength was achieved, but no improvement in bond strength was observed after aging [17]. The current trends in bonding appear to favor a single application of adhesive systems, but this could not create a thicker HL or adhesive layer in which micromechanical retention with the underlying composite resin exists. However, previous papers proposed that double or triple adhesive layers enhance dentin bond strength by improving monomer penetration into the HL and increasing chemical interactions [93,99]. Consequently, an additional layer application should be considered as a fundamental clinical step. Supplementarily, 10-MDP monomer needs an appropriate time of 20 s for its chemical interaction to take place; nevertheless, applying a second coat of such a monomer without curing the first one permits the first layer to adequately interact with HAp and, therefore, promotes additional bonding [136]. Further, it should be noted that the amplified dentin bond strength under double application is due to numerous mechanisms working concurrently. As the solvent inside adhesives is evaporated between each adhesive layer, the concentration of co-monomers that subsist after each layer application rises [93], consequently refining the quality of the HL [137]. A previous report [137] showed that there was an improvement in the dentin bond performance when multiple adhesive layers were applied but not cured. This cannot be accredited to the upsurge in adhesive layer thickness but nonetheless to the perfected quality of the adhesive layer. The thickness of the adhesive layer increases only when each coat of adhesive is light-cured. This safeguards that the demineralized dentinal substrate will be sufficiently protected, lessening the detrimental effects of oxygen inhibition by means of defective bond formation for both SE [93,100,138] and E&R adhesives [139]. All in all, double application layers are suggested for clinicians, and the material and substrate contents of each adhesive should be taken into consideration.

Additionally, an application assisted by an electric current and the active application of adhesive systems enhanced the dentin bond performance of the etching mode by facilitating the penetration of adhesives into the branches of dentinal tubules. Further, an adhesive application protocol based on the use of an electric signal has been introduced by some investigators [29,52,80,81,112]. This technique improves the chemical interaction between adhesive systems and tooth structures and, thus, increases monomer infiltration of the

demineralized dentinal substrate by altering the surface charges and hydrogen bonding potential of the dentin substrate [82,112,113,140]. Consequently, there is an enhancement of dentinal wettability, leading to solvent evaporation [112]. Furthermore, electrically assisted methods enhance dentin bond strength and reduce nanoleakage in the HL [82,83,112,140]. However, it requires a special device for the adhesive application that releases adhesive by an electrical potential difference between the adhesive system and tooth surfaces [113]. Resin monomer diffusion into etched dentin could be enhanced through the use of electric current, as polar constituents, such as HEMA, polyalkanoic acid, biphenyl dimethacrylates copolymers, and dipentaerythritol penta-acrylate phosphate, contained in the adhesive formulation might interact with the electric field [82]. It has been formerly stated that electrical currents endorse the movement of an ionized substrate [141,142]. Though, it is still uncertain whether suitable dentin hybridization could be formed by easing the impregnation of ionized substrates in diverse conditions and enhancing the removal of water for SE adhesives [143,144]. Next, the application of an electric current might also increase the water substitution rate by means of the modification of water dipoles, thus, preferring water-solvent exchange throughout resin infiltration [90]. It has been claimed that the application of electric currents between 30 and 35 μ A meaningfully improved bond strength and bonding quality [80]. This could be considered safe, as bonding procedures performed with 35 μ A could not affect cell viability [113]. Ideally, as suggested by this analysis, the use of an electric current during the application of E&R and SE adhesive systems has been claimed to increase the bonding of an adhesive to dentin by enhancing substrate impregnation.

Agitation can deliver a reliable etch; furthermore, it can enhance the interaction between the acidic monomers and dental substrate [145]. Actually, the active application of adhesives using a scrubbing technique leads to the impregnation of a higher rate of monomers inside the smear layer and facilitates solvent evaporation, hence, improving adhesive interface quality. This technique does not require any supplementary step [146]. In addition, agitation preserves freshly acidic solution in interactions with the tooth substrate. Hence, improving the immediate bond performance of the simplified E&R adhesive systems [37,84]. It seems that previous reports suggested that higher bond strength was achieved when a two-step SE adhesive system was used. This could be explained by the complete dissolution of the smear layer into the adhesive [147]. On the other hand, a dissimilar finding was detected by Miyazaki et al. when testing the same adhesion strategy [145]. Another study proposed that the performance of SE adhesive systems was related to the agitation duration time [60]. All in all, adhesive agitation was able to increase the moieties' kinetics and permit better monomer diffusion inward; however, the solvents spread outward [85].

On the other hand, it seems that the use of an ultrasonic device did not show any improvement for both SE and E&R adhesive systems in this analysis. The ultrasonic mode might not enhance the dentinal bond performance outcomes of some SE adhesive systems. Ultrasonics is a division of acoustics concerned with the help of sound vibrations that possess a frequency range above the audible level. One should state that the frequency in the oscillating instruments in dental practice is ultrasonic for frequencies ranging from 20,000 to 40,000 Hz. In addition, it is considered sonic when the frequency ranges from 1000 to 6000 Hz [120]. The application of ultrasonic agitation energy could induce acoustic streaming and upsurge infiltration of the dentin adhesive into the dentinal substrate. This conclusion seems to not support the results of this meta-analysis, as improvement in dentin bond strength was not observed in all adhesives tested.

The analysis of this review exhibited that the use of reduced application times impaired the dentin bond strength of SE adhesive systems. Currently, clinicians begin to escalate the settlements related to step reduction in both E&R [148] and SE adhesives [149]. A recently launched adhesive system by manufacturers, named G-Premio Bond universal adhesive (GC Corporation, Tokyo, Japan), delivers dental clinicians an alternative to the SE approach for adhesion to dentin without the need to wait for the adhesive to interact with the bonding substrate (no-waiting SE; Japanese version of manufacturer's instructions), or the interaction occurs after leaving the adhesive undisturbed for 10 s (10 s SE; international version of manufacturer's instructions) [123]. This new concept of a no-waiting adhesive, while pleasing to many clinicians, must not compromise the performance and durability of adhesion to dentin. The author concluded that the no-waiting SE approach prior to adhesive polymerization might gave sufficient bond strength. Nevertheless, extended application times with the 10 s SE mode instead of no-waiting mode advances its shortterm dentinal bonding performance [56]. Hence, applying a SE adhesive for shorter times than recommended by the manufacturer might not represent the best use of the adhesive. Dentists normally work without using a stopwatch to precisely time the individual application steps, and they demand a decrease in the uncomfortable treatment time for their patients. Consequently, it is expected that clinicians do not always follow the application times specified by the instructions of the manufacturers [150], and these deviations from the suggested application times could hinder the dentin bond strength of adhesive systems [151], accordingly compromising the longevity of dental resin restorations. As was proved by Hardan et al. [17], a reduced application time weakens both the immediate and aged bond strength of universal adhesives applied to dentin with E&R or SE modes. As a consequence, this modification should not be followed by clinicians.

As materials in close contact with biological tissues, both directly and indirectly, biocompatibility is one of the utmost serious desires for adhesive systems [152]. It has been established that the constituents of dental adhesives, such as TEGDMA (triethylene glycol dimethacrylate) and HEMA, might diffuse throughout the dentinal tubules and extend into the pulp tissue in concentrations considered toxic to pulp cells [153]. It is worth mentioning that the increase in bond strength observed for some of the described techniques in this review is based on the increase in the degree of conversion of the materials [129]. This increase in the degree of conversion could be related to a reduction in the release of residual monomers, leading to an improvement in the biocompatibility of dental adhesives [19], and this relationship should be addressed in future works.

The present systematic review and meta-analysis distinguished the effect of different application modalities on the bonding ability of adhesive systems to dentin when compared to the application of the adhesive according to the manufacturer's instructions. The outcomes of this review should be considered with caution as, in clinical conditions, a wet environment could lead to rapid adhesive-dentinal interface degradation. Therefore, future studies should be performed to evaluate the solubility, degree of conversion, shelf-life stability, and polymerization rate of the adhesive applied with different application modalities. Moreover, additional studies on cytotoxicity are recommended in order to analyze the best intensity when using an electric signal for adhesive application. Future reports must be directed, particularly randomized controlled clinical trials, with the drive to acquire the performance of different adhesive systems in the clinical performance of resin-based restorations to the dentinal structure. Additionally, little information exists concerning the influence of these strategies on enamel bond strength. Thus, testing these application modalities on enamel substrates could be important in future investigations. The relationship between the chemical composition of adhesive systems and these modalities are of extreme importance. Therefore, research should be directed towards testing more adhesive systems and more strategies in an attempt to achieve better bonds on tooth substrates. In this review, the best scientific evidence available regarding the dentin bonding efficacy of adhesive systems applied using different application modalities was compiled. To date, the monotonous use of simplified adhesive systems in combination with composite resin to restore dentinal margins is still doubtful and challenging. Consequently, it seems that establishing a durable and stable dentin bond by means of different application modalities could be possible when properly used. Hence, these approaches are crucial for the long-term clinical achievement of restorative treatment to dentin. All in all, essential steps also exist in the application process of various adhesive agents that necessitate recognizing the chemistry of the adhesive being used. Existing application modalities were presented

in this study to help clinicians preserve the durability of the bond to the dentin substrate. Nonetheless, no agent or material can overcome poor procedures.

5. Conclusions

Within the limitations of this systematic review of in vitro studies, the findings suggest that the application of adhesive systems using application modalities that are different than the manufacturers' recommendations may increase the bond strength of resin-based materials to dentin. The application modalities that favored the overall bond strength to dentin were an extended application time, a double-layer application, an application assisted by an electric current, the active application of the adhesive, and the application of a hydrophobic resin layer.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cells12010190/s1, Table S1: Demographic data of the included studies; Table S2: Risk of bias assessment. References [63–67,70–79,86–89,94–98,101–111,114–119,121, 122,124,154–157] are cited in Supplementary Materials.

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