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DESEMPENHO ADESIVO DE SISTEMAS ADESIVOS AUTOCONDICIONANTES – EFEITO DO MONÔMERO ÁCIDO FUNCIONAL

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de Mestre em Odontologia, Área de Concentração em Clínica Odontológica/Cariologia-Dentística

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Orientador: Prof. Dr. Eliseu Aldrighi Münchow

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RESUMO

O monômero 10-MDP (10-metacriloiloxi-decil-di-hidrogenofosfato) tem sido o mais utilizado na formulação de sistemas adesivos autocondicionantes (SAA), porém, estudos de revisão com meta-análise comparando o seu desempenho adesivo ao dente quando comparado aos adesivos contendo monômeros acídicos alternativos ainda não existem, sendo o objetivo desta dissertação. Para isso, duas revisões sistemáticas com meta-análise foram realizadas seguindo-se as recomendações do PRISMA 2021. O estudo 1 está registrado no PROSPERO sob nº CRD42020175715, cujo objetivo foi responder a seguinte pergunta: SAA contendo 10-MDP resultam em melhor desempenho adesivo imediato à dentina e ao esmalte quando comparados aos SAA sem 10-MDP? A busca (última data: 30/06/2021) foi realizada no PubMed, Scopus, Web of Science, LILACS, SciELO, IBECS e BBO. Por sua vez, o estudo 2 está registrado no *Open Science Framework* (osf.io/urtdf), tendo o objetivo de responder a seguinte pergunta: SAA contendo 10-MDP resultam em maior estabilidade adesiva à dentina e ao esmalte após envelhecimento simulado, quando comparados aos SAA sem 10-MDP? A busca (última data: 30/09/2021) foi realizada no PubMed, Scopus e Web of Science. Os critérios de elegibilidade para ambos os estudos foram: 1) desenho de estudo *in vitro*; 2) avaliação da resistência de união à dentina e/ou ao esmalte usando-se testes de microtração, microcisalhamento, cisalhamento ou tração; 3) condição do substrato dentário (humano ou bovino) livre de cárie; e 4) presença de pelo menos um grupo de adesivo contendo 10-MDP (controle) e de pelo menos um grupo contendo outros tipos de monômeros acídicos. Para o estudo 2, um critério de inclusão adicional foi utilizado: disponibilização de dados de resistência de união após envelhecimento simulado das amostras, independentemente do método. Os estudos incluídos foram analisados de forma qualitativa e por meio de análises quantitativas usando-se o programa RevMan 5.3.5 (para as meta-análises pareadas) e o programa MetaInsight V3 (para as meta-análises em rede). Relativo aos resultados do primeiro estudo, os dados de 206 artigos e de um total de 64 SAA foram analisados na meta-análise. O potencial adesivo imediato foi favorecido na presença de 10-MDP, em ambos dentina e esmalte. Contudo, nas análises de subgrupo foi possível identificar que o monômero GPDM (dimetacrilato de glicerol fosfato) contribuiu com valores de resistência de união significativamente maiores do que o 10-MDP. De maneira geral, o desempenho adesivo dos SAA dependeu do tipo de teste mecânico, tipo de substrato, composição acídica do adesivo, bem como da categoria de aplicação do material. Quanto aos resultados do segundo estudo, as meta-análises envolveram os dados de resistência de união oriundos de 72 artigos e de um total de 56 SAA. O desempenho adesivo dos SAA após envelhecimento simulado foi semelhante entre os grupos, com os adesivos contendo 10-MDP demonstrando capacidade de resistir à degradação similar à maioria das composições acídicas alternativas. A exceção se deu com 4 grupos em específico: monômeros fosfatados sem identificação, 4-META (4-metacriloiloxietil anidrotrimelítico), monômeros derivados do ácido sulfônico, e vários monômeros acídicos misturados entre si (grupo misto). O desempenho adesivo dos SAA foi favorecido na presença de 10-MDP somente após períodos maiores de envelhecimento das amostras. O método de envelhecimento teve um efeito importante na resistência adesiva dos SAA à dentina, com o armazenamento em meio úmido sendo mais prejudicial para as formulações derivadas do ácido fosfórico ou do ácido fosfônico, bem como da mistura entre vários monômeros acídicos. Quanto aos demais métodos de envelhecimento testados (termo ciclagem, ciclagem mecânica e combinação entre vários métodos de envelhecimento), todos influenciaram os grupos de maneira semelhante, apesar de se perceber uma leve tendência desfavorecendo os adesivos com composição acídica mista. Em esmalte, não houve diferença significativa entre os grupos, embora os SAA contendo derivados do ácido carboxílico ou do ácido sulfônico tenham demonstrado uma tendência a serem os piores agentes adesivos para a formação de interfaces adesivas resistentes à degradação. A estabilidade adesiva obtida com SAA depende da composição acídica do material, sendo os sistemas constituídos por 10-MDP tão adequados quanto à maioria dos adesivos livres de 10-MDP. O método de envelhecimento parece ter um efeito importante na durabilidade adesiva aos tecidos dentários. Como conclusão da presente dissertação, é possível perceber que a composição acídica dos SAA influencia diretamente na resistência adesiva à dentina e ao esmalte, tanto em períodos imediatos como após envelhecimento simulado, demonstrando ser um tópico complexo e dependente de vários fatores associados ao protocolo adesivo. Assim, a escolha de um agente adesivo deve ser realizada com cuidado, para assim se obter o máximo desempenho possível durante a restauração dentária com materiais adesivos.

Palavras-chave: sistemas adesivos autocondicionantes; adesão dentária; monômero ácido funcional; adesivos universais; dentina; esmalte

ABSTRACT

The monomer 10-MDP (10-methacryloyloxydecil dihydrogen phosphate) has been the most frequently used in the formulation of self-etch adhesive systems (SEAS), although review studies with meta-analysis comparing their dental bonding potential as compared with adhesives containing alternative acidic monomers is yet missing, being the purpose of this work. To that end, two systematic reviews with meta-analysis were conducted following the PRISMA 2021 statement. The study 1 is registered at PROSPERO under protocol nº CRD42020175715, which aimed to answer the following question: SEAS based on 10-MDP result in greater immediate bonding performance to dentin and enamel than SEAS without 10-MDP? The search (last date: 06/30/2021) was performed in PubMed, Scopus, Web of Science, LILACS, SciELO, IBECS and BBO. Concerning the study 2, it is registered at *Open Science Framework* (osf.io/urtdf), aiming to answer the following question: SEAS based on 10-MDP result in greater bonding stability to dentin and enamel after simulated aging as compared with 10-MDP-free SEAS? The search (last date: 09/30/2021) was conducted in PubMed, Scopus, and Web of Science. The eligibility criteria for both studies were: 1) an *in vitro* study design; 2) the evaluation of bond strength to dentin and/or enamel using the microtensile, microshear, shear or tensile mechanical tests; 3) the sound condition of dental substrates (human or bovine teeth without caries); and 4) presence of at least one adhesive group based on 10-MDP (control) and one group comprised of other types of acidic monomers. For study 2, an additional inclusion criterium was considered: the availability of bond strength data derived from simulated aging of the samples, regardless of the aging method. The included studies were analyzed with qualitative and quantitative (RevMan 5.3.5 software for pairwise meta-analysis; and MetaInsight V3 software for network meta-analysis) analyses. Regarding the results from the first study, the data from 206 articles and a total of 64 SEAS were analyzed. The immediate bonding potential was benefited from the presence of 10-MDP, at both dentin and enamel substrates. However, in the subgroup analyses it was verified that the monomer GPDM (glycero-phosphate dimethacrylate) contributed with bond strength values significantly higher than 10-MDP. Overall, the bonding performance of SEAS relied on the type of mechanical test, type of substrate, acidic composition of adhesive, as well as of the application category of materials. Concerning the findings from the second study, the meta-analyses consisted of bond strength data derived from 72 articles and a total of 56 SEAS. The bonding performance of SEAS after simulated aging was similar among the groups, with adhesives containing 10-MDP showing an ability to resist degradation as similar as that from alternative acidic compositions. The exception was observed with 4 specific groups: non-identified phosphate monomers, 4-META (4-methacryloxyethyl trimellitate anhydride), monomers derived from sulfonic acid, and varying acidic monomers mixed between each other (mixed group). The bonding performance of SEAS was benefited under the presence of 10-MDP only after longer aging of samples. The aging method showed an important effect on the bond strength of SEAS to dentin, with the wet storage demonstrating the most harming condition to formulations based on phosphoric acid or phosphonic acid, as well as upon the mixture of varying acidic monomers. Considering the aging methods tested (thermal-cycling, cyclic-loading and the combination of varying aging methods), all methods influenced similarly the groups, although it was verified a slight tendency non-favoring the adhesives with mixed acidic composition. In enamel, there was not any significant difference between the groups, although the SEAS based on carboxylic acid or sulfonic acid demonstrated a tendency to be the worst bonding agents in terms of resistance to bond strength degradation. The adhesive stability obtained with SEAS depends on the acidic composition of materials, with the systems comprised of 10-MDP being as adequate as most of 10-MDP-free adhesives. The aging method seems to have an important effect on the bonding durability to dental substrates. In conclusion to the present work, it is possible to observe that the acidic composition of SEAS may largely influence on the bonding potential to dentin and enamel, even at shorter periods (immediate testing) as well as after simulated aging, suggesting that this is a complex topic relying on several factors associated to the bonding protocol. Therefore, the choice of a bonding agent should be considered with caution, aiming to obtain the best performance during dental restorative procedures involving the use of adhesive materials.

Keywords: self-etch adhesive systems; dental adhesion; acidic functional monomer; universal adhesives; dentin; enamel

SUMÁRIO

1 INTRODUÇÃO

Os sistemas adesivos autocondicionantes (SAA) representam um dos mais recentes avanços em adesão, compreendendo as 6ª, 7ª e 8ª gerações de adesivos dentários. Estes diferem dos sistemas adesivos convencionais pois eliminam a etapa de condicionamento com ácido fosfórico prévio do substrato, já que a presença de monômeros ácidos garante o condicionamento dental. De fato, o monômero acídico pode ser incluído tanto no primer como no agente adesivo, sendo então responsável por desmineralizar o substrato e realizar a concomitante infiltração resinosa (SOFAN 2017). De maneira geral, os SAA são materiais fáceis de aplicar, menos sensíveis quanto à técnica operatória, e, não menos importante, resultam em menos sensibilidade pós-operatória se comparados à estratégia convencional (VAN MEERBEEK, 2020; VAN MEERBEEK, 2011).

Os SAA têm mostrado desempenho clínico favorável e bons resultados de durabilidade, principalmente quando aplicados em dentina. Por outro lado, a sua capacidade adesiva no esmalte é mais complexa devido ao maior conteúdo mineral presente neste substrato. Quando comparados à acidez dos adesivos convencionais e ao padrão de condicionamento obtido em esmalte, os SAA apresentam-se menos acídicos, e, por isso, possuem um potencial de desmineralização diminuído. Além disso, eles apresentam uma composição química geralmente mais hidrofílica, o que pode favorecer a ocorrência dos fenômenos de degradação e a hidrólise da camada adesiva (BOUSHELL, 2016; DE ASSIS, 2020; PEUMANS, 2010). Dentre todos os ingredientes pertencentes à composição química dos SAA, o monômero ácido parece ser o fator chave, já que é responsável por um mecanismo de adesão tripla, que consiste em molhamento satisfatório da superfície, desmineralização do substrato, e, por fim, da ligação química à hidroxiapatita (VAN MEERBEEK, 2020). Os monômeros ácidos mais frequentemente encontrados na formulação dos SAA derivam do ácido carboxílico, como no caso dos monômeros META, 4-AET ou MAC-10, bem como do ácido fosfórico, tendo como exemplos os monômeros 10-MDP, MEP, PENTA, MAP ou GPDM (SALZ, 2005; YOSHIHARA, 2018). Além disso, outros tipos de monômeros também podem compor os sistemas adesivos contemporâneos, dentre eles os monômeros derivados dos ácidos fosfônico e sulfônico.

De acordo com o estudo de Feitosa e cols. (2014), características como a hidrofilicidade e o comprimento da cadeia espaçadora dos monômeros funcionais desempenham um papel significativo na efetividade adesiva dos SAA, sendo estas características variáveis conforme o tipo de monômero. Atualmente, o monômero funcional popularmente conhecido por 10-MDP (10-metacriloiloxi-decil-di-hidrogenofosfato) é o mais utilizado em formulações autocondicionantes, principalmente devido ao seu confirmado efeito na durabilidade adesiva ao dente (PEUMANS, 2010) e, também, devido à sua adequada interação química com a hidroxiapatita, sendo capaz de formar um sal estável de 10-MDP-Ca (FEITOSA, 2014; YOSHIDA, 2004; YOSHIHARA, 2013). Acredita-se que o excelente desempenho deste monômero acídico se deve à sua capacidade de desmineralização suave e à sua cadeia espaçadora longa e relativamente hidrofóbica, a qual separa o metacrilato polimerizável do grupo funcional fosfato (YOSHIDA, 2004; IONUE, 2005; VAN LANDUYT, 2008). Mesmo que o uso do 10-MDP esteja associado ao aumento da resistência de união, não há na literatura revisões sistemáticas que realizem uma síntese efetiva dos estudos *in vitro* acerca do seu desempenho adesivo imediato e após envelhecimento simulado. Além disso, não há qualquer estudo de meta-análise comparativa entre materiais contendo 10-MDP e adesivos constituídos com outros tipos de monômeros funcionais, sendo um tópico merecedor de investigação.

Desse modo, o objetivo da presente dissertação foi revisar a literatura por meio de estudos de revisão sistemática com meta-análise para se averiguar o efeito do tipo de monômero ácido na resistência de união dos SAA à dentina e ao esmalte, focando na comparação entre adesivos contendo 10-MDP com aqueles constituídos de monômeros acídicos alternativos.

2 ARTIGOS

Esta dissertação é composta por dois artigos científicos. O artigo I teve como foco investigar o desempenho adesivo de sistemas adesivos autocondicionantes contendo monômeros acídicos alternativos ao 10-MDP, em comparação com aqueles adesivos constituídos pelo 10-MDP. Ainda, este primeiro artigo avaliou apenas os resultados de resistência de união imediatos à dentina e ao esmalte. Por sua vez, o artigo II teve como foco investigar o efeito da composição acídica de sistemas adesivos autocondicionantes apenas com resultados obtidos após o envelhecimento simulado das interfaces adesivas.

O artigo I foi submetido ao periódico *Dental Materials* e encontra-se publicado (doi: 10.1016/j.dental.2021.08.014) (FEHRENBACH et al., 2021). O artigo II ainda não foi submetido para apreciação em qualquer periódico, tendo a previsão de ser submetido ao periódico *Journal of Dentistry*. Os artigos foram formatados de acordo com as normas dos respectivos periódicos.

2.1 ARTIGO I

Is the presence of 10-MDP associated to higher bonding performance for self-etching adhesive systems? A meta-analysis of in vitro studies

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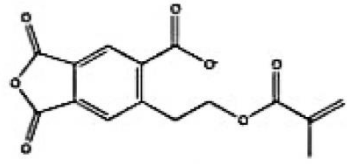
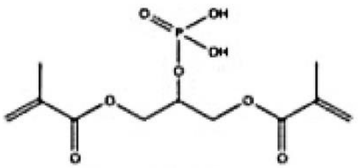
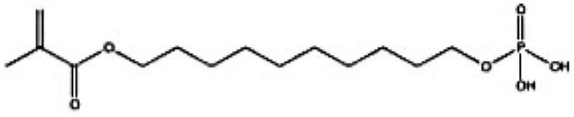
Is the presence of 10-MDP associated to higher bonding performance for self-etching adhesive systems? A meta-analysis of *in vitro* studies



4-META



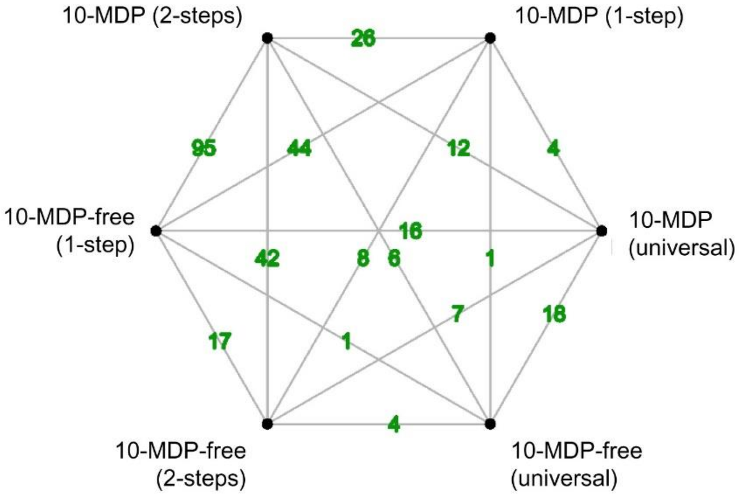
GPDM



10-MDP

Acidic monomers	10-MDP-free Total	10-MDP-based Total	Weight	Mean Difference IV, Random, 95% CI
Total (95% CI)	2962	2962	100.0%	-5.26 [-6.02, -4.50]

Heterogeneity: Tau² = 39.93; Chi² = 5681.23, df = 352 (P < 0.00001), I² = 94%
Test for overall effect: Z = 13.54 (P < 0.00001)
Test for subgroup differences: Chi² = 105.13, df = 15 (P < 0.00001); I² = 85.7%



Graphical Abstract

Abstract

Objective. The purpose of this systematic review and meta-analysis was to analyze the literature on the bond strength of self-etching (SE) adhesives containing 10-MDP or other acidic functional monomers, comparing the bonding performance of both compositions.

Methods. This study is registered in PROSPERO (CRD42020175715) and it followed the PRISMA Statement. The literature search was performed in PubMed, Web of Science, SciELO, Scopus, LILACS, IBECS, and BBO from the starting coverage date through 30 June 2021. Study eligibility criteria consisted of in vitro studies that evaluated the bond strength (microtensile, microshear, tensile or shear testing) to sound dentin/enamel of a minimum of two distinct SE systems, with at least one material containing 10-MDP and one other being comprised of a distinct acidic composition. Statistical analyses were carried out with RevMan 5.3.5 and using random-effects models with the significance level at $p < 0.05$. Also, Bayesian network meta-analysis (NMA) was conducted using MetaInsight V3 tool.

Results. From 740 relevant studies evaluated in full-text analysis, 210 were incorporated to the systematic review and 206 in meta-analysis. The majority of studies was classified as having medium risk of bias (56.7%), followed by low (35.2%) and high (8.1%) risk of bias. Data from a total of 64 adhesive systems were collected, which favored the 10-MDP-based group at both dentin (overall effect: 6.98; 95% CI: 5.61, 8.36; $p < 0.00001$) and enamel (overall effect: 2.79; 95% CI: 1.62, 3.96; $p < 0.00001$) substrates. Microtensile testing was more frequently used (73.4%) in the included studies. Adhesives based on 10-MDP showed greater bonding performance than adhesives comprised of monomers such as PENTA, 6-MHP, 4-META, 4-MET, pyrophosphate esters, mixed composition or monomers derived from sulfonic acid ($p \leq 0.01$); whereas similar bond strength values were verified between 10-MDP-based materials and those containing PEM-F, acrylamide phosphates, 4-AET, MAC-10, or monomers derived from polyacrylic and phosphonic acids ($p \geq 0.05$). Adhesives based on GPDM were the only ones that resulted in greater bonding potential than the 10-MDP-based group ($p=0.03$). Dental bonds in dentin were favored with the application of 2-step 10-MDP-based adhesives; whereas in enamel the dental bonds were favored for both 2-steps versions of adhesives, regardless of the presence of 10-MDP. Indirect evidence from NMA revealed that 1-step 10-MDP-free and universal 10-MDP-free adhesives seemed to perform worst in dentin and enamel, respectively.

Significance. Adhesives containing 10-MDP showed higher bonding performance than materials formulated with other acidic ingredients, although this result relied on the type of mechanical testing, type of the substrate, acidic composition of the adhesive, and the application category of the SE system. This review summarized the effects of the foregoing factors on the adhesion to dental substrates.

Keywords: Dental bonding; Functional acidic monomer; Universal adhesives; Dentin; Enamel

1. Introduction

Self-etching (SE) adhesives represent one of the most recent advancements in adhesive dentistry, comprising the 6th, 7th, and 8th generations of bonding systems [1]. Overall, SE adhesives differ from the older versions (i.e., the 4th and 5th generation systems – etch-and-rinse) since they incorporated the etching ingredients into the chemistry of the primer solution or adhesive resin, resulting in the so-called acidic primers and all-in-one adhesives, respectively. Notably, by eliminating the separate etching step of enamel and dentin and the consequent rinsing and drying clinical procedures typical of the etch-and-rinse strategy, SE adhesives are user-friendly, less technique-sensitive, and importantly associated to the lesser occurrence of post-operative pain [2, 3]. Despite their excellent bonding performance to dentin, the adhesion ability of SE adhesives to enamel is more challenging, first because these adhesives present lower acidity than the etch-and-rinse approach, reducing demineralization and hybridization events; and second due to their more hydrophilic composition (i.e., greater amount of solvent and functional monomers), increasing degradation and hydrolysis phenomena. In light of increasing their bonding performance to enamel, a new class of SE adhesives has been launched with the promise of guaranteeing both chemical and micromechanical adhesion to any dental substrate, namely the “universal”, “multipurpose” or “multimode” adhesives [4]. By concept, universal adhesives can be applied following the etch-and-rinse or self-etch approaches, depending on the clinical condition and type of substrate. According to recent studies [5-7], the clinical service of restorations bonded with SE adhesives is adequate and comparable to those placed with etch-and-rinse bonding agents.

Among all the ingredients pertaining the chemical composition of SE adhesives, the acidic monomer seems to be the key factor, since it is responsible for a triple bonding mechanism that consists of surface wetting, etching, and chemical bonding to hydroxyapatite [3]. Of note, the bond strength created with SE adhesives relies directly on the type of acidic monomer, which may vary from polymerizable carboxylic acids to acidic methacrylate phosphates [8, 9]. According to the study by Feitosa et al. [10], features such as hydrophilicity and the length of spacer chains of acidic functional monomers play a significant role on the bonding performance of SE adhesives. Currently, the monomer 10-methacryloyloxy-decyl-dihydrogen-phosphate (10-MDP) is the most relevant functional monomer used in SE formulations due to its confirmed effects on the longevity of dental bonds [7] as well as due to its adequate and stable chemical interaction with hydroxyapatite, i.e., it is capable of forming a water-insoluble 10-MDP-Ca salt [10-12]. It is believed that the excellent performance of 10-MDP as a functional monomer relies on its mild-etching ability and the long and relatively hydrophobic spacer separating the polymerizable methacrylate from the phosphate functional group [11, 13, 14]. Even though the use of 10-MDP is associated with increased bond strengths, it would be of utmost interest to systematically compare the bonding performance of 10-MDP-based adhesives to other SE adhesives consisting of different acidic monomers, especially targeting the application of meta-analysis. From the best of our knowledge, there is not such study available in literature.

The purpose of this systematic review and meta-analysis was to analyze the literature on the bond strength of SE adhesives containing 10-MDP or other acidic functional monomers, comparing the bonding performance of both compositions. The hypothesis was that adhesives based on 10-MDP would demonstrate greater bonding potential to dentin/enamel as compared with 10-MDP-free adhesives.

2. Materials and methods

This review and meta-analysis was registered in PROSPERO under protocol number CRD42020175715 and it was conducted in accordance with the guidelines of the PRISMA Statement [15]. The research question was “Do self-etching adhesive systems containing 10-MDP resin monomer as the acidic ingredient show greater bonding performance to dentin and enamel than 10-MDP-free adhesives?”

2.1. Literature search and information sources

The literature search strategy was performed by two independent reviewers (J.F. and C.P.I.) in seven electronic databases: PubMed/MEDLINE, Scopus, ISI Web of Science, LILACS, SciELO, IBECS, and BBO (Biblioteca Brasileira de Odontologia). The search strategy was created based on Medical Subject Heading terms and adapted for the other databases (**Table 1**). The last search was performed on 30th June 2021, without any restriction of year of publication. The grey literature was not searched in this review. The reviewers also hand-searched for this topic in the principal periodicals specific to the area.

2.2. Eligibility criteria

For inclusion in this review, the in vitro studies must have evaluated the bond strengths (to sound dentin and/or enamel) of at least two distinct SE adhesive systems, with at least one of the materials containing 10-MDP and one other material being comprised of a distinct acidic composition. Only studies that assessed the microtensile, microshear, tensile or shear bond strengths of adhesives, in MPa, were included; studies that used human and animal (i.e., bovine teeth) substrates were included. Studies focusing on deciduous and caries-affected teeth as well as material-based substrates (e.g., resin composites, ceramics, metals) were not included. Studies investigating the adhesion between orthodontic brackets and enamel or the bonding performance of self-etch/-adhesive resin cements were also excluded. Lastly, studies that presented bond strength data derived from aged conditions only, i.e., after thermal-cycling or long-term water storage, as well as the evaluation of experimental compositions only, were also excluded.

2.3. Study selection and data extraction

Duplicates were removed in EndNoteX9 (Thomson Reuters), followed by the screening of titles and abstracts for relevance based on the eligibility criteria. In case of disagreement, a third reviewer (E.A.M.) was recruited to reach consensus. Data of interest from the manuscripts included were tabulated using Microsoft Office Excel 2013 spreadsheets (Microsoft Corporation, Redmont, WA, USA). The extracted information were as follow: year of publication, sample size, substrate, surface treatment prior adhesive application, bond strength test, materials with or without 10-MDP, bond strength results (mean and standard deviation/SD values), mode of failure, and additional tests performed (e.g., SEM evaluation). Partially missing data were retrieved by contacting the corresponding author of the study via e-mail.

2.4. Quality assessment

The methodological quality of each included study was assessed by two reviewers (J.F. and E.A.M.) based on the parameters suggested in a previous study [16]: random sequence generation, sample size calculation, and attendance to the manufacturer's directions of use. Moreover, the coefficient of variation (CV) of the presented data was calculated for each study and classified as low, medium and high, as demonstrated elsewhere [4]. If the studies presented the parameter, the article received a "+"; if the parameter was not mentioned, the article received a "–"; when there was a doubt whether the presence or absence of the parameter, the article received a "?". Articles that reported on one item only were classified as having a high (H) risk of bias, regardless of the CV rating; two items or three items associated to medium (20-40%) or high CV (>40%), respectively, the article was classified as having a moderate (M) risk of bias; last, the presence of two or three items associated to low CV (<20%) resulted in the classification of the article as having a low (L) risk of bias.

Disagreements between the reviewers in relation to quality assessment were resolved by consensus.

2.5. Statistical analysis

The meta-analyses were performed using Review Manager Software version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The analyses were conducted using a random-effect model, and pooled-effect estimates were obtained by comparing the mean difference between bond strength values of 10-MDP-based and 10-MDP-free adhesives. The studies were grouped according to the bond strength method (microtensile [μTBS], microshear [μSBS], tensile [TBS], or shear [SBS]) and type of substrate (dentin or enamel); data derived from different sources of substrates (i.e., human or animal) were grouped together within the same substrate condition. One additional set of meta-analysis was also performed by comparing the bond strength data of adhesive systems containing 10-MDP with those comprised of other functional acidic monomers, which were allocated into six main groups: 1) phosphoric acid-derived; 2) carboxylic acid-derived; 3) phosphonic acid-derived; 4) sulfonic acid-derived; 5) mixed composition; and 6) unknown composition.

Bayesian network meta-analysis (NMA) was performed on bond strength data of distinct adhesives comprised of 10-MDP or other acidic ingredients and classified within the “two-step” (2-st), “one-step” (1-st) or “universal” application categories. To that end, six subgroups of adhesives were designed: 10-MDP (2-steps; control); 10-MDP (1-step); 10-MDP (universal); 10-MDP-free (2-steps); 10-MDP-free (1-step); and 10-MDP-free (universal). Separated analyses were conducted for dentin and enamel. Network plots and league tables were derived using MetaInsight V3 [17] and using the Markov Chain Monte Carlo method simulation [18], with 20,000 iterations for adaptation. The Bayesian NMA was created using the random-effects model and the estimates were given as mean difference (MD) with 95% confidence intervals (95%–CI). 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 [19].

3. Results

3.1. Search strategy

Figure 1 summarizes the article selection process according to the PRISMA Statement [15]. The literature search yielded 7,355 titles and abstracts in 30th June

2021. After duplicates were removed and analysis of titles and abstracts was conducted, 770 articles were selected to access the full-text. In total, 560 studies were not included in the qualitative analysis based on eligibility criteria (503); no access to the article (30); unavailability of data (20); and due to same data derived from other included study (7). Two-hundred and ten studies fulfilled the eligibility criteria and were included in the review [8, 20-228]. However, meta-analyses were conducted with a total of 206 studies, whose main data (i.e., bond strength means, standard deviation and number of samples/specimens tested) could be retrieved or were derived from methacrylate-based materials [8, 20-33, 35-77, 79-94, 96-107, 109-228]. Additional articles were not found from manual search of the principal periodicals specific to the area.

3.2. Descriptive analysis

The studies included in the review were published between 1998 and 2021. Most studies (68%) evaluated the bonding performance of adhesives using the microtensile bond strength test. Human dentin accounted for 61.6% of the substrates gathered in the review, followed by human enamel (17.3%), bovine dentin (12.2%), and bovine enamel (8.9%). The majority of studies (54.3%) applied a #600-grit SiC abrasive paper at the surface of dentin/enamel prior adhesive application; the other studies considered a wider range of grit sizes of SiC, ranging from #80-grit to #1200-grit or a sequence of SiC at varying final grits. Concerning the resin composites used to prepare the restorations, the materials most frequently employed were purchased from 3M ESPE industry (e.g., Filtek Z250, Filtek Z350, and Filtek Z100), followed by Kuraray (Clearfil A-PX), Ivoclar-Vivadent (Tetric Ceram), Kulzer (Charisma), Dentsply (TPH), VOCO (Grandio), and FGM (Opallis). Ten studies (4.8%) did not report on the restorative material used. Most studies (52.9%) stored the samples in distilled water at 37°C for 24 h, although other variants of this protocol were also reported, varying the storage medium (tap water, deionized water, artificial saliva) or the temperature/duration of storage. The majority of included studies reported on the failure modes of the fractured adhesive interfaces (81%) and 67% performed microscopic analyses in addition to the bond strength test. The results for the foregoing aspects can be fully verified in **Appendix A**.

Figure 2 depicts the adhesive systems mostly used in this review, which were allocated according to their acidic composition. Clearfil SE Bond (Kuraray) was the adhesive most frequently investigated. From the list of adhesives containing 10-MDP, 11 materials were used in total: five proprietary from Kuraray (Clearfil SE Bond, Clearfil S3 Bond, Clearfil Protect Bond, Clearfil Liner Bond, and Clearfil Universal), two from GC (G-Bond and G-Premio Bond), two from Ivoclar (AdheSE Universal and Tetric N-Bond Universal), one from 3M ESPE (Scotchbond Universal), and one from Bisco (All Bond Universal). The other adhesive systems were comprised of alternative acidic monomers, derived from phosphoric acid, carboxylic acid, sulfonic acid, and phosphonic acid monomers, or from a mixture of distinct acidic ingredients. Some adhesive systems were classified within the "unknown composition" since the information on their main acidic composition was not clearly supplied by the manufacturer. In total, 52 adhesive systems were used and reported in at least two distinct studies, whereas 12 bonding agents were reported only once in the review.

3.3. Risk of bias

According to the parameters considered in the analysis of bias (**Figure 3**), the majority of studies were classified with low risk of bias in the items concerning sample randomization (68%) and attendance to the protocols/instructions of the manufacturers (95.7%); whereas in the other items of sample size calculation and coefficient of variation, most of studies were classified with moderate risk of bias, i.e., 96.7% and 51.4%, respectively. Overall, the majority of studies was classified as having medium risk of bias (56.7%), followed by low (35.2%) and high (8.1%) risk of bias, as presented in the **Appendix B**.

3.4. Meta-analyses

A global meta-analysis was not performed with all the 206 studies due to their heterogeneous distribution, so that they were first allocated into subgroups according to the type of bond strength test (microtensile, microshear, tensile or shear) as well as per the type of substrate (dentin or enamel). **Figures 4 and 5** show the meta-analysis results obtained in dentin and enamel, respectively, having the mechanical test as main variable factor. Overall, there was a significant difference between groups, showing evidence that adhesives containing 10-MDP produced greater resin-dentin and resin-enamel bonds than 10-MDP-free adhesives ($p<0.00001$). In dentin, the mean differences between 10-MDP-based and 10-MDP-free adhesives were higher when tested using µTBS and µSBS methods ($p\leq0.0002$), but not using TBS and SBS tests ($p\geq0.06$). In enamel, the groups presented similar bond strengths when tested with µTBS (effect size: 2.20, 95% CI: -0.68, 5.08; $p=0.13$), whereas the bonds were favored with the presence of 10-MDP when the µSBS, TBS, and SBS tests were used ($p \leq 0.01$). The heterogeneity was high for both set of analyses ($I^2 \geq 89\%$).

Meta-analysis according to the acidic composition of adhesives (**Figure 6**) showed a significant difference between groups, favoring 10-MDP ($p<0.00001$). Considering phosphoric acid-derived monomers, adhesives comprised of PENTA (dipentaerythritol penta-acrylate phosphate), 6-MHP (6-methacryloyloxyhexyl dihydrogen phosphate), pyrophosphate esters and unspecified phosphate esters displayed lower bonding potential than the 10-MDP-based adhesives ($p \leq 0.01$). However, similar dental bonds were verified for materials based on PEM-F (pentamethacryloxyethyl cyclophosphazen mono fluoride) or acrylamide phosphates ($p \geq 0.05$), and the presence of GPDM (glycero-phosphate dimethacrylate) resulted in greater mean difference values than the 10-MDP group (effect size: 2.78, 95% CI: 0.20, 5.36; $p=0.03$). For adhesives containing monomers derived from carboxylic acids such as 4-AET (4-acryloyloxyethoxycarbonylphthalic acid), MAC-10 (11-methacryloyloxy-1, 10-undecanedicarboxylic acid) and polyacrylic acid, similar bond strengths were verified as compared with 10-MDP ($p \geq 0.48$), and significant lower bonding potential for adhesives based on 4-META (4-methacryloxyethyl trimellitate anhydride) and 4-MET (4-methacryloxyethyl trimetellitic acid) monomers ($p \leq 0.0002$). Concerning the other pairwise analyses in this set, phosphonic acid-derived materials and 10-MDP-based adhesives performed similarly to each other ($p=0.06$), although adhesives based on sulfonic acids, mixed composition and unspecified acidic ingredients demonstrated lower bonding potential than those containing 10-MDP ($p \leq 0.0001$). Heterogeneity was considered high in this set of analyses ($I^2 = 94\%$).

The NMA was conducted on studies grouped according to their acidic composition (with or without 10-MDP) and application category (2-steps, 1-step or universal), so that a total of 6 arms were compared to each other. Two sets of NMA were created (**Figure 7**), one for data collected at dentin (**Panel A**) and one at enamel substrate (**Panel B**). Most of the pairwise comparisons were between “10-MDP (2-steps)” and “10-MDP-free (1-step)” groups, for both dentin and enamel. Direct comparisons were performed with all arms in the dentin subgroup, whereas for enamel there was a lack of four direct comparisons: two between “10-MDP (2-steps)” and universal adhesives; and two between “10-MDP-free (universal)” and 1-step adhesives (**Figure 7** – images a). The forest plot comparing individual adhesive groups to “10-MDP (2-steps)” demonstrated that the latter was associated to significantly greater resin-dentin and resin-enamel bonds, ranging from 4.93 to 11.32 MPa increment at dentin and from 1.05 to 7.26 MPa increment at enamel (**Figure 7** – images b); the only exception was verified with “10-MDP-free (2-steps)” group, which resulted in similar resin-enamel mean difference to the control (effect size: -1.05, 95% CI: -3.31, 1.21).

The league-tables derived by the Bayesian model comparing the six adhesive groups at both dentin and enamel substrates are shown in **Figure 7** – images c. The dental bonds were significantly greater with the application of 2-step 10-MDP-based adhesives as compared to the other systems, except when bonding to enamel with 2-step 10-MDP-free adhesives, which resulted in similar bonding potential than the 10-MDP-based counterpart. Considering the findings from indirect comparisons, 10-MDP-free adhesives categorized in the “1-step” and “universal” conditions seemed to result in the lowest resin-dentin and resin-enamel bonds, respectively. Overall, node-split model demonstrated statistical consistency between the estimates from direct and indirect comparisons ($p \geq 0.06$ for dentin and $p \geq 0.13$ for enamel), which results are shown in **Appendices C and D**; inconsistent results were verified only in comparisons made at dentin and between the control and the “10-MDP (universal)” and “10-MDP-free (1-step)” groups ($p \leq 0.03$).

4. Discussion

This is the first meta-analysis study comparing the bonding performance of SE adhesives containing 10-MDP to materials comprised of other acidic monomers. Here, our main goal was to verify whether 10-MDP would be an essential ingredient for the predictable adhesion to dental substrates, as suggested by several studies in literature as well as by the common sense of worldwide researchers. Information of a considerable number of studies was gathered, making our findings solid and relevant to the scientific community. Overall, dental bonds were favored under the presence of 10-MDP, although this result relied on the type of mechanical testing, substrate, acidic composition, and application category, thus partially accepting the study’s hypothesis.

4.1. Effects of the type of bond strength test

Most of the analyzed bond strength data were derived from microtensile testing (~65%), followed by shear (~20%), microshear (~12%), and tensile (3%) tests. It is already known that microtensile testing gained popularity throughout the last two decades due to its better accuracy in detecting differences between the bonding ability of adhesive systems as well as because of its larger discriminative power than traditional shear test [229]. Taking into consideration microtensile data only, adhesives containing 10-MDP presented greater bond strengths to dentin as compared to their 10-MDP-free counterparts (**Figure 4**), probably due to some inherent characteristics that allow the formation of a strong hybrid layer with dentin. For instance, 10-MDP is capable of establishing an intense chemical interaction with hydroxyapatite (HAp), forming stable water-insoluble MDP-Ca salts, which protect collagen fibers from degradation [230]. Remarkably, 10-MDP seems to possess three desirable properties that may favor dental bonds: (i) the ability to form stable calcium salts; (ii) an equilibrium between hydrophilic and hydrophobic domains, producing adequate wetting of the substrate; and (iii) copolymerization capacity [231]. Differently from the results collected in dentin, the microtensile bond strengths to enamel were similarly distributed between the two groups of adhesives (**Figure 5**), regardless of the presence of 10-MDP. Enamel is indeed a more challenging substrate to achieve effective resin-enamel bonds with SE systems, first because of the less acidic composition of these adhesives, reducing the etching mechanism and the possibility of forming adequate mechanical interlocking with the substrate; and second because SE adhesives possess a hydrophilic composition that creates a physical unbalance with the typically hydrophobic structure of enamel [3]. Our findings corroborate with the literature since the bonding performance of SE adhesives in enamel is expected to be lower than dentin [230], regardless the presence of 10-MDP, which seems to result in less predictable bonds when applied to the highly mineralized enamel [9].

One interesting aspect of our findings relies on the higher resin-enamel bonds when the 10-MDP-based adhesives were tested using tensile, shear and microshear testing (**Figure 5**). In this case, essential characteristics inherent to the latter tests should be considered before extrapolating our findings. First, “macro” tests like the shear and tensile methods may result in a higher incidence of cohesive failures [232], limiting the acquisition of data that are properly related to the adhesive interface zone. Second, shear testing has no apparent value in the prediction of clinical performance of dental adhesives [233], differing from microtensile data that shows well correlation to clinical findings. Last, microshear testing has a less discriminating ability in evaluating the adhesive performance of bonding agents than microtensile [234]. Thus, from the pooled estimates of microtensile data, which seems to be the most relevant condition when evaluating the bonding performance of dental adhesives, we can suggest that SE adhesives containing 10-MDP may perform better than the 10-MDP-free counterparts if applied to dentin, but not when applied to enamel.

4.2. Effects of the source of the substrate

Most of the analyzed bond strength data were derived from human substrates (~79%), followed by animal (bovine teeth) substrates. Despite the questionable reliability of using animal teeth in bond strength experiments, a systematic review and meta-analysis study [235] has already demonstrated the appropriateness of bovine teeth as substitutes of human ones, for both enamel and dentin experimental designs. Worth mentioning, subgroup meta-analysis comparing the bonding performance of 10-MDP-based adhesives was favored as compared to the 10-MDP-free counterparts at both human and bovine substrates (**Appendix E**), reinforcing the idea that bovine teeth are adequate and may correlate well to human teeth.

4.3. Effects of the type of functional acidic monomer

From the 209 studies included in this review, a total of 64 different adhesive systems were investigated (**Figure 2**), with Clearfil™ SE Bond representing the material most frequently reported in the studies (~67%). This adhesive is a 2-step 10-MPD-based system, and it was one of the first bonding agents containing 10-MDP launched in the dental market, thus explaining its vast usage in several in vitro and clinical studies. The patent on the original 10-MDP monomer was applied by Kuraray in 1981 [236], and since then several products (e.g., dental adhesives, resin cements) were launched having this monomer as the special acidic ingredient. The second adhesive system most frequently reported in our review was Clearfil™ S3 Bond (~26% of the studies), which is also manufactured by Kuraray; this adhesive represents a 1-step version of SE systems, and it is also comprised of 10-MDP [237]. Meanwhile, other functional monomers have been considered in the formulation of SE adhesives, especially those derived from phosphoric acid (e.g., GPDM, PENTA, 6-MHP, PEM-F) or carboxylic acid (e.g., 4-META, 4-MET, 4-AET, MAC-10, polyacrylic acid); no less important, other functionalities such as phosphonic acid or sulfonic acid derivatives as well as a mixture of distinct acidic moieties were also observed in this review.

Phenyl-P (2-methacryloxyethyl phenyl hydrogen phosphate) was one of the pioneers in SE chemistry; it possesses a very acidic behavior (pH = 1.4), resulting in enamel-prism contours that slightly resemble the keyhole enamel-prism structures created by phosphoric acid (etch-and-rinse systems) [9]. Despite its higher etching efficacy as compared to other monomers, Phenyl-P is capable of releasing enormous amounts of Ca^{+2} ions from HAp, resulting in deep demineralization of dental substrates [9, 238]. It is well understood that by using functional monomers with lower acidic behavior (mild adhesives), the hybridization process may be benefited, since the formation of water insoluble monomer-Ca salts are more prone to occur [3]. Considering the diverse acidic composition of adhesives identified in our review, subgroup meta-analyses were performed on data derived from materials with functional monomers that appeared more frequently in the studies.

One subgroup meta-analysis compared the bond strengths between 10-MDP-based adhesives to those based on varying acidic ingredients ("mixed composition" group). As shown in **Figure 6**, the results favored 10-MDP. Again, 10-MDP is considered a unique monomer that combines etching ability to an intense chemical bonding potential to HAp, forming 10-MDP-Ca salts that are hydrolysis-resistant, making the adhesive interface stable over time (nano-layering mechanism) [239]. According to the study by Salz et al. [231], each acidic monomer has a specific pKa value, and consequently specific etching efficacy and ability of dissolving HAp-based tissues. Depending on the foregoing characteristics, functional monomers may chemically interact with HAp following either an adhesion or decalcification route, a process broadly known as adhesion-decalcification (AD) concept [2, 240]. Simply speaking, acidic monomers with soluble Ca salts (e.g., Phenyl-P) tend to form hybrid layers in the same fashion to the etch-and-rinse adhesive systems, creating moderately thick interfaces with abundant collagen exposure, i.e., a consequence of an intense decalcification process without adequate resin infiltration and chemical bonding into the demineralized tissue. On the other hand, acidic monomers resulting in stable Ca salts (e.g., 10-MDP) seem to produce less thick hybrid layers due to a less pronounced etching mechanism, keeping collagen fibrils protected by HAp; this process allows a "true" adhesion, adding strength to the adhesive interface [241]. Having this in mind, one may suggest that the mixture of several acidic monomers into the same adhesive solution may result in a more heterogeneous composition, perhaps potentiating the etching efficacy of the material and the decalcification process of HAp, thus resulting in lower dental bonds. In our review, the SE adhesives allocated into the "mixed composition" group were mainly comprised of resin monomers derived from phosphoric and carboxylic acids. Besides the possible higher etching efficacy obtained with the combination of those monomers, we may also suggest that hydrophilicity of the adhesive is probably greater in heterogeneous mixtures like that [3], with hydrolysis being more feasible to occur, favoring the bond strength results towards the 10-MDP-based group.

In light of verifying the bonding effects of more homogeneous acidic compositions, additional subgroup meta-analyses were conducted by comparing 10-MDP-based adhesives to those comprised of one main acidic monomer. When the adhesive was based on phosphoric acid derivatives, the bond strength results were largely dependent on the type of monomer (**Figure 6**). For instance, the presence of GPDM resulted in greater bonding potential than 10-MDP, being the only comparison of our review that non-favored the latter class of adhesive; conversely, monomers such as PENTA, 6-MHP, pyrophosphate, and unspecified phosphate esters produced lower dental bonds than 10-MDP, whereas monomers like PEM-F and acrylamide phosphates created similar mean difference values as compared with 10-MDP.

One may suggest that GPDM has the ability to form stable monomer-Ca salts when applied to dentin/enamel, allowing an adequate hybridization and a better bonding performance than 10-MDP. However, the etching efficacy of the former was revealed to be higher than the latter [10, 242], which would impair the formation of water-insoluble Ca salts; additionally, the inherent hydrophilic behavior of GPDM would probably induce decalcification events to occur [10]. Thus, there is something related to the chemistry of GPDM that makes this monomer interesting, as suggested in the study by Wang et al. [242], in which an adhesive system based on GPDM (Optibond XTR; Kerr) resulted in considerably greater immediate bond strength values (~65% higher microtensile resin-dentin bonds) when compared to Clearfil SE Bond. It was demonstrated that the former bonding agent created resin tags of 15-30 µm in length extending into dentinal tubules, probably due to its intense etching ability resembling the resin tags obtained with etch-and-rinse systems. Here, hydrophilicity of GPDM allowed its deep penetration into dentin, producing adequate resin infiltration and the formation of a strong micromechanical interlocking [3]. No less important, GPDM possesses two polymerizable groups capable of cross-linking with other resin monomers, improving mechanical properties and polymerization of the adhesive layer [243].

The other phosphate-based monomers analyzed in this review produced lower bond strength values (in the case of PENTA, 6-MHP, pyrophosphate, and unspecified phosphate esters) or an almost significantly lower bonding potential (in the case of PEM-F) than 10-MDP.   PENTA and 6-MHP are both mildly acidic monomers (like 10-

MDP) [114, 244]. While 6-MHP has a linear structure, PENTA possesses a 3D spatial molecule, having a shorter main chain with five vinyl groups that inherently increases steric hindrance and viscosity characteristics [245, 246]. In theory, these monomers were expected to chemically interact with HAp, since the presence of hydroxyls within their phosphate groups could form coordinate bonds with cationic compounds derived from HAp [245]. In this aspect, the lower bonding effectiveness of the latter monomers may be related to the chemistry of the other adhesive ingredients rather than the acidic monomers. Of note, acetone is a solvent typically found in the composition of PENTA- and 6-MHP-based adhesives, and it may prevent chemical bonding of acidic monomers to HAp, as suggested elsewhere [148, 247]. Concerning pyrophosphate esters, they have a strong acidic behavior due to the presence of more than one phosphate moiety per molecule and several hydroxyls, which may turn the resin monomer hydrophilic and less capable of forming stable Ca^{+2} salts [248]. PEM-F has also a specific configuration, including 5 methacrylate-alkyl chains grafted onto a ring structure (i.e., cyclophosphazene) and a fluoride functionality that aids in the scavenging of Ca^{+2} to intensify demineralization effects [248]. The only exception occurred for the adhesives containing acrylamide phosphates, which demonstrated similar dental bonds to the 10-MDP counterparts (**Figure 6**). Acrylamides have an amide group in lieu of an ester group, impacting positively on the hydrolytic resistance of materials [8, 249].

Concerning adhesives based on carboxylic acid derivatives, they were allocated into five main acidic groups: 4-META, 4-MET, 4-AET, MAC-10, and polyacryic acid. Compared to 10-MDP, statistically lower dental bonds were verified in the presence of 4-META and 4-MET monomers, differing from the other monomers that contributed for similar bonding mean values (**Figure 6**). 4-META and 4-MET are both characterized by the presence of two carboxylic groups in each molecule, rendering these monomers the ability to form Ca salts with HAp [250, 251]. They share a similar molecular structure, although the molecular mechanics and molecular orbital characteristics may largely differ between each other, owing these monomers with intrinsic and unique abilities to interact with HAp-based tissues [252]. One would suggest that adhesives containing 4-META and 4-MET would perform properly as bonding agents; however, several studies demonstrated their inferior bonding performance to dentin and enamel [11, 131, 143, 148, 158, 206, 211], indicating a lesser capability to create stable monomer-Ca salts, as verified by our findings. One main aspect should be considered here: 4-META and 4-MET are more hydrophilic than 10-MDP [10], and taking into consideration that hydrophilicity increases the acidity of SE resins [2, 3, 14], it is possible to assume that the etching efficacy of carboxylic-based adhesives is greater than the 10-MDP-based counterparts, thus limiting their adhesion ability to HAp [114]. On the other hand, the monomer 4-AET is also a carboxylic acid-derived molecule with a divalent $–(COOH)_2$ group, similarly to the monomers discussed earlier, but due to its mild solubility in water this monomer may penetrate beyond the superficial smear layer, establishing a chemical interaction with dentin apatite and formation of Ca-carboxylate salts [253], and the similar bonding performance with 10-MDP group.

The two other carboxylic acid-derived monomers that guaranteed similar bonding potential to 10-MDP were as follows: MAC-10 and polyacrylic acid-derivatives. The former resembles the molecular structure of 10-MDP, i.e., both monomers have a spacer group containing 10 carbon atoms [254]; in turn, MAC-10 is hydrolytically stable due to the hydrophobic behavior of the long carbon chain separating the polymerizable group and the divalent $–(COOH)_2$ groups [248], which may increase the possibility towards the formation of stable Ca-MAC-10 salts, in the same fashion to 10-MDP. The latter class of monomers are derived from acrylic acids, which are typically weak acids (pH > 3.0) [255], so that they have lower acidic potential than other carboxylic acid monomers. One should note that acrylic acid derivatives are capable of chelating with HAp, as it happens with the application of glass ionomer cements to mineralized substrates [256]. It is noteworthy to suggest that the lower etching ability of these monomers as well as their chelating ability to calcium can both allow the formation of intricate hybrid layers (i.e., adhesion process prevailing over decalcification), perhaps explaining their similar bond strength results as compared with the 10-MDP group.

Despite all rationale discussed up to here, three last subgroup meta-analyses in this set were also conducted. Some adhesive systems analyzed in this review were comprised of sulfonic acid-derivatives or unknown acidic ingredients, which demonstrated a lower bonding potential than 10-MDP-based adhesives. While we may not give explanations regarding the “unknown composition” group due to the lack of information supplied by the manufacturers on their acidic ingredients, we may tough suggest that in the case of sulfonic acids, their high acidity would have contributed for decreasing the bonding potential of the adhesives, since their etching aggressiveness is substantially greater than phosphonic acids, phosphorics acids and carboxylic acids, in this order [249, 257]; of note, sulfonic acids have a greater capability to dissociate into more protons while in solution [258]. Concerning adhesives based on phosphonic acids, they did not differ from the 10-MDP group. Of note, phosphonic acids have been interestingly considered for the formulation of SE systems over the past decade, probably due to their superior hydrolytic stability and improved bonding potential to mineralized tissues, as suggested elsewhere [249]. Originally, this type of acidic monomer displayed low solubility in water, reducing its bonding ability to dentin, but several efforts were made to improve solubility properties, enabling phosphonic acids to perform their adhesion-promoting function with HAp [259]. It is worth mentioning that monomers based on this acidic moiety have a ligand characteristic [260], since the phosphonic acid group may undergo ionization in water, forming oxygen anions that enhance bonding effectiveness [261], and according to our findings, in the same fashion to 10-MDP.

4.4. Effects of the steps of application

It has been broadly accepted that 2-step SE adhesives perform better than the 1-step versions, since the separate application of primer and resin bond solutions may create a more appropriate etching and resin infiltration, contributing to stronger dental bonds [229]. Despite some clinical studies demonstrate similar success and survival rates when bonding composite restorations with both 2-step and 1-step SE systems [262], laboratory data show almost unanimously a distinct trend, with the former adhesives resulting in considerably greater bonding performance than the latter [263-265]. In our review, we allocated all the bond strength data into six different groups aiming a network meta-analysis, varying the groups in terms of the presence/absence of 10-MDP as well as on their classification into a 2-step, 1-step, or universal modes of application. Overall, we considered the 2-step 10-MDP-based materials as the gold standard, as widely accepted in the SE approach [229], and according to data shown in **Figure 7**, we confirmed the superiority of these adhesives when compared to the other classes of materials, especially in dentin. This is an important finding that highlights the enhanced bonding mechanisms achievable with the use of materials that combine a 10-MDP composition with the separate application of primer and resin bond, thus contrasting to the more simplified all-in-one systems. Here, the creation of less permeable hybrid layers by using 2-step agents may guarantee an even resin penetration within dentin as well as the formation of a homogeneous adhesive interface [3]; more importantly, the possibility of removing residual solvent molecules during drying of the primer and before the application of the hydrophobic adhesive coating layer, seems to strengthen the hybrid layer. This aspect was also observed when comparing the 2-step 10-MDP-free adhesive group to the all-in-one groups, in which the former resulted in overall greater resin-dentin and resin-enamel bonds, suggesting that not only the presence of 10-MDP plays a significant role in dental bonding, but also the type/classification and application protocol of adhesives.

Concerning the all-in-one materials, the adhesives based on 10-MDP performed similarly to each other at both dentin and enamel, but they demonstrated better bonding ability to dentin than the 1-step MDP-free group. Notably, the latter displayed the worst bond strength potential of the study, so that 1-step adhesives that lack in 10-MDP may not create the best scenario when bonding restorations to dentin that require the most of adhesiveness (e.g., the case of non-retentive Class IV and Class V tooth cavities). It is possible to understand that the highly hydrophilic content of one bottle adhesives combined to their low acidic potential and possible immiscibility between polar and nonpolar ingredients, make them the least reliable SE systems available for use [3].

Interestingly, the groups consisting of universal adhesives demonstrated similar bonding potential to dentin and enamel when compared to each other. However, and different from findings collected in dentin, the universal 10-MDP-free adhesives seemed to perform worst in enamel than in dentin, probably due to their more heterogeneous composition and hydrolytic instability [255]. While at the one hand SE adhesives are expected to work poorly in enamel due to an insufficient etching ability as compared to the total-etch approach using phosphoric acid (i.e., the gold standard in terms of enamel bonding [4]); at the other hand our findings reveal that universal adhesives may benefit from the presence of 10-MDP. Nevertheless, estimates comparing the bonding potential of 10-MDP-free universal adhesives to other versions of adhesives relates to indirect comparisons obtained with the network meta-analysis, since there is a lack of direct evidence comparing the foregoing groups. Thus, interpretation of our findings should be considered with caution. As shown in previous studies, other aspects can be also associated to greater bonding performance of SE adhesives in enamel, including but not limited to the application of an extra hydrophobic layer [266] and the selective etching of enamel with phosphoric acid prior the application of the SE bonding agent [4, 267, 268]. Even so, enamel is still a challenging substrate when bonding dental restorations with SE adhesives [269], regardless of the presence of 10-MDP, and this acidic resin monomer does not seem to act as a determinant ingredient in this type of substrate.

4.5. Quality analysis of included studies

In our review, the majority of studies scored as having medium risk of bias (56.7%), and this may be explained by the non-standardized protocols used in the bonding procedures and due to the enormous variety of materials (e.g., adhesive systems, resin composites) (**Figure 2 and Appendix A**). Concerning the surface treatment of dentin/enamel prior bonding, most of studies (54.3%) prepared the substrate using a #600-grit SiC paper, although the study by De Munck et al. [229] recommends the use of a dental bur in order to simulate a clinically prepared smear layer. It is worth mentioning that 18.1% of studies prepared the substrates prior bonding by using a sequence of SiC papers, with the last grit size used varying from the #600- to the #4000-grit; and 4.3% of studies did not mention any surface treatment before application of adhesives. A similar trend was also observed during the storage of bonded restorations before testing. Indeed, the protocols ranged from immersion in distilled water (52.9%) or tap water (14.3%) at 37°C for 24 h to other protocols varying the storage temperature or storage medium (e.g., humid condition, deionized water, artificial saliva, dry storage).

Considering all the range of surface treatment protocols and storage conditions verified in our review, future studies should prepare their samples by using more standardized instruments and protocols, aiming to minimize variability of data. Heterogeneity was high in this review, probably explained by the variety of mechanical tests, tooth substrates, surface treatment, adhesive systems, resin composites, and storage conditions reported in the studies. However, subgroup analyses were, as much as possible, conducted by allocating the bond strength data into more homogenous group sets, perhaps allowing a proper statistical analysis and comparisons between groups.

Last, it is also important to highlight that the majority of studies performed additional qualitative analyses of the adhesive interfaces, e.g., verification/calculation of the failure mode of resin-dentin and resin-enamel bonds and/or the conduction of scanning electron microscopy analysis to evaluate the hybrid layer or the fracture pattern of tested samples. While the mechanical bond strength test quantifies the bonding potential of different adhesives to dental substrates, the foregoing qualitative analyses offer additional clues to the interpretation of data, which may aid in the establishment of adequate conclusions.

4.6. Fields requiring further investigation

From all meta-analyses performed in the present review, some pairwise comparisons were not possible to conduct due to the inexistence of sufficient data. This was especially true for data collected in enamel, in which studies comparing the bonding performance of 2-step 10-MDP-based materials to that from universal adhesives applied in SE mode are still lacking, as well as for comparing 1-step adhesives to 10-MDP-free universal adhesives (**Figure 7B-c**). Also, all blank cells shown in table c correspond to a lack of direct evidence comparing the interconnected groups, thereby guaranteeing further studies.

5. Conclusion

Despite the moderate-to-high heterogeneity of studies, and based on this meta-analysis, we demonstrated the overall superiority of adhesives containing 10-MDP when compared to materials formulated with other acidic resin monomers, although this result relied on the type of mechanical test, type of the substrate, acidic composition of the adhesive, and the application category of the SE system. In dentin, the dental bonds were benefited from the use of 2-step 10-MDP-based adhesives, reinforcing the positive effect of this acidic monomer as well as of the separate application of acidic primer and resin adhesive solutions. In enamel, the dental bonds were benefited from the use of 2-step adhesive systems, regardless of the presence of 10-MDP. From the list of available acidic functional monomers used in the formulation of SE adhesives and gathered in this review, GPDM was the only ingredient that demonstrated greater bonding potential to dentin/enamel as compared with 10-MDP, whereas all other acidic monomers contributed to reduced or statistically similar bond strengths to 10-MDP.

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Tables

Table 1. Search strategy and search date (initial and final) for the electronic databases.

Database	First and final searches	Search strategy
MEDLINE/PubMed	April 1st 2020; June 30th 2021	(bond strength OR µSBS OR microshear bond strength OR µTBS OR microtensile bond strength) AND (dentin OR enamel) AND (self-adhesive resin cement OR self-adhesive composite OR self-adhesive composite resin OR self-etching adhesive OR self-etch adhesive OR universal adhesive OR acidic monomer OR acidic resin monomer OR monomer acid OR functional monomer OR acidic functional monomer)
Scopus	April 1st 2020; June 30th 2021	“bond strength” OR “µSBS” OR “microshear bond strength” OR “µTBS” OR “microtensile bond strength” AND “dentin” OR “enamel” AND “self-adhesive resin cement” OR “self-adhesive composite” OR “self-adhesive composite resin” OR “self-etching adhesive” OR “self-etch adhesive” OR “universal adhesive” OR “acidic monomer” OR “acidic resin monomer” OR “monomer acid” OR “functional monomer” OR “acidic functional monomer”
Web of Science	April 1st 2020; June 30th 2021	(“bond strength” OR “µSBS” OR “microshear bond strength” OR “µTBS” OR “microtensile bond strength”) AND (“dentin” OR “enamel”) AND (“self-adhesive resin cement” OR “self-adhesive composite” OR “self-adhesive composite resin” OR “self-etching adhesive” OR “self-etch adhesive” OR “universal adhesive” OR “acidic monomer” OR “acidic resin monomer” OR “monomer acid” OR “functional monomer” OR “acidic functional monomer”)
Lilcas, SciElo, BBO, IBECS	April 1st 2020; June 30th 2021	“bond strength” OR “resistência de união” OR “fuerza de unión” OR “µSBS” OR “microshear bond strength” OR “resistência de união ao microcisalhamento” OR “resistencia al cizallamiento” OR “µTBS” OR “microtensile bond strength” OR “resistência de união à microtração” OR “resistencia a la tracción” AND “dentin” OR “dentina” OR “enamel” OR “esmalte” AND “self-adhesive resin cement” OR “cimento resinoso autoadesivo” OR “cemento de resina autoadhesivo” OR “self-adhesive composite” OR “compósito autoadesivo” OR “composite autoadhesivo” OR “self-adhesive composite resin” OR “resina composta autoadesiva” OR “compuesto de resina autoadhesiva” OR “self-etching adhesive” OR “adesivo autocondicionante” OR “adhesivo autograbante” OR “self-etch adhesive” OR “universal adhesive” OR “adesivo universal” OR “adhesivo universal” OR “acidic monomer” OR “monômero acídico” OR “monómero ácido” OR “acidic resin monomer” OR “monômero resinoso acídico” OR “monómero resinoso ácido” OR “monomer acid” OR “monômero ácido” OR “monómero ácido” OR “functional monomer” OR “monômero funcional” OR “monómero funcional” OR “acidic functional monomer” OR “monômero funcional acídico” OR “monómero funcional ácido”

Figures

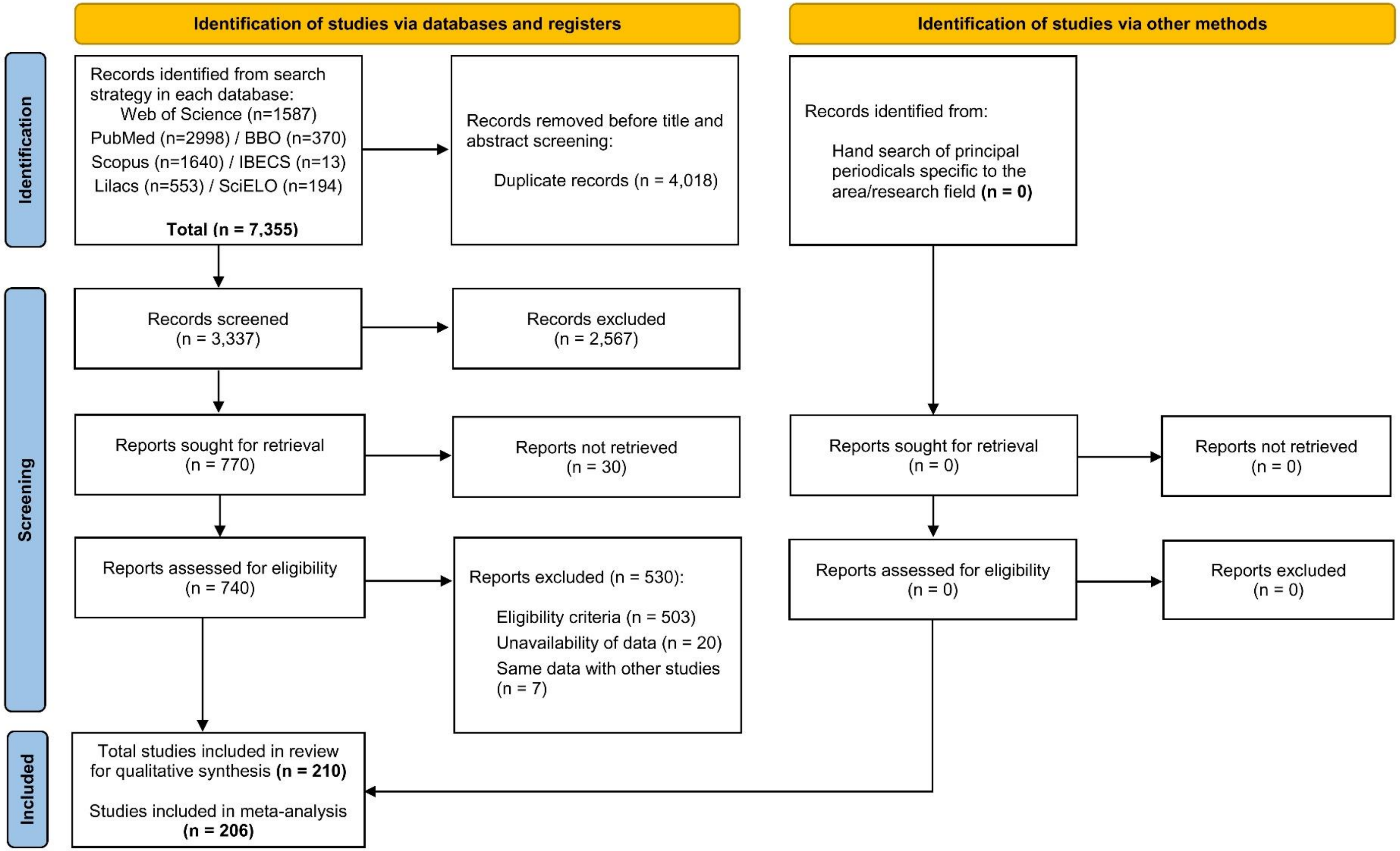


Figure 1. Search flowchart of the study selection according to the PRISMA statement.

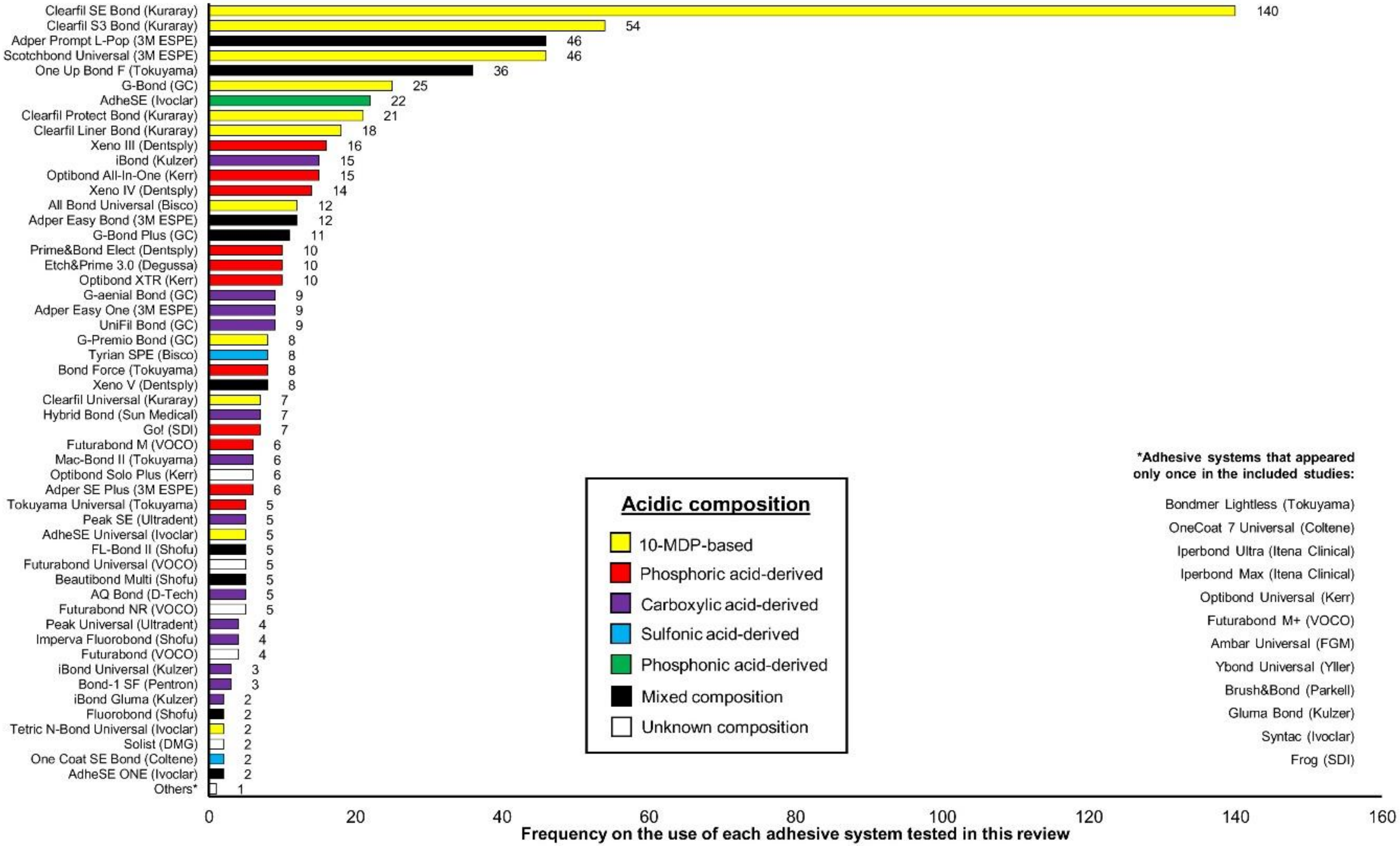


Figure 2. Graph showing the list and frequency of adhesive systems used in the included studies, allocated by the acidic composition.

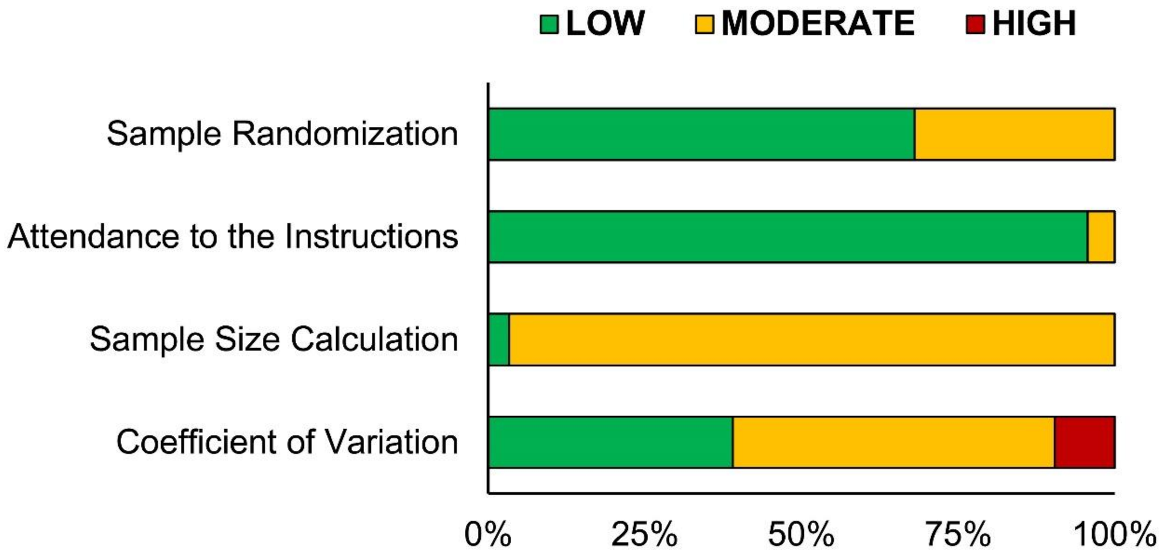


Figure 3. Review authors' judgments about each risk of bias item for each included in vitro study, classified as having low, moderate or high risk of bias.

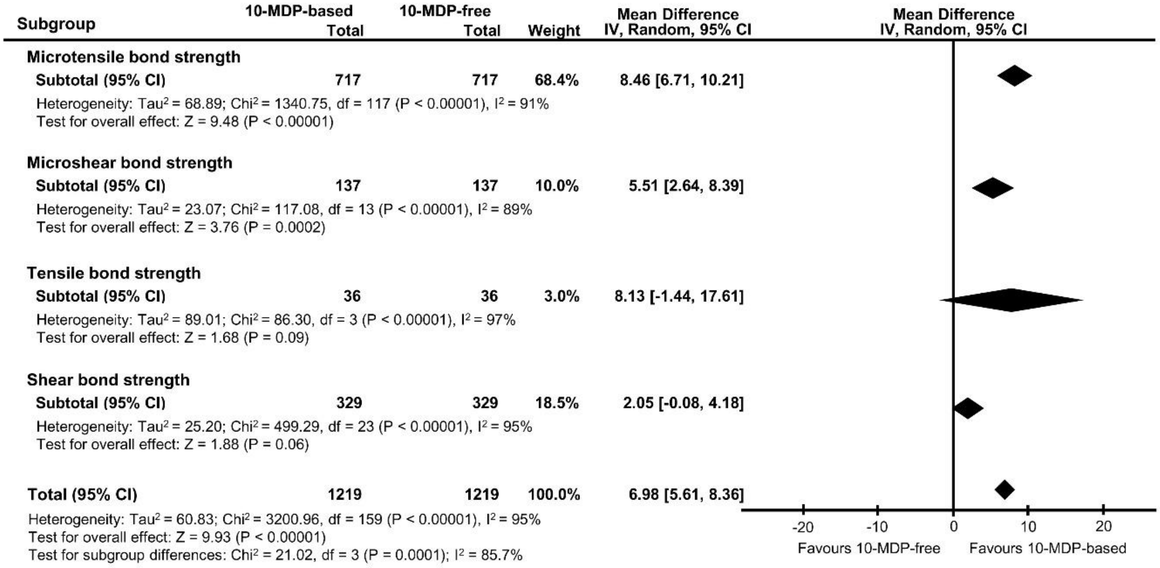
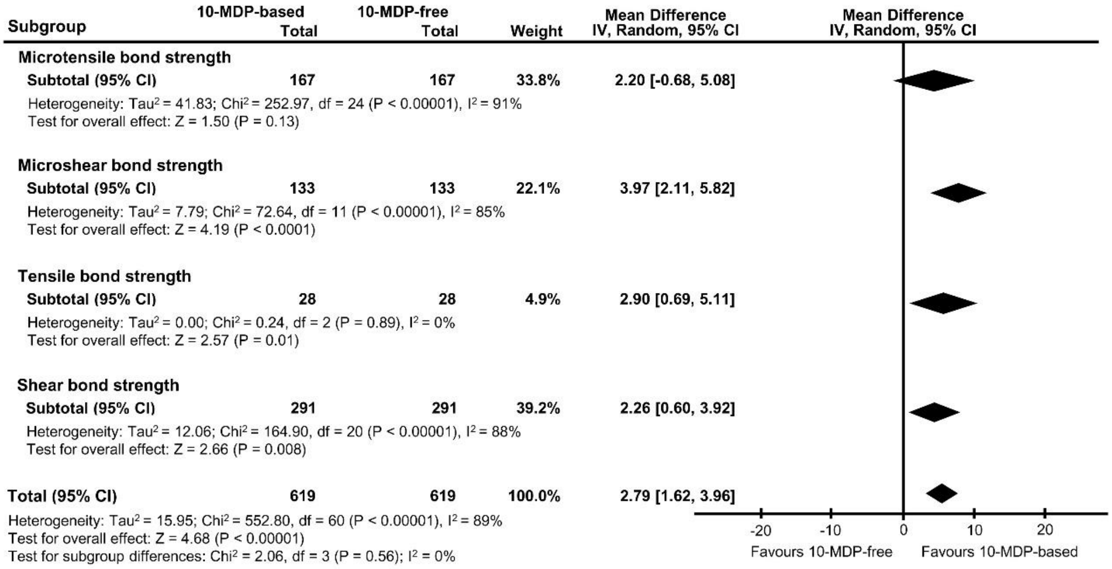


Figure 4. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives in dentin. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).



Subgroup	10-MDP-based Total	10-MDP-free Total	Weight	Mean Difference IV, Random, 95% CI
Microtensile bond strength				
Subtotal (95% CI)	**167**	**167**	**33.8%**	**2.20 [-0.68, 5.08]**
Heterogeneity: Tau^2 = 41.83; Chi^2 = 252.97, df = 24 (P < 0.00001), I^2 = 91%				
Test for overall effect: Z = 1.50 (P = 0.13)				
Microshear bond strength				
Subtotal (95% CI)	**133**	**133**	**22.1%**	**3.97 [2.11, 5.82]**
Heterogeneity: Tau^2 = 7.79; Chi^2 = 72.64, df = 11 (P < 0.00001), I^2 = 85%				
Test for overall effect: Z = 4.19 (P < 0.0001)				
Tensile bond strength				
Subtotal (95% CI)	**28**	**28**	**4.9%**	**2.90 [0.69, 5.11]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.24, df = 2 (P = 0.89), I^2 = 0%				
Test for overall effect: Z = 2.57 (P = 0.01)				
Shear bond strength				
Subtotal (95% CI)	**291**	**291**	**39.2%**	**2.26 [0.60, 3.92]**
Heterogeneity: Tau^2 = 12.06; Chi^2 = 164.90, df = 20 (P < 0.00001), I^2 = 88%				
Test for overall effect: Z = 2.66 (P = 0.008)				
Total (95% CI)	**619**	**619**	**100.0%**	**2.79 [1.62, 3.96]**

Heterogeneity: Tau^2 = 15.95; Chi^2 = 552.80, df = 60 (P < 0.00001), I^2 = 89%
Test for overall effect: Z = 4.68 (P < 0.00001)
Test for subgroup differences: Chi^2 = 2.06, df = 3 (P = 0.56); I^2 = 0%

Figure 5. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives in enamel. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).

Acidic monomers	10-MDP-free Total	10-MDP-based Total	Weight	Mean Difference IV, Random, 95% CI
Mixed composition				
Subtotal (95% CI)	**802**	**802**	**30.2%**	**-7.82 [-9.35, -6.28]**
Heterogeneity: Tau² = 51.84; Chi² = 1662.28, df = 110 (P < 0.00001), I² = 93%				
Test for overall effect: Z = 9.96 (P < 0.00001)				
Phosphoric acid-derived				
GPDM				
Subtotal (95% CI)	**264**	**264**	**7.7%**	**2.78 [0.20, 5.36]**
Heterogeneity: Tau² = 34.02; Chi² = 260.99, df = 25 (P < 0.00001), I² = 90%				
Test for overall effect: Z = 2.11 (P = 0.03)				
PENTA				
Subtotal (95% CI)	**273**	**273**	**7.2%**	**-6.24 [-9.11, -3.37]**
Heterogeneity: Tau² = 40.87; Chi² = 451.14, df = 23 (P < 0.00001), I² = 95%				
Test for overall effect: Z = 4.26 (P < 0.0001)				
6-MHP				
Subtotal (95% CI)	**48**	**48**	**1.6%**	**-4.54 [-7.08, -2.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.87, df = 5 (P = 0.97), I² = 0%				
Test for overall effect: Z = 3.51 (P = 0.0005)				
PEM-F				
Subtotal (95% CI)	**136**	**136**	**4.5%**	**-3.67 [-7.33, -0.01]**
Heterogeneity: Tau² = 41.84; Chi² = 273.80, df = 16 (P < 0.00001), I² = 94%				
Test for overall effect: Z = 1.97 (P = 0.05)				
Pyrophosphate esters				
Subtotal (95% CI)	**59**	**59**	**2.2%**	**-15.92 [-20.75, -11.08]**
Heterogeneity: Tau² = 34.61; Chi² = 31.19, df = 8 (P = 0.0001), I² = 74%				
Test for overall effect: Z = 6.45 (P < 0.00001)				
Acrylamide phosphate				
Subtotal (95% CI)	**8**	**8**	**0.4%**	**-2.73 [-20.34, 14.87]**
Heterogeneity: Tau² = 130.77; Chi² = 4.96, df = 1 (P = 0.03), I² = 80%				
Test for overall effect: Z = 0.30 (P = 0.76)				
Phosphate ester (unspecified)				
Subtotal (95% CI)	**136**	**136**	**4.5%**	**-2.72 [-4.81, -0.63]**
Heterogeneity: Tau² = 17.40; Chi² = 138.75, df = 21 (P < 0.00001), I² = 85%				
Test for overall effect: Z = 2.55 (P = 0.01)				
Carboxylic acid-derived				
4-META				
Subtotal (95% CI)	**416**	**416**	**12.7%**	**-6.84 [-8.09, -5.58]**
Heterogeneity: Tau² = 10.72; Chi² = 236.51, df = 41 (P < 0.00001), I² = 83%				
Test for overall effect: Z = 10.69 (P < 0.00001)				
4-MET				
Subtotal (95% CI)	**67**	**67**	**2.5%**	**-5.00 [-8.18, -1.81]**
Heterogeneity: Tau² = 13.69; Chi² = 37.53, df = 8 (P < 0.00001), I² = 79%				
Test for overall effect: Z = 3.08 (P = 0.0002)				
4-AET				
Subtotal (95% CI)	**28**	**28**	**1.0%**	**-1.78 [-6.67, 3.11]**
Heterogeneity: Tau² = 13.43; Chi² = 16.28, df = 3 (P = 0.0010), I² = 82%				
Test for overall effect: Z = 0.71 (P = 0.48)				
MAC-10				
Subtotal (95% CI)	**39**	**39**	**1.5%**	**0.06 [-4.28, 4.40]**
Heterogeneity: Tau² = 15.90; Chi² = 25.64, df = 5 (P = 0.0001), I² = 81%				
Test for overall effect: Z = 0.03 (P = 0.98)				
Polyacrylic acid-derived				
Subtotal (95% CI)	**180**	**180**	**6.0%**	**-0.43 [-3.15, 2.29]**
Heterogeneity: Tau² = 28.57; Chi² = 175.26, df = 19 (P < 0.00001), I² = 89%				
Test for overall effect: Z = 0.31 (P = 0.76)				
Phosphonic acid-derived				
Subtotal (95% CI)	**182**	**182**	**6.0%**	**-2.89 [-5.96, 0.18]**
Heterogeneity: Tau² = 38.93; Chi² = 212.04, df = 21 (P < 0.00001), I² = 90%				
Test for overall effect: Z = 1.85 (P = 0.06)				
Sulfonic acid-derived				
Subtotal (95% CI)	**78**	**78**	**3.0%**	**-8.04 [-11.09, -4.98]**
Heterogeneity: Tau² = 16.23; Chi² = 45.05, df = 9 (P < 0.00001), I² = 80%				
Test for overall effect: Z = 5.15 (P < 0.00001)				
Unknown composition				
Subtotal (95% CI)	**185**	**185**	**6.7%**	**-5.72 [-8.56, -2.88]**
Heterogeneity: Tau² = 36.56; Chi² = 289.85, df = 22 (P < 0.00001), I² = 92%				
Test for overall effect: Z = 3.95 (P < 0.0001)				
Total (95% CI)	**2962**	**2962**	**100.0%**	**-5.26 [-6.02, -4.50]**
Heterogeneity: Tau² = 39.93; Chi² = 5681.23, df = 352 (P < 0.00001), I² = 94%				
Test for overall effect: Z = 13.54 (P < 0.00001)				
Test for subgroup differences: Chi² = 105.13, df = 15 (P < 0.00001); I² = 85.7%				

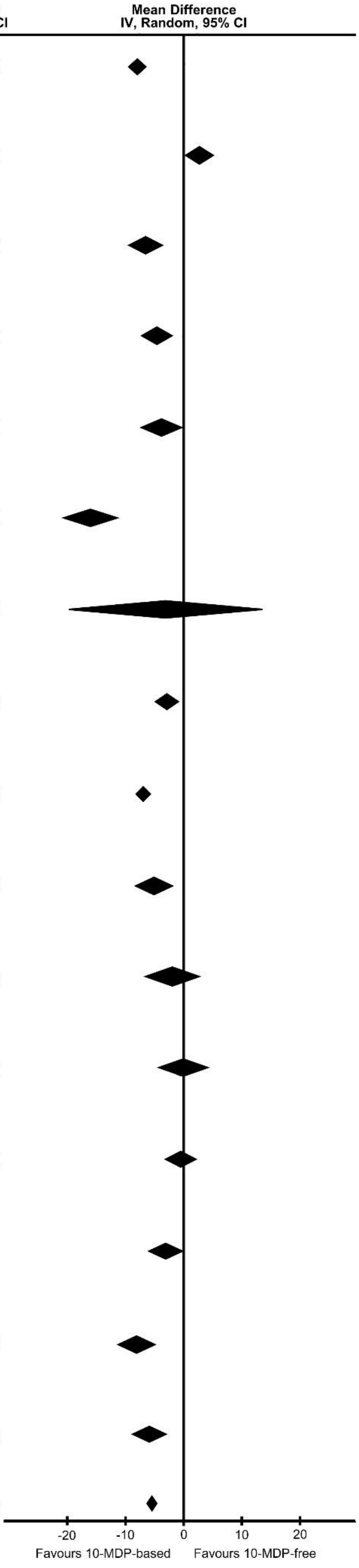
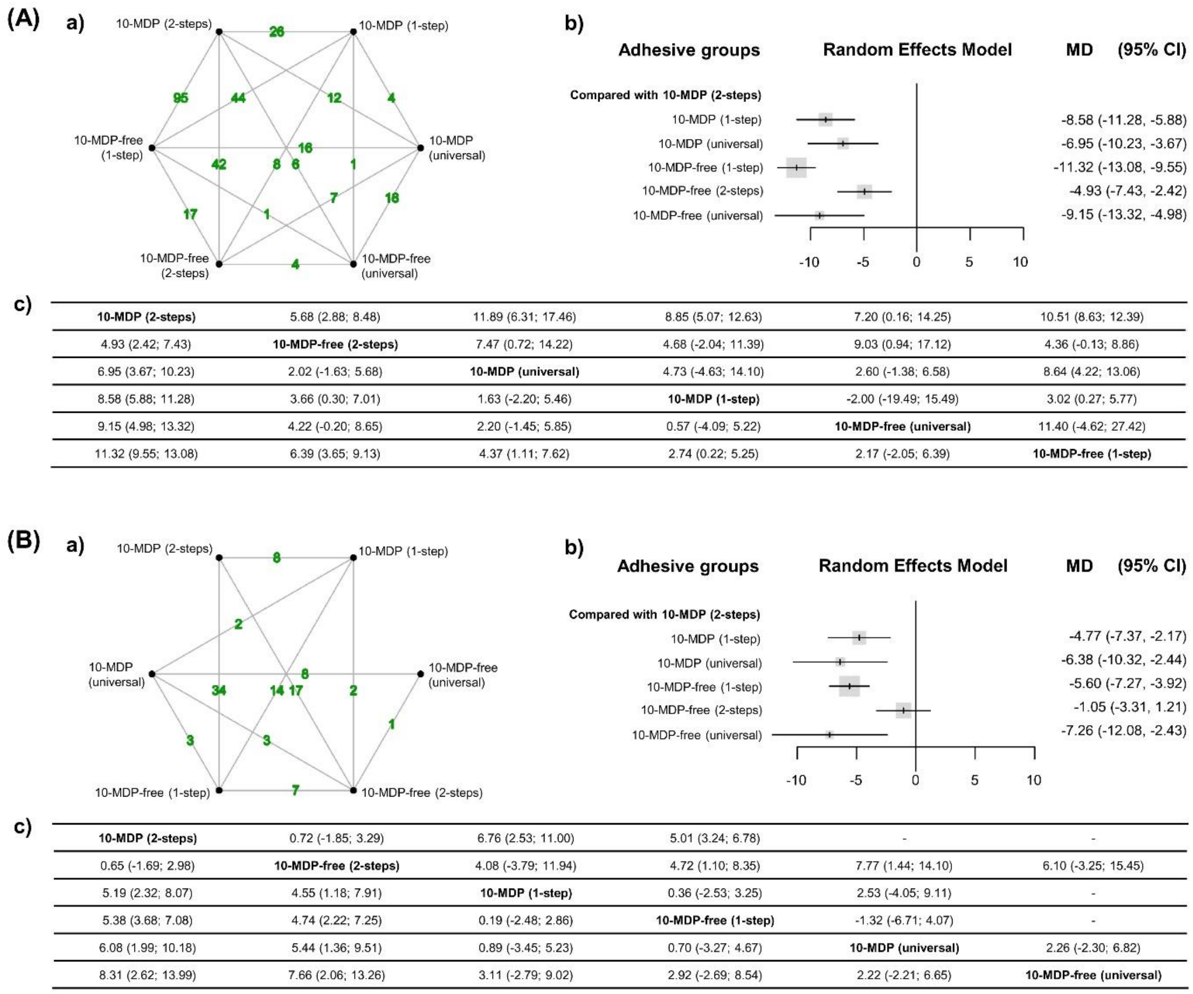


Figure 6. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and adhesives containing different acidic composition, as follows: mixed composition; monomers derived from phosphoric acid (GPDM, PENTA, 6-MHP, PEM-F, pyrophosphate esters, acrylamide phosphate, and unspecified phosphate esters); monomers derived from carboxylic acid (4-META, 4-MET, 4-AET, MAC-10, polyacrylic acid); monomers derived from phosphonic or sulfonic acids; and unknown composition. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).



Adhesive groups	MD (95% CI)
Compared with 10-MDP (2-steps)	
10-MDP (1-step)	-8.58 (-11.28, -5.88)
10-MDP (universal)	-6.95 (-10.23, -3.67)
10-MDP-free (1-step)	-11.32 (-13.08, -9.55)
10-MDP-free (2-steps)	-4.93 (-7.43, -2.42)
10-MDP-free (universal)	-9.15 (-13.32, -4.98)

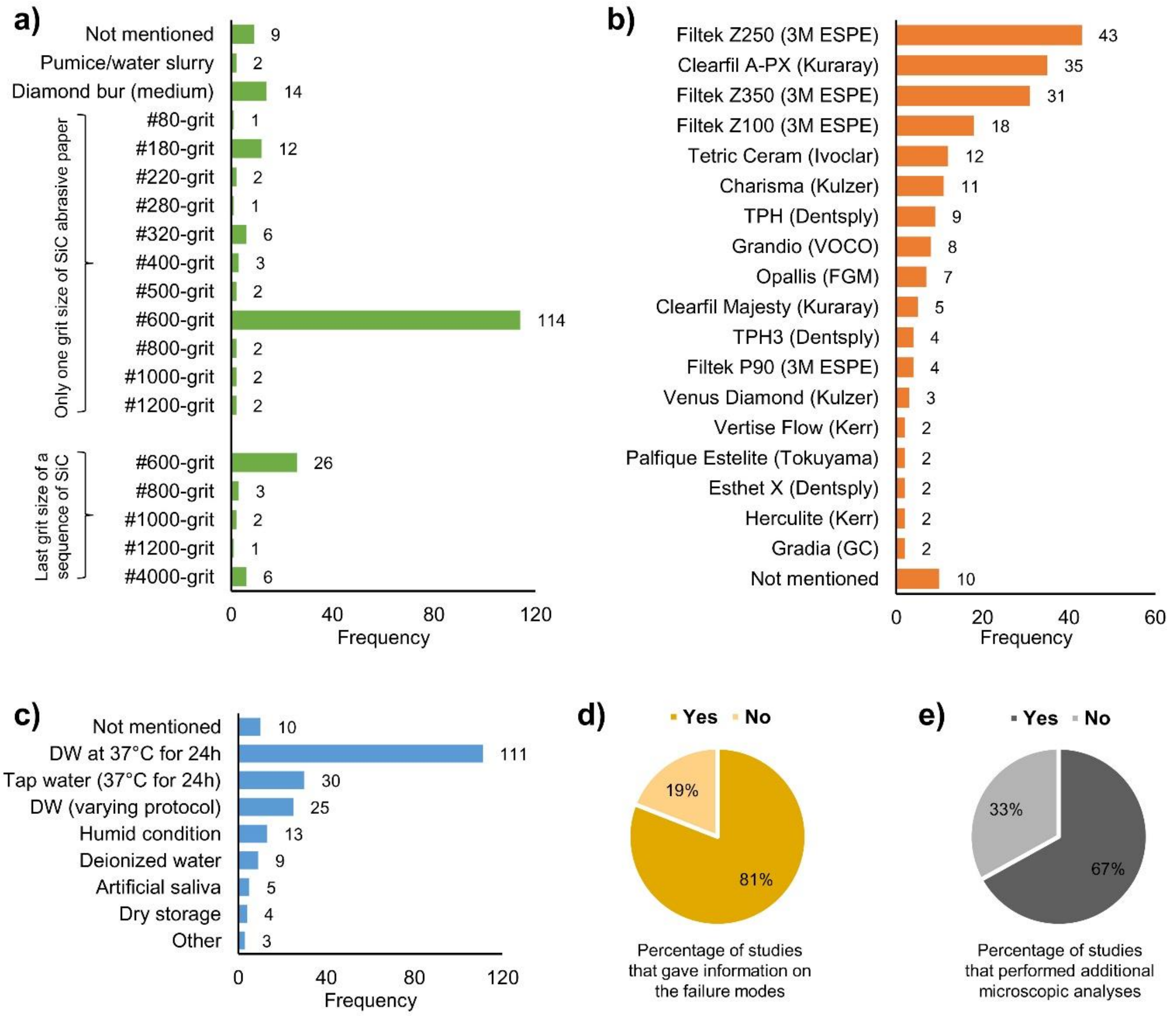
10-MDP (2-steps)	5.68 (2.88; 8.48)	11.89 (6.31; 17.46)	8.85 (5.07; 12.63)	7.20 (0.16; 14.25)	10.51 (8.63; 12.39)
4.93 (2.42; 7.43)	**10-MDP-free (2-steps)**	7.47 (0.72; 14.22)	4.68 (-2.04; 11.39)	9.03 (0.94; 17.12)	4.36 (-0.13; 8.86)
6.95 (3.67; 10.23)	2.02 (-1.63; 5.68)	**10-MDP (universal)**	4.73 (-4.63; 14.10)	2.60 (-1.38; 6.58)	8.64 (4.22; 13.06)
8.58 (5.88; 11.28)	3.66 (0.30; 7.01)	1.63 (-2.20; 5.46)	**10-MDP (1-step)**	-2.00 (-19.49; 15.49)	3.02 (0.27; 5.77)
9.15 (4.98; 13.32)	4.22 (-0.20; 8.65)	2.20 (-1.45; 5.85)	0.57 (-4.09; 5.22)	**10-MDP-free (universal)**	11.40 (-4.62; 27.42)
11.32 (9.55; 13.08)	6.39 (3.65; 9.13)	4.37 (1.11; 7.62)	2.74 (0.22; 5.25)	2.17 (-2.05; 6.39)	**10-MDP-free (1-step)**

Adhesive groups	MD (95% CI)
Compared with 10-MDP (2-steps)	
10-MDP (1-step)	-4.77 (-7.37, -2.17)
10-MDP (universal)	-6.38 (-10.32, -2.44)
10-MDP-free (1-step)	-5.60 (-7.27, -3.92)
10-MDP-free (2-steps)	-1.05 (-3.31, 1.21)
10-MDP-free (universal)	-7.26 (-12.08, -2.43)

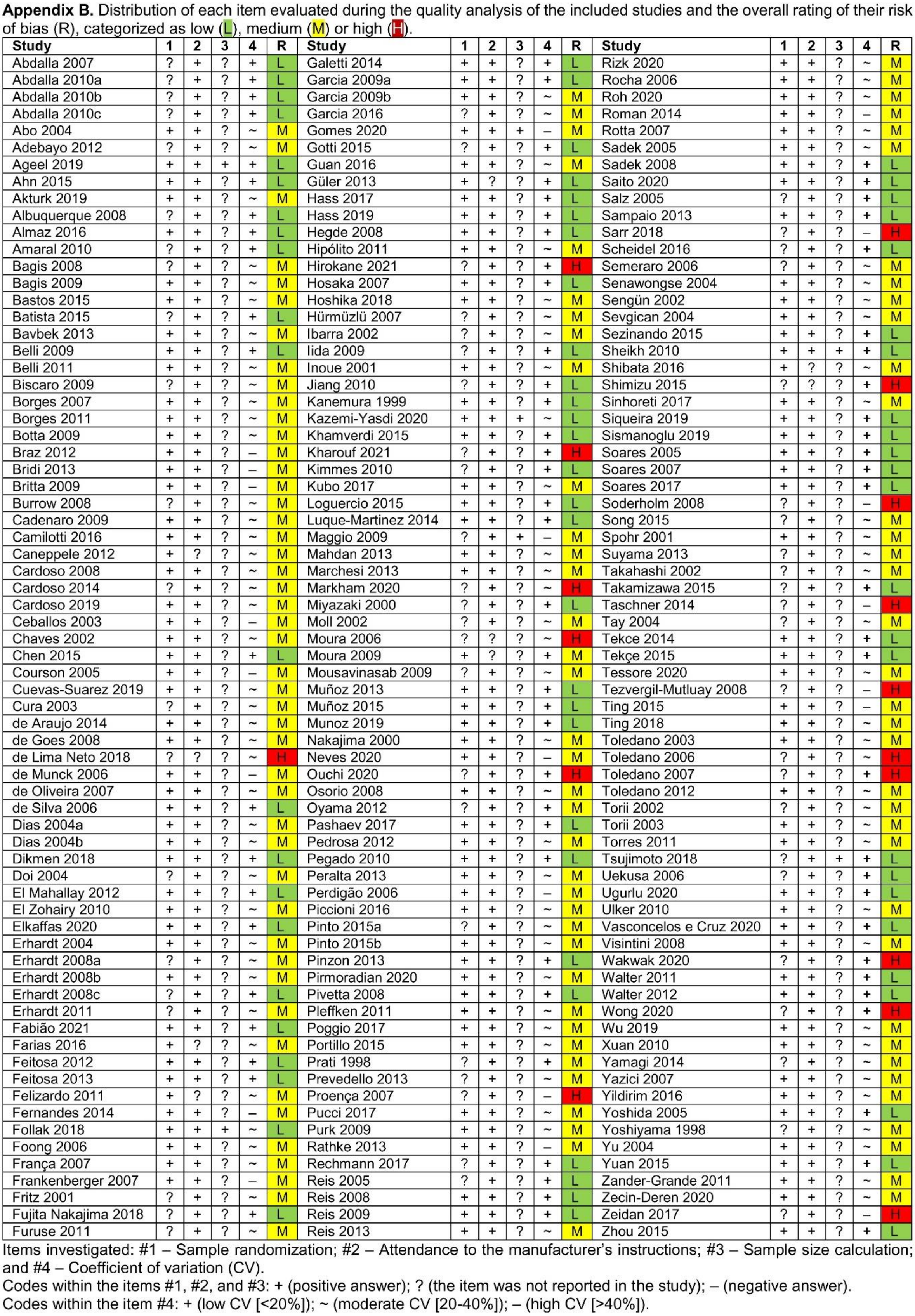
10-MDP (2-steps)	0.72 (-1.85; 3.29)	6.76 (2.53; 11.00)	5.01 (3.24; 6.78)	-	-
0.65 (-1.69; 2.98)	**10-MDP-free (2-steps)**	4.08 (-3.79; 11.94)	4.72 (1.10; 8.35)	7.77 (1.44; 14.10)	6.10 (-3.25; 15.45)
5.19 (2.32; 8.07)	4.55 (1.18; 7.91)	**10-MDP (1-step)**	0.36 (-2.53; 3.25)	2.53 (-4.05; 9.11)	-
5.38 (3.68; 7.08)	4.74 (2.22; 7.25)	0.19 (-2.48; 2.86)	**10-MDP-free (1-step)**	-1.32 (-6.71; 4.07)	-
6.08 (1.99; 10.18)	5.44 (1.36; 9.51)	0.89 (-3.45; 5.23)	0.70 (-3.27; 4.67)	**10-MDP (universal)**	2.26 (-2.30; 6.82)
8.31 (2.62; 13.99)	7.66 (2.06; 13.26)	3.11 (-2.79; 9.02)	2.92 (-2.69; 8.54)	2.22 (-2.21; 6.65)	**10-MDP-free (universal)**

Figure 7. Network meta-analysis comparing bond strengths among 6 adhesive/group arms, in dentin (Panel A) and enamel (Panel B). (a) Network plot where each node indicates a direct comparison [10-MDP (2-steps), 10-MDP (1-step), 10-MDP (universal), 10-MDP-free (2-steps), 10-MDP-free (1-step), and 10-MDP-free (universal)] with connecting lines between nodes representing number of studies making each comparison. (b) Bayesian random effect consistency model forest plot of the pooled effects estimates of bond strengths expressed in mean difference (MD) and respective 95% confidence interval (95% CI) for different adhesive groups compared with 10-MDP (2-steps) – control. (c) League table showing Bayesian comparison of all adhesive pairs: the table displays the results for all adhesive pairs in both the upper (direct comparisons) and lower (indirect comparisons) triangles, but with the comparison switched over; for both above and below the leading diagonal, the results are for the adhesive group at the top of the same column vs. adhesive group at the left hand side of the same row.

Appendices



Appendix A. Graphs showing the list and frequency of (a) the surface treatment protocols performed on dental substrates prior bonding; (b) the resin composites used to prepare the restorations after bonding; (c) the storage protocols applied to the bonded specimens prior bond strength testing; and total amount (%) of studies that performed failure mode (d) and microscopy (e) analyses as additional qualitative measures in the included studies.

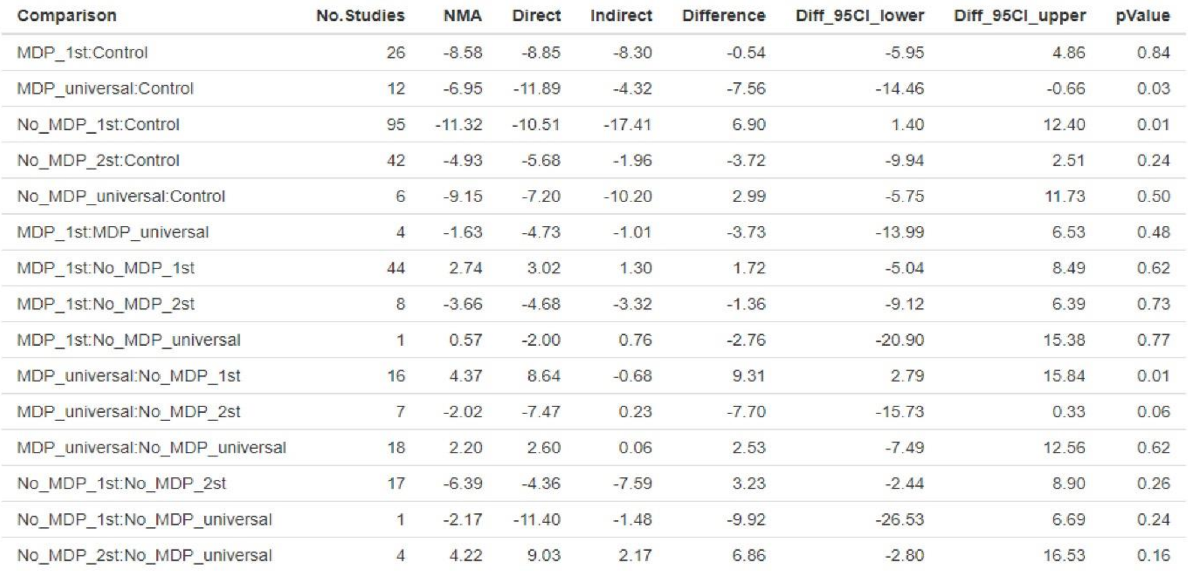


Appendix B. Distribution of each item evaluated during the quality analysis of the included studies and the overall rating of their risk of bias (R), categorized as low (L), medium (M) or high (H).

Study	1	2	3	4	R	Study	1	2	3	4	R	Study	1	2	3	4	R
Abdalla 2007	?	+	?	+	L	Galetti 2014	+	+	?	+	L	Rizk 2020	+	+	?	~	M
Abdalla 2010a	?	+	?	+	L	Garcia 2009a	+	+	?	+	L	Rocha 2006	+	+	?	~	M
Abdalla 2010b	?	+	?	+	L	Garcia 2009b	+	+	?	~	M	Roh 2020	+	+	?	~	M
Abdalla 2010c	?	+	?	+	L	Garcia 2016	?	+	?	~	M	Roman 2014	+	+	?	–	M
Abo 2004	+	+	?	~	M	Gomes 2020	+	+	+	–	M	Rotta 2007	+	+	?	~	M
Adebayo 2012	?	+	?	~	M	Gotti 2015	?	+	?	+	L	Sadek 2005	+	+	?	~	M
Ageel 2019	+	+	+	+	L	Guan 2016	+	+	?	~	M	Sadek 2008	+	+	?	+	L
Ahn 2015	+	+	?	+	L	Güler 2013	+	?	?	+	L	Saito 2020	+	+	?	+	L
Akturk 2019	+	+	?	~	M	Hass 2017	+	+	?	+	L	Salz 2005	?	+	?	+	L
Albuquerque 2008	?	+	?	+	L	Hass 2019	+	+	?	+	L	Sampaio 2013	+	+	?	+	L
Almaz 2016	+	+	?	+	L	Hegde 2008	+	+	?	+	L	Sarr 2018	?	+	?	–	H
Amaral 2010	?	+	?	+	L	Hipólito 2011	+	+	?	~	M	Scheidel 2016	?	+	?	+	L
Bagis 2008	?	+	?	~	M	Hirokane 2021	?	+	?	+	H	Semeraro 2006	?	+	?	~	M
Bagis 2009	+	+	?	~	M	Hosaka 2007	+	+	?	+	L	Senawongse 2004	+	+	?	~	M
Bastos 2015	+	+	?	~	M	Hoshika 2018	+	+	?	~	M	Sengün 2002	+	+	?	~	M
Batista 2015	?	+	?	+	L	Hürmüzlü 2007	?	+	?	~	M	Sevgican 2004	+	+	?	~	M
Bavbek 2013	+	+	?	~	M	Ibarra 2002	?	+	?	~	M	Sezinando 2015	+	+	?	+	L
Belli 2009	+	+	?	+	L	Iida 2009	?	+	?	+	L	Sheikh 2010	+	+	+	+	L
Belli 2011	+	+	?	~	M	Inoue 2001	+	+	?	~	M	Shibata 2016	+	?	?	~	M
Biscaro 2009	?	+	?	~	M	Jiang 2010	?	+	?	+	L	Shimizu 2015	?	?	?	+	H
Borges 2007	+	+	?	~	M	Kanemura 1999	+	+	?	+	L	Sinhoreti 2017	+	+	?	~	M
Borges 2011	+	+	?	~	M	Kazemi-Yasdi 2020	+	+	+	~	L	Siqueira 2019	+	+	?	+	L
Botta 2009	+	+	?	~	M	Khamverdi 2015	+	+	?	+	L	Sismanoglu 2019	+	+	?	+	L
Braz 2012	+	+	?	–	M	Kharouf 2021	?	+	?	+	H	Soares 2005	+	+	?	+	L
Bridi 2013	+	+	?	–	M	Kimmes 2010	?	+	?	+	L	Soares 2007	+	+	?	+	L
Britta 2009	+	+	?	–	M	Kubo 2017	+	+	?	~	M	Soares 2017	+	+	?	+	L
Burrow 2008	?	+	?	~	M	Loguercio 2015	+	+	?	+	L	Soderholm 2008	?	+	?	–	H
Cadenaro 2009	+	+	?	~	M	Luque-Martinez 2014	+	+	?	+	L	Song 2015	?	+	?	~	M
Camilotti 2016	+	+	?	~	M	Maggio 2009	?	+	+	–	M	Spohr 2001	+	+	?	~	M
Caneppele 2012	+	?	?	~	M	Mahdan 2013	+	+	?	~	M	Suyama 2013	?	+	?	~	M
Cardoso 2008	+	+	?	~	M	Marchesi 2013	+	+	?	~	M	Takahashi 2002	?	+	?	~	M
Cardoso 2014	?	+	?	~	M	Markham 2020	?	+	?	~	H	Takamizawa 2015	?	+	?	+	L
Cardoso 2019	+	+	?	~	M	Miyazaki 2000	?	+	?	+	L	Taschner 2014	?	+	?	–	H
Ceballos 2003	+	+	?	–	M	Moll 2002	?	+	?	~	M	Tay 2004	?	+	?	~	M
Chaves 2002	+	+	?	~	M	Moura 2006	?	?	?	~	H	Tekce 2014	+	+	?	+	L
Chen 2015	+	+	?	+	L	Moura 2009	+	?	?	+	M	Tekçe 2015	+	+	?	+	L
Courson 2005	+	+	?	–	M	Mousavinasab 2009	?	+	?	~	M	Tessore 2020	+	+	?	~	M
Cuevas-Suarez 2019	+	+	?	~	M	Muñoz 2013	+	+	?	+	L	Tezvergil-Mutluay 2008	?	+	?	–	H
Cura 2003	?	+	?	~	M	Muñoz 2015	+	+	?	+	L	Ting 2015	+	+	?	–	M
de Araujo 2014	+	+	?	~	M	Munoz 2019	+	+	?	+	L	Ting 2018	+	+	?	~	M
de Goes 2008	+	+	?	~	M	Nakajima 2000	+	+	?	~	M	Toledano 2003	+	+	?	~	M
de Lima Neto 2018	?	?	?	~	H	Neves 2020	+	+	?	–	M	Toledano 2006	?	+	?	~	H
de Munck 2006	+	+	?	–	M	Ouchi 2020	?	+	?	+	H	Toledano 2007	?	+	?	+	H
de Oliveira 2007	+	+	?	~	M	Osorio 2008	+	+	?	~	M	Toledano 2012	+	+	?	~	M
de Silva 2006	+	+	?	+	L	Oyama 2012	?	+	?	+	M	Torii 2002	?	+	?	~	M
Dias 2004a	+	+	?	~	M	Pashaev 2017	+	+	?	+	L	Torii 2003	+	+	?	~	M
Dias 2004b	+	+	?	~	M	Pedrosa 2012	+	+	?	~	M	Torres 2011	+	+	?	~	M
Dikmen 2018	+	+	?	+	L	Pegado 2010	+	+	?	+	L	Tsujimoto 2018	?	+	+	+	L
Doi 2004	?	+	?	~	M	Peralta 2013	+	+	?	~	M	Uekusa 2006	?	+	?	+	L
El Mahallay 2012	+	+	?	+	L	Perdigão 2006	+	+	?	–	M	Ugurlu 2020	+	+	?	+	L
El Zohairy 2010	+	+	?	~	M	Piccioni 2016	+	+	?	~	M	Ulker 2010	+	+	?	~	M
Elkaffas 2020	+	+	?	+	L	Pinto 2015a	?	+	?	~	M	Vasconcelos e Cruz 2020	+	+	?	+	L
Erhardt 2004	+	+	?	~	M	Pinto 2015b	+	+	?	~	M	Visintini 2008	+	+	?	~	M
Erhardt 2008a	?	+	?	~	M	Pinzon 2013	+	+	?	+	L	Wakwak 2020	?	+	?	+	H
Erhardt 2008b	+	+	?	~	M	Pirmoradian 2020	+	+	?	~	M	Walter 2011	+	+	?	+	L
Erhardt 2008c	?	+	?	+	L	Pivetta 2008	+	+	?	+	L	Walter 2012	+	+	?	+	L
Erhardt 2011	?	+	?	~	M	Pleffken 2011	+	+	?	~	M	Wong 2020	?	+	?	+	H
Fabião 2021	+	+	?	+	L	Poggio 2017	+	+	?	~	M	Wu 2019	+	+	?	~	M
Farias 2016	+	?	?	~	M	Portillo 2015	+	+	?	~	M	Xuan 2010	+	+	?	~	M
Feitosa 2012	+	+	?	+	L	Prati 1998	?	+	?	+	M	Yamagi 2014	?	+	?	~	M
Feitosa 2013	+	+	?	+	L	Prevedello 2013	?	+	?	~	M	Yazici 2007	+	+	?	~	M
Felizardo 2011	+	?	?	~	M	Proença 2007	?	+	?	–	H	Yildirim 2016	+	+	?	~	M
Fernandes 2014	+	+	?	–	M	Pucci 2017	+	+	?	~	M	Yoshida 2005	+	+	?	+	L
Follak 2018	+	+	+	~	L	Purk 2009	+	+	?	~	M	Yoshiyama 1998	?	+	?	~	M
Foong 2006	+	+	?	~	M	Rathke 2013	+	+	?	–	M	Yu 2004	+	+	?	~	M
França 2007	+	+	?	~	M	Rechmann 2017	?	+	?	+	L	Yuan 2015	+	+	?	+	L
Frankenberger 2007	+	+	?	–	M	Reis 2005	?	+	?	+	L	Zander-Grande 2011	+	+	?	~	M
Fritz 2001	?	+	?	~	M	Reis 2008	+	+	?	+	L	Zecin-Deren 2020	+	+	?	~	M
Fujita Nakajima 2018	?	+	?	+	L	Reis 2009	+	+	?	+	L	Zeidan 2017	?	+	?	–	H
Furuse 2011	?	+	?	~	M	Reis 2013	+	+	?	~	M	Zhou 2015	+	+	?	+	L

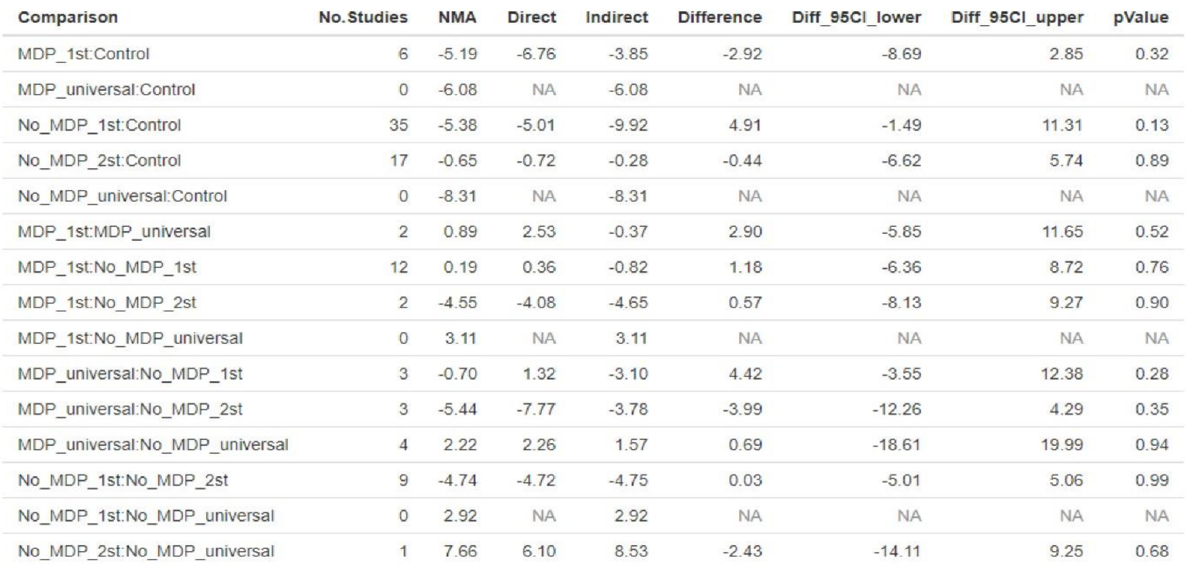
Items investigated: #1 – Sample randomization; #2 – Attendance to the manufacturer's instructions; #3 – Sample size calculation; and #4 – Coefficient of variation (CV).
Codes within the items #1, #2, and #3: + (positive answer); ? (the item was not reported in the study); – (negative answer).
Codes within the item #4: + (low CV [<20%]); ~ (moderate CV [20-40%]); – (high CV [>40%]).

Appendix B. Risk of bias results for each included study of the review.



Comparison	No.Studies	NMA	Direct	Indirect	Difference	Diff_95CI_lower	Diff_95CI_upper	pValue
MDP_1st:Control	26	-8.58	-8.85	-8.30	-0.54	-5.95	4.86	0.84
MDP_universal:Control	12	-6.95	-11.89	-4.32	-7.56	-14.46	-0.66	0.03
No_MDP_1st:Control	95	-11.32	-10.51	-17.41	6.90	1.40	12.40	0.01
No_MDP_2st:Control	42	-4.93	-5.68	-1.96	-3.72	-9.94	2.51	0.24
No_MDP_universal:Control	6	-9.15	-7.20	-10.20	2.99	-5.75	11.73	0.50
MDP_1st:MDP_universal	4	-1.63	-4.73	-1.01	-3.73	-13.99	6.53	0.48
MDP_1st:No_MDP_1st	44	2.74	3.02	1.30	1.72	-5.04	8.49	0.62
MDP_1st:No_MDP_2st	8	-3.66	-4.68	-3.32	-1.36	-9.12	6.39	0.73
MDP_1st:No_MDP_universal	1	0.57	-2.00	0.76	-2.76	-20.90	15.38	0.77
MDP_universal:No_MDP_1st	16	4.37	8.64	-0.68	9.31	2.79	15.84	0.01
MDP_universal:No_MDP_2st	7	-2.02	-7.47	0.23	-7.70	-15.73	0.33	0.06
MDP_universal:No_MDP_universal	18	2.20	2.60	0.06	2.53	-7.49	12.56	0.62
No_MDP_1st:No_MDP_2st	17	-6.39	-4.36	-7.59	3.23	-2.44	8.90	0.26
No_MDP_1st:No_MDP_universal	1	-2.17	-11.40	-1.48	-9.92	-26.53	6.69	0.24
No_MDP_2st:No_MDP_universal	4	4.22	9.03	2.17	6.86	-2.80	16.53	0.16

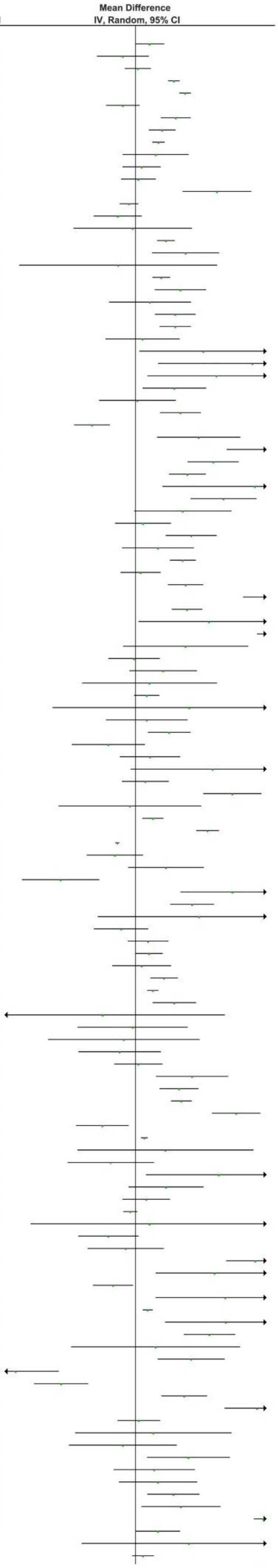
Appendix C. Assessment of inconsistency for all studies included in the review having dentin as the adhesive substrate and the following comparative groups: [10-MDP (2-steps), 10-MDP (1-step), 10-MDP (universal), 10-MDP-free (2-steps), 10-MDP-free (1-step), and 10-MDP-free (universal)].

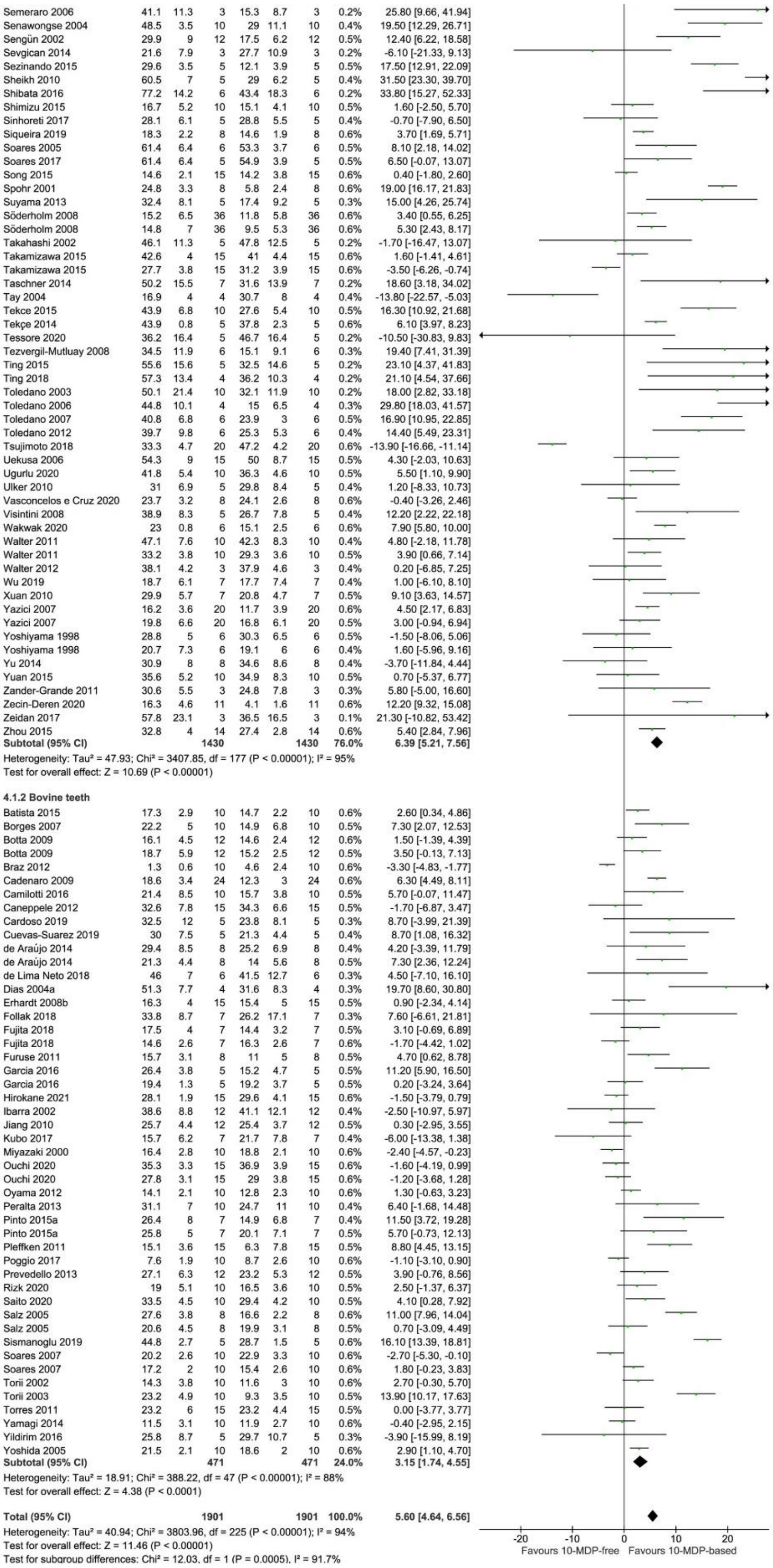


Comparison	No.Studies	NMA	Direct	Indirect	Difference	Diff_95Cl_lower	Diff_95Cl_upper	pValue
MDP_1st:Control	6	-5.19	-6.76	-3.85	-2.92	-8.69	2.85	0.32
MDP_universal:Control	0	-6.08	NA	-6.08	NA	NA	NA	NA
No_MDP_1st:Control	35	-5.38	-5.01	-9.92	4.91	-1.49	11.31	0.13
No_MDP_2st:Control	17	-0.65	-0.72	-0.28	-0.44	-6.62	5.74	0.89
No_MDP_universal:Control	0	-8.31	NA	-8.31	NA	NA	NA	NA
MDP_1st:MDP_universal	2	0.89	2.53	-0.37	2.90	-5.85	11.65	0.52
MDP_1st:No_MDP_1st	12	0.19	0.36	-0.82	1.18	-6.36	8.72	0.76
MDP_1st:No_MDP_2st	2	-4.55	-4.08	-4.65	0.57	-8.13	9.27	0.90
MDP_1st:No_MDP_universal	0	3.11	NA	3.11	NA	NA	NA	NA
MDP_universal:No_MDP_1st	3	-0.70	1.32	-3.10	4.42	-3.55	12.38	0.28
MDP_universal:No_MDP_2st	3	-5.44	-7.77	-3.78	-3.99	-12.26	4.29	0.35
MDP_universal:No_MDP_universal	4	2.22	2.26	1.57	0.69	-18.61	19.99	0.94
No_MDP_1st:No_MDP_2st	9	-4.74	-4.72	-4.75	0.03	-5.01	5.06	0.99
No_MDP_1st:No_MDP_universal	0	2.92	NA	2.92	NA	NA	NA	NA
No_MDP_2st:No_MDP_universal	1	7.66	6.10	8.53	-2.43	-14.11	9.25	0.68

Appendix D. Assessment of inconsistency for all studies included in the review having enamel as the adhesive substrate and the following comparative groups: [10-MDP (2-steps), 10-MDP (1-step), 10-MDP (universal), 10-MDP-free (2-steps), 10-MDP-free (1-step), and 10-MDP-free (universal)].

	10-MDP-based			10-MDP-free				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
4.1.1 Human teeth								
Abdalla 2007	41	3.7	10	38	3.4	10	0.5%	3.00 [-0.11, 6.11]
Abdalla 2010a	35.4	5.1	6	38.1	4.7	6	0.5%	-2.70 [-8.25, 2.85]
Abdalla 2010c	18.5	2.2	6	18	2.7	6	0.6%	0.50 [-2.29, 3.29]
Abo 2004	76.5	1	5	68.3	1	5	0.6%	8.20 [6.96, 9.44]
Abo 2004	35.8	1	5	25.2	1	5	0.6%	10.60 [9.36, 11.84]
Adebayo 2012	14.7	4.9	12	17.4	4	12	0.5%	-2.70 [-6.28, 0.88]
Adebayo 2012	22	4.5	12	13.4	3.4	12	0.5%	8.60 [5.41, 11.79]
Ageel 2019	23.1	2.2	15	17.4	5.2	15	0.6%	5.70 [2.84, 8.56]
Ageel 2019	17.5	2.2	15	12.6	1.4	15	0.6%	4.90 [3.58, 6.22]
Ahn 2015	25.3	4.1	2	21	3	2	0.4%	4.30 [-2.74, 11.34]
Akturk 2019	20.3	5.5	10	19	3.6	10	0.5%	1.30 [-2.77, 5.37]
Albuquerque 2008	27.8	3.6	5	27.2	2.2	5	0.5%	0.60 [-3.10, 4.30]
Albuquerque 2008	29.2	6.8	5	11.8	4.9	5	0.4%	17.40 [10.05, 24.75]
Almaz 2016	11.5	2.6	12	12.9	2.4	12	0.6%	-1.40 [-3.40, 0.60]
Amaral 2010	19.4	4.5	5	23.2	3.8	5	0.5%	-3.80 [-8.96, 1.36]
Bagis 2008	34.7	10.3	6	35.3	12	6	0.3%	-0.60 [-13.25, 12.05]
Bavbek 2013	12.3	1.8	20	5.8	3.9	20	0.6%	6.50 [4.62, 8.38]
Belli 2009	30.5	5	3	19.8	3.9	3	0.4%	10.70 [3.52, 17.88]
Belli 2011	45.1	15	4	48.8	15.5	4	0.2%	-3.70 [-24.84, 17.44]
Biscaro 2009	12.2	2.2	10	6.7	2.1	10	0.6%	5.50 [3.61, 7.39]
Borges 2011	25	3.5	5	15.4	5.2	5	0.5%	9.60 [4.11, 15.09]
Bridi 2013	19.3	8.4	6	16.2	7	6	0.4%	3.10 [-5.65, 11.85]
Burrow 2008	36.8	4.8	15	28.3	7.1	15	0.5%	8.50 [4.16, 12.84]
Burrow 2008	26.5	4.7	15	18	4.7	15	0.5%	8.50 [5.14, 11.86]
Cadenaro 2009	30.5	9.4	10	29	8.7	10	0.4%	1.50 [-6.44, 9.44]
Cardoso 2008	32.4	8.6	4	17.9	11	4	0.3%	14.50 [0.82, 28.18]
Cardoso 2014	69.6	15.5	5	44.6	17	5	0.2%	25.00 [4.84, 45.16]
Ceballos 2003	35.5	11.6	4	18.2	9.6	4	0.2%	17.30 [2.54, 32.06]
Chaves 2002	21.1	4.3	3	12.8	4.2	3	0.5%	8.30 [1.50, 15.10]
Chen 2015	52.7	8.7	10	52.3	10	10	0.4%	0.40 [-7.82, 8.62]
Courson 2005	15.8	6.1	10	6.2	3.5	10	0.5%	9.60 [5.24, 13.96]
Cura 2003	16.2	2.6	10	25.5	5.6	10	0.5%	-9.30 [-13.13, -5.47]
de Goes 2008	32.9	9.3	6	19.4	6.1	6	0.4%	13.50 [4.60, 22.40]
de Munck 2006	41.3	8.4	3	7.2	9.8	3	0.2%	34.10 [19.49, 48.71]
de Oliveira 2007	41.5	2.9	5	24.9	5.5	5	0.5%	16.60 [11.15, 22.05]
de Silva 2006	24.9	3.9	5	13.8	2.2	5	0.5%	11.10 [7.18, 15.02]
Dias 2004b	59.3	12.4	3	33.8	12.3	3	0.2%	25.50 [5.74, 45.26]
Dikmen 2018	39.5	5.2	4	20.7	5	4	0.4%	18.80 [11.73, 25.87]
Doi 2004	41.2	10	5	31.1	6.4	5	0.3%	10.10 [-0.31, 20.51]
El Mahallay 2012	35.4	5.1	5	33.8	4.5	5	0.5%	1.60 [-4.36, 7.56]
El Zohairy 2010	27.5	3.4	6	15.6	5.9	6	0.5%	11.90 [6.45, 17.35]
El Zohairy 2010	21.2	7.3	5	16.4	4.9	5	0.4%	4.80 [-2.91, 12.51]
Elkaffas 2020	21.8	4	10	11.7	2	10	0.6%	10.10 [7.33, 12.87]
Erhardt 2004	17.2	6.8	12	16.1	3.3	12	0.5%	1.10 [-3.18, 5.38]
Erhardt 2004	19.2	4.5	12	8.5	4.9	12	0.5%	10.70 [6.94, 14.46]
Erhardt 2008a	44	12.2	5	8.8	6.7	5	0.3%	35.20 [23.00, 47.40]
Erhardt 2008c	39.2	5.2	24	28.2	6.3	24	0.5%	11.00 [7.73, 14.27]
Erhardt 2011	44.1	12.2	3	28.4	5.3	3	0.2%	15.70 [0.65, 30.75]
Fabião 2021	61.2	9.5	4	23.2	7.8	4	0.3%	38.00 [25.95, 50.05]
Farias 2016	45.9	6.9	5	35.2	13.6	5	0.3%	10.70 [-2.67, 24.07]
Feitosa 2013	41.4	3.9	5	41.7	4.9	5	0.5%	-0.30 [-5.79, 5.19]
Felizardo 2011	28.6	7	5	22.7	4.3	5	0.4%	5.90 [-1.30, 13.10]
Fernandes 2014	19.4	7.2	6	16.4	16.5	6	0.3%	3.00 [-11.40, 17.40]
Foong 2006	15.3	3.8	14	12.9	3.5	14	0.6%	2.40 [-0.31, 5.11]
Frankenberger 2007	45.4	15.4	2	33.9	14.4	2	0.1%	11.50 [-17.72, 40.72]
França 2007	31.8	7.5	6	29.4	7.9	6	0.4%	2.40 [-6.32, 11.12]
Fritz 2001	23.9	5.8	10	16.7	4.5	10	0.5%	7.20 [2.65, 11.75]
Galleti 2014	36.6	7.1	6	42.4	6.7	6	0.4%	-5.80 [-13.61, 2.01]
Garcia 2009a	32.3	5.4	5	29.2	5	5	0.5%	3.10 [-3.35, 9.55]
Garcia 2009b	47.1	1.4	2	30.6	12.6	2	0.2%	16.50 [-1.07, 34.07]
Gomes 2020	14.9	7.1	15	12.8	6.9	15	0.5%	2.10 [-2.91, 7.11]
Gotti 2015	69	4.1	6	48.3	6.6	6	0.5%	20.70 [14.48, 26.92]
Guan 2016	63.1	15.5	8	64.3	15.6	8	0.2%	-1.20 [-16.44, 14.04]
Hass 2017	15.2	3.8	12	11.5	1.1	12	0.6%	3.70 [1.46, 5.94]
Hass 2019	46.9	2.9	10	31.5	2.6	10	0.6%	15.40 [12.99, 17.81]
Hegde 2008	21	0.8	20	24.9	0.6	20	0.6%	-3.90 [-4.34, -3.46]
Hipólito 2011	17.9	3.1	4	22.3	5.3	4	0.5%	-4.40 [-10.42, 1.62]
Hosaka 2007	41.8	8.4	5	35.3	3.8	5	0.4%	6.50 [-1.58, 14.58]
Hoshika 2018	16.7	7.1	5	32.7	6.2	5	0.4%	-16.00 [-24.26, -7.74]
Hurmuzlu 2007	42.8	10	4	22.1	5.3	4	0.3%	20.70 [9.61, 31.79]
Iida 2009	46.3	4.4	5	34.2	3	5	0.5%	12.10 [7.43, 16.77]
Inoue 2001	46.5	15	3	32.9	11.9	3	0.1%	13.60 [-8.07, 35.27]
Kanemura 1999	28.4	4.1	5	31.5	5.2	5	0.5%	-3.10 [-8.90, 2.70]
Kazemi-Yasdi 2020	18	5.5	16	15.3	6.9	16	0.5%	2.70 [-1.62, 7.02]
Kharouf 2021	18.5	4.6	15	15.6	3.5	15	0.6%	2.90 [-0.03, 5.83]
Kimmes 2010	36.6	7.8	10	35.3	6.5	10	0.5%	1.30 [-4.99, 7.59]
Kimmes 2010	33.9	3.2	10	27.8	3.5	10	0.6%	6.10 [3.16, 9.04]
Loguercio 2015	19.5	1.7	16	15.8	1.8	16	0.6%	3.70 [2.49, 4.91]
Luque-Martinez 2014	27.2	4.6	5	18.9	2.6	5	0.5%	8.30 [3.67, 12.93]
Maggio 2009	43.5	16.3	5	50.5	24.9	5	0.1%	-7.00 [-33.09, 19.09]
Mahdan 2013	37.6	7.6	4	38.2	9.3	4	0.3%	-0.60 [-12.37, 11.17]
Marchesi 2013	37.7	12.4	5	40.2	13.7	5	0.2%	-2.50 [-18.70, 13.70]
Markham 2020	27.7	10.2	15	31.1	14.1	15	0.4%	-3.40 [-12.21, 5.41]
Markham 2020	28.6	7.2	15	28	7.2	15	0.5%	0.60 [-4.55, 5.75]
Moll 2002	22.2	8.3	5	10.1	2.9	5	0.4%	12.10 [4.39, 19.81]
Moura 2006	18.7	4.6	6	9.4	2.4	6	0.5%	9.30 [5.15, 13.45]
Moura 2009	22.7	1.8	6	12.9	2.1	6	0.6%	9.80 [7.59, 12.01]
Mousavinasab 2009	33.3	5.8	8	11.8	4.7	8	0.5%	21.50 [16.33, 26.67]
Muñoz 2015	32.4	3.9	5	39.5	5.1	5	0.5%	-7.10 [-12.73, -1.47]
Muñoz 2019	20.2	1.1	20	18.3	1.2	20	0.6%	1.90 [1.19, 2.61]
Nakajima 2000	43.2	14.8	4	36.8	12.2	4	0.2%	6.40 [-12.40, 25.20]
Neves 2019	11.5	10	9	16.8	10	9	0.4%	-5.30 [-14.54, 3.94]
Osorio 2008	40.2	8	2	22.4	7.9	2	0.2%	17.80 [2.22, 33.38]
Pashaev 2017	35.4	5.5	5	28.9	7.3	5	0.4%	6.50 [-1.51, 14.51]
Pedrosa 2012	20.1	6.5	10	17.8	5	10	0.5%	2.30 [-2.78, 7.38]
Pegado 2010	17.7	1.7	8	18.8	1.3	8	0.6%	-1.10 [-2.58, 0.38]
Perdigão 2006	39.5	16.4	4	36.5	20.1	4	0.1%	3.00 [-22.42, 28.42]
Piccioni 2016	15.1	7	9	20.9	7	9	0.5%	-5.80 [-12.27, 0.67]
Pinto 2015b	27.9	8.5	5	30	3.7	5	0.4%	-2.10 [-10.23, 6.03]
Pinzon 2013	50.6	4.6	3	25	3	3	0.5%	25.60 [19.39, 31.81]
Pirmoradian 2020	50	11.6	5	33.1	8.5	5	0.3%	16.90 [4.29, 29.51]
Pivetta 2008	20.3	4.2	6	25.1	3.3	6	0.5%	-4.80 [-9.07, -0.53]
Portillo 2015	43.3	10.9	3	24.1	7.4	3	0.2%	19.20 [4.29, 34.11]
Prati 1998	14.3	1	12	11.7	1.6	12	0.6%	2.60 [1.53, 3.67]
Proença 2007	42.7	10.7	6	23.4	12.2	6	0.3%	19.30 [6.32, 32.28]
Pucci 2017	34.2	7.9	10	18.4	4	10	0.5%	15.80 [10.31, 21.29]
Purk 2009	59.3	16.6	6	55	15.3	6	0.2%	4.30 [-13.76, 22.36]
Rathke 2013	20.5	9.9	10	8.6	6	10	0.4%	11.90 [4.73, 19.07]
Rechmann 2017	33.2	3.6	6	58.8	10.9	6	0.4%	-25.60 [-34.79, -16.41]
Rechmann 2017	15.6	3.9	6	31.5	6.1	6	0.5%	-15.90 [-21.69, -10.11]
Reis 2005	40.6	4.7	6	30.2	3.9	6	0.5%	10.40 [5.51, 15.29]
Reis 2008	54.2	4.4	4	28.2	5.6	4	0.4%	26.00 [19.02, 32.98]
Reis 2009	22	3.2	6	21.3	4.7	6	0.5%	0.70 [-3.85, 5.25]
Reis 2013	31.6	8.6	3	27.8	12	3	0.2%	3.80 [-12.91, 20.51]
Reis 2013	17.6	6.9	3	20.3	7.5	3	0.3%	-2.70 [-14.23, 8.83]
Rocha 2006	28.5	7	4	17.2	5.7	4	0.4%	11.30 [2.45, 20.15]
Roh 2020	25	12.5	10	21	6.3	10	0.4%	4.00 [-4.68, 12.68]
Roman 2014	17.1	6.9	5	12.3	6.6	5	0.4%	4.80 [-3.57, 13.17]
Rotta 2007	15	6.5	6	6.9	2.5	6	0.5%	8.10 [2.53, 13.67]
Sadek 2005	40.4	2.6	3	30.7	7	3	0.4%	9.70 [1.25, 18.15]
Sadek 2008	53.3	2.9	10	26	1.5	10	0.6%	27.30 [25.28, 29.32]
Sampaio 2013	34.3	3.5	5	29.5	4.1	5	0.5%	4.80 [0.07, 9.53]
Sarr 2018	31.8	15.1	3	20.4	13.5	3	0.1%	11.40 [-11.52, 34.32]
Scheidel 2016	42.6	4	25	41	4.4	25	0.6%	1.60 [-0.73, 3.93]





Semeraro 2006	41.1	11.3	3	15.3	8.7	3	0.2%	25.80 [9.66, 41.94]
Senawongse 2004	48.5	3.5	10	29	11.1	10	0.4%	19.50 [12.29, 26.71]
Sengün 2002	29.9	9	12	17.5	6.2	12	0.5%	12.40 [6.22, 18.58]
Sevgican 2014	21.6	7.9	3	27.7	10.9	3	0.2%	-6.10 [-21.33, 9.13]
Sezinando 2015	29.6	3.5	5	12.1	3.9	5	0.5%	17.50 [12.91, 22.09]
Sheikh 2010	60.5	7	5	29	6.2	5	0.4%	31.50 [23.30, 39.70]
Shibata 2016	77.2	14.2	6	43.4	18.3	6	0.2%	33.80 [15.27, 52.33]
Shimizu 2015	16.7	5.2	10	15.1	4.1	10	0.5%	1.60 [-2.50, 5.70]
Sinhoreti 2017	28.1	6.1	5	28.8	5.5	5	0.4%	-0.70 [-7.90, 6.50]
Siqueira 2019	18.3	2.2	8	14.6	1.9	8	0.6%	3.70 [1.69, 5.71]
Soares 2005	61.4	6.4	6	53.3	3.7	6	0.5%	8.10 [2.18, 14.02]
Soares 2017	61.4	6.4	5	54.9	3.9	5	0.5%	6.50 [-0.07, 13.07]
Song 2015	14.6	2.1	15	14.2	3.8	15	0.6%	0.40 [-1.80, 2.60]
Spohr 2001	24.8	3.3	8	5.8	2.4	8	0.6%	19.00 [16.17, 21.83]
Suyama 2013	32.4	8.1	5	17.4	9.2	5	0.3%	15.00 [4.26, 25.74]
Söderholm 2008	15.2	6.5	36	11.8	5.8	36	0.6%	3.40 [0.55, 6.25]
Söderholm 2008	14.8	7	36	9.5	5.3	36	0.6%	5.30 [2.43, 8.17]
Takahashi 2002	46.1	11.3	5	47.8	12.5	5	0.2%	-1.70 [-16.47, 13.07]
Takamizawa 2015	42.6	4	15	41	4.4	15	0.6%	1.60 [-1.41, 4.61]
Takamizawa 2015	27.7	3.8	15	31.2	3.9	15	0.6%	-3.50 [-6.26, -0.74]
Taschner 2014	50.2	15.5	7	31.6	13.9	7	0.2%	18.60 [3.18, 34.02]
Tay 2004	16.9	4	4	30.7	8	4	0.4%	-13.80 [-22.57, -5.03]
Tekce 2015	43.9	6.8	10	27.6	5.4	10	0.5%	16.30 [10.92, 21.68]
Tekçe 2014	43.9	0.8	5	37.8	2.3	5	0.6%	6.10 [3.97, 8.23]
Tessore 2020	36.2	16.4	5	46.7	16.4	5	0.2%	-10.50 [-30.83, 9.83]
Tezvergil-Mutluay 2008	34.5	11.9	6	15.1	9.1	6	0.3%	19.40 [7.41, 31.39]
Ting 2015	55.6	15.6	5	32.5	14.6	5	0.2%	23.10 [4.37, 41.83]
Ting 2018	57.3	13.4	4	36.2	10.3	4	0.2%	21.10 [4.54, 37.66]
Toledano 2003	50.1	21.4	10	32.1	11.9	10	0.2%	18.00 [2.82, 33.18]
Toledano 2006	44.8	10.1	4	15	6.5	4	0.3%	29.80 [18.03, 41.57]
Toledano 2007	40.8	6.8	6	23.9	3	6	0.5%	16.90 [10.95, 22.85]
Toledano 2012	39.7	9.8	6	25.3	5.3	6	0.4%	14.40 [5.49, 23.31]
Tsujimoto 2018	33.3	4.7	20	47.2	4.2	20	0.6%	-13.90 [-16.66, -11.14]
Uekusa 2006	54.3	9	15	50	8.7	15	0.5%	4.30 [-2.03, 10.63]
Ugurlu 2020	41.8	5.4	10	36.3	4.6	10	0.5%	5.50 [1.10, 9.90]
Ulker 2010	31	6.9	5	29.8	8.4	5	0.4%	1.20 [-8.33, 10.73]
Vasconcelos e Cruz 2020	23.7	3.2	8	24.1	2.6	8	0.6%	-0.40 [-3.26, 2.46]
Visintini 2008	38.9	8.3	5	26.7	7.8	5	0.4%	12.20 [2.22, 22.18]
Wakwak 2020	23	0.8	6	15.1	2.5	6	0.6%	7.90 [5.80, 10.00]
Walter 2011	47.1	7.6	10	42.3	8.3	10	0.4%	4.80 [-2.18, 11.78]
Walter 2011	33.2	3.8	10	29.3	3.6	10	0.5%	3.90 [0.66, 7.14]
Walter 2012	38.1	4.2	3	37.9	4.6	3	0.4%	0.20 [-6.85, 7.25]
Wu 2019	18.7	6.1	7	17.7	7.4	7	0.4%	1.00 [-6.10, 8.10]
Xuan 2010	29.9	5.7	7	20.8	4.7	7	0.5%	9.10 [3.63, 14.57]
Yazici 2007	16.2	3.6	20	11.7	3.9	20	0.6%	4.50 [2.17, 6.83]
Yazici 2007	19.8	6.6	20	16.8	6.1	20	0.5%	3.00 [-0.94, 6.94]
Yoshiyama 1998	28.8	5	6	30.3	6.5	6	0.5%	-1.50 [-8.06, 5.06]
Yoshiyama 1998	20.7	7.3	6	19.1	6	6	0.4%	1.60 [-5.96, 9.16]
Yu 2014	30.9	8	8	34.6	8.6	8	0.4%	-3.70 [-11.84, 4.44]
Yuan 2015	35.6	5.2	10	34.9	8.3	10	0.5%	0.70 [-5.37, 6.77]
Zander-Grande 2011	30.6	5.5	3	24.8	7.8	3	0.3%	5.80 [-5.00, 16.60]
Zecin-Deren 2020	16.3	4.6	11	4.1	1.6	11	0.6%	12.20 [9.32, 15.08]
Zeidan 2017	57.8	23.1	3	36.5	16.5	3	0.1%	21.30 [-10.82, 53.42]
Zhou 2015	32.8	4	14	27.4	2.8	14	0.6%	5.40 [2.84, 7.96]
Subtotal (95% CI)			**1430**			**1430**	**76.0%**	**6.39 [5.21, 7.56]**

Heterogeneity: Tau² = 47.93; Chi² = 3407.85, df = 177 (P < 0.00001); I² = 95%
Test for overall effect: Z = 10.69 (P < 0.00001)

4.1.2 Bovine teeth

Batista 2015	17.3	2.9	10	14.7	2.2	10	0.6%	2.60 [0.34, 4.86]
Borges 2007	22.2	5	10	14.9	6.8	10	0.5%	7.30 [2.07, 12.53]
Botta 2009	16.1	4.5	12	14.6	2.4	12	0.6%	1.50 [-1.39, 4.39]
Botta 2009	18.7	5.9	12	15.2	2.5	12	0.5%	3.50 [-0.13, 7.13]
Braz 2012	1.3	0.6	10	4.6	2.4	10	0.6%	-3.30 [-4.83, -1.77]
Cadenaro 2009	18.6	3.4	24	12.3	3	24	0.6%	6.30 [4.49, 8.11]
Camilotti 2016	21.4	8.5	10	15.7	3.8	10	0.5%	5.70 [-0.07, 11.47]
Caneppele 2012	32.6	7.8	15	34.3	6.6	15	0.5%	-1.70 [-6.87, 3.47]
Cardoso 2019	32.5	12	5	23.8	8.1	5	0.3%	8.70 [-3.99, 21.39]
Cuevas-Suarez 2019	30	7.5	5	21.3	4.4	5	0.4%	8.70 [1.08, 16.32]
de Araújo 2014	29.4	8.5	8	25.2	6.9	8	0.4%	4.20 [-3.39, 11.79]
de Araújo 2014	21.3	4.4	8	14	5.6	8	0.5%	7.30 [2.36, 12.24]
de Lima Neto 2018	46	7	6	41.5	12.7	6	0.3%	4.50 [-7.10, 16.10]
Dias 2004a	51.3	7.7	4	31.6	8.3	4	0.3%	19.70 [8.60, 30.80]
Erhardt 2008b	16.3	4	15	15.4	5	15	0.5%	0.90 [-2.34, 4.14]
Follak 2018	33.8	8.7	7	26.2	17.1	7	0.3%	7.60 [-6.61, 21.81]
Fujita 2018	17.5	4	7	14.4	3.2	7	0.5%	3.10 [-0.69, 6.89]
Fujita 2018	14.6	2.6	7	16.3	2.6	7	0.6%	-1.70 [-4.42, 1.02]
Furuse 2011	15.7	3.1	8	11	5	8	0.5%	4.70 [0.62, 8.78]
Garcia 2016	26.4	3.8	5	15.2	4.7	5	0.5%	11.20 [5.90, 16.50]
Garcia 2016	19.4	1.3	5	19.2	3.7	5	0.5%	0.20 [-3.24, 3.64]
Hirokane 2021	28.1	1.9	15	29.6	4.1	15	0.6%	-1.50 [-3.79, 0.79]
Ibarra 2002	38.6	8.8	12	41.1	12.1	12	0.4%	-2.50 [-10.97, 5.97]
Jiang 2010	25.7	4.4	12	25.4	3.7	12	0.5%	0.30 [-2.95, 3.55]
Kubo 2017	15.7	6.2	7	21.7	7.8	7	0.4%	-6.00 [-13.38, 1.38]
Miyazaki 2000	16.4	2.8	10	18.8	2.1	10	0.6%	-2.40 [-4.57, -0.23]
Ouchi 2020	35.3	3.3	15	36.9	3.9	15	0.6%	-1.60 [-4.19, 0.99]
Ouchi 2020	27.8	3.1	15	29	3.8	15	0.6%	-1.20 [-3.68, 1.28]
Oyama 2012	14.1	2.1	10	12.8	2.3	10	0.6%	1.30 [-0.63, 3.23]
Peralta 2013	31.1	7	10	24.7	11	10	0.4%	6.40 [-1.68, 14.48]
Pinto 2015a	26.4	8	7	14.9	6.8	7	0.4%	11.50 [3.72, 19.28]
Pinto 2015a	25.8	5	7	20.1	7.1	7	0.5%	5.70 [-0.73, 12.13]
Pleffken 2011	15.1	3.6	15	6.3	7.8	15	0.5%	8.80 [4.45, 13.15]
Poggio 2017	7.6	1.9	10	8.7	2.6	10	0.6%	-1.10 [-3.10, 0.90]
Prevedello 2013	27.1	6.3	12	23.2	5.3	12	0.5%	3.90 [-0.76, 8.56]
Rizk 2020	19	5.1	10	16.5	3.6	10	0.5%	2.50 [-1.37, 6.37]
Saito 2020	33.5	4.5	10	29.4	4.2	10	0.5%	4.10 [0.28, 7.92]
Salz 2005	27.6	3.8	8	16.6	2.2	8	0.6%	11.00 [7.96, 14.04]
Salz 2005	20.6	4.5	8	19.9	3.1	8	0.5%	0.70 [-3.09, 4.49]
Sismanoglu 2019	44.8	2.7	5	28.7	1.5	5	0.6%	16.10 [13.39, 18.81]
Soares 2007	20.2	2.6	10	22.9	3.3	10	0.6%	-2.70 [-5.30, -0.10]
Soares 2007	17.2	2	10	15.4	2.6	10	0.6%	1.80 [-0.23, 3.83]
Torii 2002	14.3	3.8	10	11.6	3	10	0.6%	2.70 [-0.30, 5.70]
Torii 2003	23.2	4.9	10	9.3	3.5	10	0.5%	13.90 [10.17, 17.63]
Torres 2011	23.2	6	15	23.2	4.4	15	0.5%	0.00 [-3.77, 3.77]
Yamagi 2014	11.5	3.1	10	11.9	2.7	10	0.6%	-0.40 [-2.95, 2.15]
Yildirim 2016	25.8	8.7	5	29.7	10.7	5	0.3%	-3.90 [-15.99, 8.19]
Yoshida 2005	21.5	2.1	10	18.6	2	10	0.6%	2.90 [1.10, 4.70]
Subtotal (95% CI)			**471**			**471**	**24.0%**	**3.15 [1.74, 4.55]**

Heterogeneity: Tau² = 18.91; Chi² = 388.22, df = 47 (P < 0.00001); I² = 88%
Test for overall effect: Z = 4.38 (P < 0.0001)

Total (95% CI)			**1901**			**1901**	**100.0%**	**5.60 [4.64, 6.56]**

Heterogeneity: Tau² = 40.94; Chi² = 3803.96, df = 225 (P < 0.00001); I² = 94%
Test for overall effect: Z = 11.46 (P < 0.00001)
Test for subgroup differences: Chi² = 12.03, df = 1 (P = 0.0005), I² = 91.7%

Appendix E. Summary of meta-analysis findings (forest plot) comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives in dentin/enamel of human or bovine teeth. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).

2.2 ARTIGO II

Can self-etch adhesive systems containing 10-MDP result in more stable dental bonds than 10-MDP-free counterparts? A network meta-analysis review study

Short title. *Bonding stability of self-etch adhesive systems*

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Keywords: Dental bonding; Functional acidic monomer; Universal adhesives; Dentin; Enamel

Abstract

Objectives: This review aimed to evaluate the long-term bond strength of self-etch (SE) adhesives containing 10-MDP (control) or other acidic monomers.

Data: This report is registered at OSF (osf.io/urtdf) and it followed the PRISMA Statement. In total, 72/76 studies were included for meta-analysis.

Sources: Two reviewers conducted a literature search (30 September 2021) in PubMed, Web of Science, and Scopus.

Study selection: The articles should have evaluated bond strength data of aged samples bonded to sound dentin/enamel and using different SE adhesives, with at least one group based on 10-MDP and other on alternative acidic composition. Statistical analyses were carried out with RevMan 5.3.5 and Bayesian network meta-analysis.

Results: In total, 15/56 adhesive systems were based on 10-MDP. Most groups of adhesives demonstrated a similar bonding stability as compared with the control ($p \geq 0.07$), although the presence of 10-MDP resulted in greater resistance to degradation than, 4-META, sulfonic acid, unspecified phosphates, or mixed monomers ($p \leq 0.04$). Overall, the dental bonds were benefited from the presence of 10-MDP upon longer periods of aging (> 6 months). Adhesives based on 10-MDP ranked better in dentin after wet storage than the other compositions, whereas adhesives with mixed composition ranked as the worst materials. In enamel, adhesives containing carboxylic acid or sulfonic acid resulted in less stable dental bonds than the control.

Conclusion: The presence of 10-MDP in SE adhesives has an overall positive effect in the durability of resin/enamel-dentin bonds after aging, although the aging condition and duration influenced on the bond strength results.

Clinical significance. The acidic composition of self-etch adhesives affects the durability of dental bonds after simulated aging, with 10-MDP showing an overall better performance than other compositions. However, while adhesives based on phosphonic acids ranked better upon thermal-cycling, cyclic-loading and mixed aging conditions, 10-MDP-based adhesives resisted better to wet storage.

1. Introduction

Self-etch (SE) adhesive systems are more user-friendly than the etch-and-rinse systems, reducing the chances for errors during the operative procedure,[1, 2] thus representing a class of bonding agents with great importance in dental restoration. Notably, SE adhesives offer exceptional bonding potential to dentin substrate, although their performance is directly dependent on compositional factors, especially with regards to the type of the acidic functional monomer, which is the very ingredient responsible for the adhesion mechanism consisting of substrate demineralization, surface wetting and chemical bonding to hydroxyapatite crystals.[1] Several acidic monomers are commonly used in the formulation of SE adhesives, deriving from phosphoric acids as well as from other acidic functionalities (e.g., carboxylic acids, sulfonic acids, and phosphonic acids) or a mixture of distinct moieties.[3]

There are some inherent characteristics that may directly influence on the bonding potential of acidic monomers to the tooth, including the length of spacer chain, the etching capacity, pH, hydrophilicity, and the ability of the monomer to form stable calcium salts with the substrate.[4] The resin monomer 10-methacryloyloxy-decyl-dihydrogen-phosphate (10-MDP) is considered the gold standard in adhesive dentistry, and it has been broadly used in the formulation of contemporary SE systems.[5] According to a recent review study by Fehrenbach et al.,[3] the presence of 10-MDP demonstrated an overall superior bonding performance than the presence of alternative acidic monomers. However, the latter study considered only bond strength data obtained at the immediate moment, and to the best of our knowledge, there is no previous study that revised the literature on the effects of 10-MDP at the longer-term and considering the results after simulated aging, thereby deserving a careful revision on the topic.

According to some previous studies,[6-8] the main failures that may result in the replacement of composite resin restorations consist of marginal staining, debonding of the restoration, and secondary caries, which are all related to the quality of the adhesive interface created during the application of bonding agents.[9] Indeed, the quality and the stability of resin-dentin/enamel bonds may be compromised over time due to several processes such as the enzymatic degradation of the collagen fibrils found within the hybrid layer,[10, 11] the hydrolytic degradation of the adhesive components,[12] and due to mechanical fatigue and the constant temperature change (i.e., thermal shocking) typical of the oral environment.[13] In light to simulate these different adverse scenarios, several *in vitro* tests have been proposed, with the wet storage representing the most frequently used in laboratory research. Storage in distilled water, artificial saliva or even into organic solutions like sodium hypochlorite can all accelerate hydrolysis of the adhesive interface.[14] Concerning thermal-cycling, this method can stimulate hydrolysis of the hybrid layer due to the repeated application of hot and cold water, inducing repetitive contraction/expansion stress at the adhesive interface.[15] Last, cyclic loading applies mechanical stresses at the bonded restoration, causing fatigue in the same fashion to the masticatory forces created during oral function.[16]

In summary, the effects of different aging conditions on the stability of dental bonds created with SE adhesives is an interesting topic that may contribute to the better understanding of the bonding potential of these adhesives over time. Moreover, the role of 10-MDP as the main acidic ingredient and its relation to the aging condition of bonded restorations is still poorly understood, needing investigation. Hence, this study aimed to conduct a systematic review with meta-analysis to elucidate on the bonding stability of self-etch adhesive systems with varying acidic composition.

2. Materials and Methods

A protocol of this review was registered at the Open Science Framework (osf.io/urtdf) and this report followed the directions of the PRISMA Statement.[17] The research question was "Can self-etch adhesive systems containing 10-MDP result in more stable dental bonds than 10-MDP-free counterparts? A network meta-analysis review study".

2.1 Literature search

The search strategy was created using *Medical Subject Heading* (MeSH) terms and free terms found in articles of the research topic (**Table 1**), in accordance with each database. The search was performed by two independent reviewers (J.F. and E.A.M), in the following electronic databases: PubMed/MEDLINE, Scopus and ISI Web of Science. Also, the reviewers carried out a hand-search in the reference list of included studies to identify further articles. The search in the gray literature was not performed in this review.

2.2 Eligibility criteria

The present review included only *in vitro* studies, which analyzed immediate and long-term bond strength data of commercial SE adhesives containing 10-MDP and with different acidic compositions. To be included, the articles should have evaluated bond strength data using the microtensile, microshear, shear or tensile mechanical methods; to have at least one group of adhesives containing 10-MDP and at least another group containing a distinct acidic composition (i.e., alternative monomer); and to have used only sound dentin and enamel substrates (from human or bovine origin) for bonding. The exclusion criteria were as follow: studies evaluating the bonding potential of adhesives to caries-affected dentin, to primary teeth, and to substrates such as composite resin, dental ceramics and metals. Articles that reported on bond strength data involving orthodontic brackets or that used experimental adhesives were also excluded, as well as those that presented immediate bond strength data only without aging.

2.3 Study selection and data extraction

The retrieved references were imported into software EndNoteX9 (Thomson Reuters), where the duplicates were removed. In sequence, the screening of titles and abstracts was performed according to the eligibility criteria by two independent reviewers (J.F. and E.A.M). In case of disagreement, the reviewers discussed until reaching consensus. After the selection process, the relevant data from each study were extracted and tabulated using Microsoft Office Excel 2013 spreadsheets (Microsoft Corporation, Redmont, WA, USA). The following data was extracted: the first author, year of publication, the type of substrate, the surface treatment performed prior adhesive application, the bond strength test, the adhesive systems allocated according to their acidic composition (10-MDP or other functional monomers), the immediate and the long-term bond strength data (mean and standard deviation/SD values), the number of specimens used in each group tested, and the type and duration of the aging process. Partially missing data were retrieved by contacting the corresponding author of the study via e-mail; only two attempts were made with a one-month space duration.

2.4 Quality assessment

The quality analysis was performed by two independent reviewers (L.S.M. and L.L.M.) using a pre-established methodology,[18] evaluating the following parameters: (i) sample randomization, (ii) application of materials following the manufacturer's directions of use, (iii) sample size calculation, and (iv) the coefficient of variation (CV) of the bond strength data. For the CV criteria, the study was categorized as having low CV (<20%), medium CV (20-40%) or high CV (>40%). The articles that reported on only one of the three former items were classified as having a high risk of bias, regardless of the CV category; when they reported on two or three items combined with a medium or high CV, the article was classified as having a moderate risk of bias; last, the reporting of two or three items combined with a low CV was used to classify the study as having a low risk of bias.[3]

2.5 Statistical analysis

The bond strength values derived from the aged samples of included studies were used for meta-analysis. The analysis was carried out using two statistical methods: standard pairwise meta-analysis (SMA) and network meta-analysis (NMA). For both methods, superiority was defined if the groups comprised of the alternative acidic monomer(s) resulted in significantly higher bond strength than the groups based on 10-MDP (control).

The SMA was performed in Review Manager version 3.5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) using the Inverse Variance method, a random-effects model, and having the mean difference (MD) estimate with 95% confidence interval (95% CI). Two sets of meta-analyses were performed allocating studies according to the acidic composition (phosphoric acid-derived, carboxylic acid-derived, phosphonic acid-derived, sulfonic acid-derived, or mixed composition) and the total period of aging (3, 6, 12 or 24 months). Subgroup analyses were also conducted by grouping studies according to the type of acidic monomer, when applicable.

The NMA was performed in MetaInsight V3 tool[19] using Bayesian random effects models and a Markov chain Monte Carlo simulation with 20,000 iterations for adaptation.[20] Convergence was assessed by trace plots and inconsistency by split node method.[21] After inspection for transitivity and statistical inconsistency, the networks were constructed by plotting different treatments (as nodes) and comparisons (as edges) and having the effect size measure estimated as mean difference (MD) with 95% credible intervals (95% Crl). The baseline treatment consisted of 10-MDP group, which was compared to the other treatments allocated by the acidic composition. Four independent analyses were conducted with values collected from dentin substrate, which were allocated according to the method of aging (wet storage, thermal-cycling, cyclic-loading, or mixed aging). For data collected from enamel substrate, only one analysis was conducted, which estimated the relative ranking of each treatment to be the best, so all combinations were ranked according to their probability of having the highest versus the lowest values.[22]

3. Results

3.1 Search strategy

A total of 4870 potentially relevant records were identified in the search strategy. After duplicates removal, 1982 records were screened by their titles and abstracts, and 1 new record was identified from the reference lists of 133 articles accessed during full-text analysis. In total, 58 studies were excluded due to eligibility criteria (Supplementary Table – **S1**). Seventy-six studies were included in this review for quality analysis.[23-98] Four studies were excluded from meta-analysis due to the unavailability of any data,[58] the existence of only pooled data,[24] the existence of only shelf-life data,[34] and the use of a non-standardized protocol during the aging of the samples.[74] The meta-analysis was conducted with 72 studies in total.[23, 25-33, 35-57, 59-73, 75-98] The flowchart summarizing the article selection process according to the PRISMA 2020 Statement is shown in **Fig. 1**.

3.2 Descriptive analysis

The studies included in the review were published between 2005 and 2021. The bond strength test mostly reported was the microtensile (82.9%), followed by shear (13.2%) and microshear (3.9%) tests. Human dentin was more frequently used (72.5%), followed by human enamel (15%) and bovine dentin (12.5%); three studies investigated both the dentin and enamel substrates.[23, 81, 89] Concerning the surface treatment applied to dentin/enamel prior bonding, the majority of studies used a #600-grit SiC abrasive paper (47.4%) or a sequence of SiC grits (18.4%); the other studies used distinct methods, including the application of diamond burs of medium, fine or extra-fine grit size (13.2%), other SiC grits (#60-, #180-, #320-, #400, #620- or #4000-grit), or the study did not report on the surface treatment protocol (5.3%). From the list of resin composites used to restore the tooth samples, Filtek Z250 (3M ESPE) was the most frequently employed (26.3%). The other restorative materials were purchased from the following industries: 3M ESPE (Filtek Z350, Filtek Z100, Valux Plus), Kuraray (Clearfil AP-X), Ivoclar-Vivadent (Tetric Ceram, Tetric N-Ceram Bulk Fill), Kulzer (Charisma), Dentsply (TPH3, TPH Spectrum), FGM (Opallis), VOCO (GrandioSO), Kerr (Herculite XRV Ultra), and Itena Clinical (Reflectys). Two studies used several types of resin composites,[58, 62] whereas only one study did not report on the restorative material that was used.[84]

The adhesive systems reported in this review are listed in **Fig. 2**. Clearfil SE Bond (Kuraray) was the material most frequently tested (68.4%). Other 14 adhesives based on 10-MDP were also reported in the studies: three from Kuraray (Clearfil S3 Bond, Clearfil Universal, and Clearfil Protect), two from GC (G-Bond and G-Premio Bond), two from Ivoclar-Vivadent (Tetric N-Bond Universal and AdheSE Universal), one from 3M ESPE (Scotchbond Universal), one from Bisco (All Bond Universal), one from Dentsply (Prime&Bond Active), one from Coltene (OneCoat7 Universal), one from Itena Clinical (Iperbond Max), one from VOCO (Futurabond M+), and one from FGM (Ambar Universal). The other bonding agents (41 in total) were based on different acidic ingredients, which were derived from phosphoric acids (Optibond All-In-One, Optibond XTR, Prime&Bond Elect, Adper SE Plus, Bond Force, AdheSE ONE, Xeno IV, Go!, Futurabond M, Optibond Versa, Optibond Universal, and Xeno III), carboxylic acids (iBond, Adper Easy One, G-aenial Bond, Peak Universal, AQ Bond, Bond-1 SF, Imperva Fluorobond, Hybrid Bond, Mac-Bond II, iBond Universal, Brush&Bond, and Unifil Bond), sulfonic acids (Tyrian SPE), phosphonic acids (AdheSE), varying acidic monomers with mixed composition (Adper Prompt L-Pop, One Up Bond F, Adper Easy Bond, G-Bond Plus, Xeno V, AdheSE One F, Absolute, and Beautibond Multi), or an unknown acidic composition (Optibond Solo Plus, Futurabond, Futurabond Universal, Iperbond Ultra, Futurabond NR, Ybond Universal, and Solist).

3.3 Risk of bias

According to the parameters considered in the analysis of bias (**Fig. 3**), most of studies randomized the samples prior bonding (67.1%) and attended to the manufacturer's instructions during the application of the bonding agents (98.7%). In terms of sample size calculation, this information was not mentioned in most of studies (94.7%). Overall, the studies included in the review were classified as having moderate risk of bias (39.5%), followed by low (35.5%) and high (25%) risk of bias (Supplementary Table – **S2**).

3.4 Meta-analyses

A global meta-analysis was not performed since the collected data varied in terms of the type of substrate, the type of the bond strength test, the composition of adhesives, the method used during aging of samples, as well as regarding the total period used during aging. Thus, subgroup analyses were conducted allocating studies with similar characteristics and using up to two analytical methods: standard meta-analysis (SMA) and network meta-analysis (NMA).

Concerning the SMA findings, two sets of analyses were conducted. The first considered the acidic composition and the type of acidic monomer of adhesives as the main variable factor, which results are shown in Supplementary Figures – **S3**, **S4**, **S5**, **S6** and **S7**. The dental bonds created using 10-MDP-free adhesives were more negatively affected after aging as compared to the control, although this effect relied on the main acidic composition of the bonding agent. A statistically lower dental bond was verified when adhesives based on unspecified phosphate resin monomers, 4-META, sulfonic acids, or a mixed acidic composition were applied to dentin/enamel ($p \leq 0.04$). Conversely, the bonds created with adhesives containing phosphonic acids, polyacrylic acids or phosphate monomers such as GPDM, PENTA, MHP, and acrylamide phosphates, were reduced similarly to the bonds obtained with the application of 10-MDP-based adhesives ($p \geq 0.07$). Heterogeneity ranged from low ($I^2 = 5\%$) to high ($I^2 = 96\%$) in this set of analyses. The second set of the SMA considered the total period of aging as the main variable factor, and the results are presented in Supplementary Figure – **S8**. Overall, aging for up to 3 months did not result in significant differences between the two groups of adhesive systems (alternative monomers vs. 10-MDP; $p=0.17$), although at longer periods of aging, the dental bonds created under the presence of 10-MDP were higher than that obtained with the application of 10-MDP-free adhesives ($p \leq 0.003$). Heterogeneity ranged from low ($I^2 = 0\%$) to high ($I^2 = 95\%$) in this set of analysis.

The results from the NMA were separated according to the type of substrate (dentin or enamel) and the method used during aging. In dentin (**Fig. 4**), the aging method most frequently reported was wet storage, followed by thermal-cycling, cyclic-loading, or a combination of the latter methods (mixed aging). Wet storage reduced more significantly the resin-dentin bonds created with phosphonic acid-derived adhesives (MD -31.5, 95% CrI -45.8, -17.5) or those based on phosphoric acids (MD -8.76, 95% CrI -12.8, -4.73), mixed acidic monomers (MD -11.8, 95% CrI -15.8, -7.84) or an unknown composition (MD -8.11, 95% CrI -15.7, -0.586), as compared with 10-MDP group (**Fig. 4 – images b**). Thermal-cycling affected more intensively the bonds created with adhesives of mixed composition (MD -8.84, 95% CrI -15.7, -2.17), whereas cyclic-loading and mixed aging influenced similarly the resin-dentin bonds when comparing both groups of adhesives between each other. Adhesives containing 10-MDP ranked as best dentin bonding agents upon wet storage conditions (**Fig. 4 – images c**). On the other hand, adhesives based on phosphonic acids ranked better than the others upon thermal-cycling, cyclic-loading and mixed aging conditions. Overall, adhesives containing mixed acidic ingredients ranked as the worst bonding agents regardless of the aging method.

Considering the NMA findings obtained in enamel, which results are shown in **Fig. 5**, aging affected similarly the resin-enamel bonds regardless of the acidic composition of adhesives (**Fig. 5b**). Adhesives based on phosphonic acids, 10-MDP or a mixture of acidic ingredients ranked slightly better than the other compositions (**Fig. 5c**), especially for the sulfonic acid-derived adhesives, which tended to be the worst options to resist the effects of aging. Overall, adhesive systems containing 10-MDP can resist bond degradation better than carboxylic acid-derived (MD 3.68, 95% CrI 0.3, 7.1) and sulfonic acid-derived (MD 7.52, 95% CrI 1.7, 13.4) systems (**Fig. 5d**).

4. Discussion

The positive role of 10-MDP in the immediate bond strength of SE adhesives to dentin has been already demonstrated elsewhere,[3] but to the best of our knowledge, its effects on the long-term adhesion to dentin and enamel has never been revised, becoming the purpose of this review. It is well known that the dental bonds tested in *in vitro* studies are highly influenced by several factors, including but not limited to the type and origin of the substrate, the acidic composition and pH of adhesives, the application category of the system, and the type of mechanical method used during testing.[3] However, considering that most of the analyzed data in this review consisted of human dentin samples tested with the microtensile bond strength method, we focused the analyses on factors such as the acidic composition of materials and the method and duration of the aging process.

Only four acidic compositions showed a lower ability to resist bond degradation as compared with 10-MDP: the groups based on (i) unspecified phosphate monomers, (ii) 4-META, (iii) sulfonic acids, and (iv) a mixture of distinct functional monomers. Resin monomers derived from phosphoric acids are important ingredients used in the formulation of SE adhesives,[2] but without knowing exactly the molecular structure of the monomer turns it difficult to properly understand on the bonding durability potential of the materials after aging. According to the study by Fehrenbach et al.,[3] it was revealed that while some types of phosphate monomers may perform similarly or better than 10-MDP at the immediate moment (i.e., after minor wet storage – up to 24 h), other phosphoric acid-derived monomers may result in lower bonding potential to dentin. Of note, characteristics such as the length of spacer chains, hydrophilicity, and the total amount of functional moieties of the acidic monomer, can influence on the adhesion-decalcification process,[4] which is crucial for a stable hybridization between resinous materials and the tooth. While at the one hand it is a benefiting right of the manufacturer to keep the compositional information of adhesives secret from the dental community, at the other hand it may prevent the complete understanding of which aspects could be influencing on the higher bond degradation suffered by the adhesives categorized into the unspecified phosphate monomers subgroup.

Fortunately, we can suggest more clear explanations concerning to the other acidic ingredients. 4-META is a carboxylic acid-derived monomer that contains two carboxylic groups in each molecule, rendering this monomer the ability to form Ca salts with hydroxyapatite crystals. However, 4-META is more hydrophilic than 10-MDP,[4] increasing the etching ability of the adhesive and making the decalcification process more prone to occur, prevailing over the adhesion process, and ultimately decreasing the formation of stable Ca salts.[99] Regarding the other acidic monomers that resulted in less stable dental bonds over time, both groups ("sulfonic acid" and "mixed composition") consist of highly acidic adhesives. Besides, sulfonic acids may result in higher amounts of protons while in solution,[100] presenting one of the greatest etching aggressiveness among SE formulations.[101, 102] Similarly, adhesives based on a mixture of acidic resin monomers are hydrophilic in nature and they may display a more acidic behavior, reaching pH values as low as the etchants used during the application of etch-and-rinse systems (i.e., 37% phosphoric acid).[2] Within this scenario, dentin may get extensively etched, leaving areas poorly infiltrated by the resinous monomers, so hydrolysis is more feasible to occur, inducing to bond strength degradation. Worth mentioning, adhesives of mixed composition are typically formulated with phosphoric acid- and carboxylic acid-derived monomers,[3] especially phosphate esters and 4-META, reinforcing the idea that the foregoing monomers contribute to the formation of less durable bonds, at least having 10-MDP as the main comparator.

The ability of 10-MDP to form a water-insoluble 10-MDP-Ca salt with the mineral phase of the tooth has been already demonstrated. First, 10-MDP possesses an etching ability that dissolves dentin at the nano extent, so only minor Ca^{+2} ions are released from the hydroxyapatite crystals. Second, the less acidic behavior of 10-MDP (i.e., mild acidity) allows chemical bonding to the superficial Ca^{+2} ions of the substrate, resulting in the formation of 10-MDP-Ca salts. The combination of the foregoing events is recognized as a nano-layering mechanism that contributes for the excellent bonding performance of 10-MDP-based adhesives.[103] Nonetheless, hydrolytic degradation is not always prevented upon the presence of 10-MDP since other factors rather than hydrolysis can also explain the reduction of dental bonds. For instance, enzymatic-driven degradation caused by matrix metalloproteinases (MMPs) and endogenous cathepsins is an additional reason affecting the stability of the adhesive interface.[10] Despite their significant contribution to the loss of adhesiveness, the latter enzymes are more involved in collagen degradation, which is not the focus of this review, so we concentrated our results on the hydrolysis-driven degradation at the adhesive layer.

The storage time was a significant factor influencing the effects of the adhesive interfaces investigated in this review. At shorter periods of aging (e.g., 3 months) there was not any significant difference between adhesives regardless of the presence of 10-MDP, whereas adhesives based on 10-MDP resisted better after long-term aging. Overall, the hydrolytic degradation of dental bonds depends on the hydrophilic components of the adhesive, which are more prone to undergo the negative effects of hydrolysis than the hydrophobic counterparts. We can suggest that the better resistance associated to the presence of 10-MDP was due to its structural characteristics and the adequate balance between hydrophilic and hydrophobic functionalities.[4, 8] 10-MDP has a long spacer chain separating the polymerizable moiety to the acidic phosphate group, conferring hydrophobicity to its molecule and ultimately a lower susceptibility to undergo hydrolysis. It is also noteworthy that the hybrid layers created with adhesives based on monomers with distinct structure and functionalities to 10-MDP (e.g., carboxylic acids), may suffer more negatively from the enzymatic-driven degradation, as demonstrated elsewhere,[104] in which water was revealed as a critical factor for the activation of bound MMPs, so hydrophilic adhesives can accelerate hydrolysis in a faster fashion than upon the use of more equilibrated adhesives. More importantly, 10-MDP is a unique monomer capable of keeping collagen fibrils protected by hydroxyapatite crystals during adhesive application, probably due to its mild etching aggressiveness,[103] thereby allowing the formation of more stable bonds over time. Despite all the foregoing discussion, it is important to highlight that *in vitro* aging of adhesive interfaces may underestimate the *in vivo* durability of bonded restorations,[105, 106] so the results of this review should be interpreted with caution.

As verified from the data collected in this review, there are several methods used by researchers to simulate the aging of resin-dentin and resin-enamel bonds, so the studies were grouped according to their similar aging condition. Considering dentin, it was possible to observe that the reduction in the bond strength results was more intense for some acidic compositions when the wet storage was used as main aging condition. Of note, the presence of 10-MDP contributed to stronger dental bonds than the groups based on phosphate monomers, mixed composition, or phosphonic acids. Storage in water or other humid conditions (i.e., artificial saliva, tap water) was the method most commonly used for the aging of samples, probably due to its easiness and confirmed effects in the degradation of dental bonds. Comparing the 10-MDP group to the phosphoric acid counterpart, it is unanimous to admit that from the list of different phosphate-based monomers used in SE formulations, the 10-MDP is the gold standard. Notwithstanding, it should be mentioned that from the review study by Fehrenbach et al.,[3] GPDM phosphate monomer contributed to improved immediate dental bonds than 10-MDP, so the mechanisms involved in the hydrolytic degradation of adhesives seems to depend largely on the acidic composition factor, with minor differences between the resin monomers playing a significant role on their overall dental bonding potential.

Regarding the comparisons made with the mixed group, it is already understood that bonding agents comprised of a mixture of distinct acidic monomers are highly acidic, so they are more aggressive in terms of dentin etching, perhaps reducing the possibility to create stable chemical bonding to hydroxyapatite crystals during hybridization.[3] This idea is reinforced by the ranking probability graph shown in **Fig. 4c**, in which the bonding agents containing mixed composition ranked mostly as the worst options, especially after thermal-cycling, cyclic-loading and mixed aging conditions, indicating their less feasible composition to resist bond strength degradation. Last, phosphonic acids have been used in adhesive dentistry since they may show a superior hydrolytic stability than other contemporary monomers,[101] but as verified in the network meta-analysis, the dental bonds created using phosphonic acid-based adhesives were considerably affected by wet storage, resulting in nearly 31.5 MPa (95% Crl 17.5, 45.8) lower bond strengths than the control. Chemically speaking, phosphonic acids possess a ligand characteristic that undergoes ionization in water, forming oxygen anions that could contribute to the chemical bonding to dentin.[107, 108] This is indeed corroborated at the immediate testing condition, in which adhesives based on this type of monomer resulted in similar resin-dentin bonds as compared with 10-MDP.[3] However, at the long-term analysis demonstrated here, we can infer that something related to the chemistry of phosphonic acids may suffer more intensively from direct water aging, perhaps a consequence of their acidic functionality which differs from phosphate-based monomers. While phosphoric acids have a phosphate moiety containing three hydroxyls per molecule, phosphonic acids have only two hydroxyls connected to the phosphate group and a pendant linkage commonly replaced with amino groups, so it is possible to infer that the presence of the latter can intensify water-driven hydrolysis. In addition to the lower dental bonds verified for the phosphonic acid group, the cumulative probability analysis has also confirmed that this very group ranked as the worst option of bonding agent under the circumstances of wet aging. This topic should be further investigated in future studies, aiming to better understand on the higher susceptibility of this class of adhesives to suffer from hydrolysis.

Considering the other aging methods tested in this review, it was possible to observe that there were not considerable differences among the groups for the thermal-cycling, cyclic-loading and mixed aging methods. In enamel, we could not perform a subgroup analysis having the aging condition as main variable due to a lower amount of data testing different aging methods on enamel, warranting further studies that investigate the durability of SE adhesives on this substrate. Despite all aging methods tested here consisted of a wet storage protocol (i.e., in all methods the bonded samples were immersed into a humid environment), there are some peculiarities of each test. In cyclic-loading tests, specimens are subjected to mechanical stress aiming to lead to material fatigue, leading to failure through cracks, scratches and cracks that will cause fracture. In thermal-cycling aging, the samples are submerged in intermittent baths with varying temperature (5ºC and 55ºC), causing thermal shocks at the adhesive interface, leading to thermal expansion of the different materials of the restorative complex, causing stress and perhaps leading to failures in the hybrid and adhesive layers.

Last, the network meta-analysis performed only with enamel data revealed that there was no statistical difference between the monomers of different derivations, but the ranking probability of being the best material suggests that the compositions based on 10-MDP are more likely to create more stable dental bonds. Despite the higher ability of some phosphate esters and 4-META to dissociate into H^+ ions, showing greater etching potential to enamel (i.e., an essential aspect to increase mechanical interlocking and the formation of stronger resin tags), the foregoing compositions tended to undergo more degradation of the resin-enamel bonds after aging as compared with 10-MDP. This may be explained since 10-MDP possesses a high affinity with the mineral phase of the tooth, forming stable 10-MDP-Ca salts that chemically bond to dentin/enamel, favoring bond stability. The same trend does not seem feasible to occur upon the presence of 4-META and other phosphate monomers.

From the results evidenced in the present study, it is possible to observe that the storage in water demonstrated a more effective and more sensitive method for aging restorations made with self-etching adhesives. The thermal and mechanical cycling does not seem to have a significant effect on the durability of dental bonds, but it was not possible to perform the analysis according to the number of cycles performed because there were not sufficient studies to run the analyses. Therefore, it is essential that other studies are designed to evaluate the possible effects of different aging methods and protocols on the bonding stability of SE adhesives to dentin and enamel.

Conclusion

From the results evidenced in the present study, it was possible to conclude that 10-MDP has an important effect on the adhesive durability while using self-etching adhesives in dentin. Aging affects differently the resin-dentin bonds, depending on the method used to simulate the hydrolytic degradation of adhesive interfaces. In enamel, 10-MDP does not seem to have a significant effect on long-term results, showing similar bonding stability as compared with other alternative acidic monomers.

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Tables

Table 1. Search strategy and final search date for the electronic databases.

Database	Final searches	Search strategy
MEDLINE/PubMed	September 30th 2021	(bond strength OR aging OR bond durability OR long-term OR water storage OR thermal-cycling) AND (dentin OR enamel OR tooth) AND (self-etch adhesive OR universal adhesive OR acidic monomer OR functional monomer)
Scopus	September 30th 2021	"bond strength" OR "aging" OR "bond durability" OR "long-term" OR "water storage" OR "thermal-cycling" AND "dentin" OR "enamel" OR "tooth" AND "self-etch adhesive" OR "universal adhesive" OR "acidic monomer" OR "functional monomer"
Web of Science	September 30th 2021	("bond strength" OR “aging” OR “bond durability” OR “long-term” OR “water storage” OR “thermal-cycling”) AND (“dentin” OR “enamel” OR “tooth”) AND (“self-etch adhesive” OR “universal adhesive” OR “acidic monomer” OR “functional monomer”)

Figures

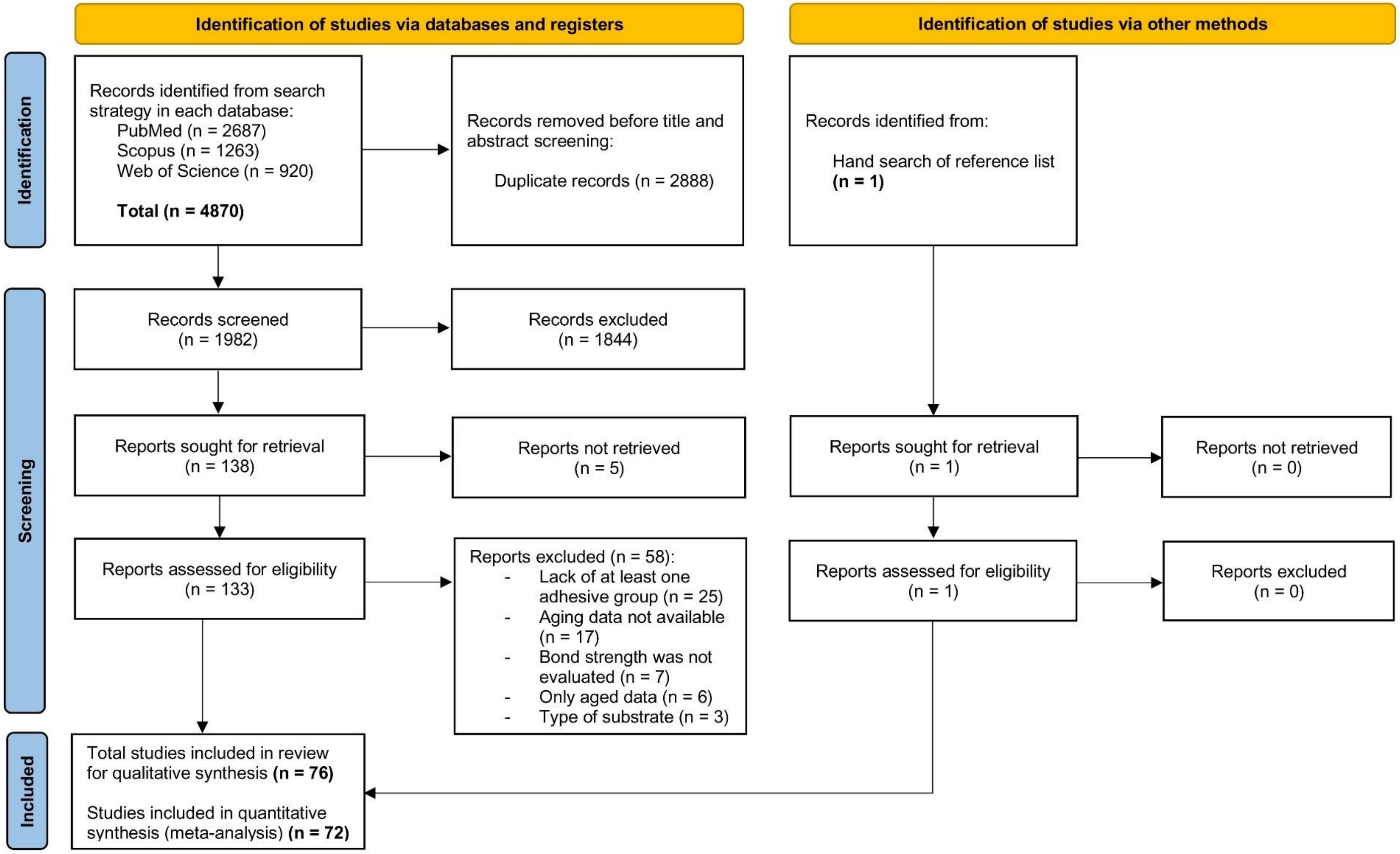
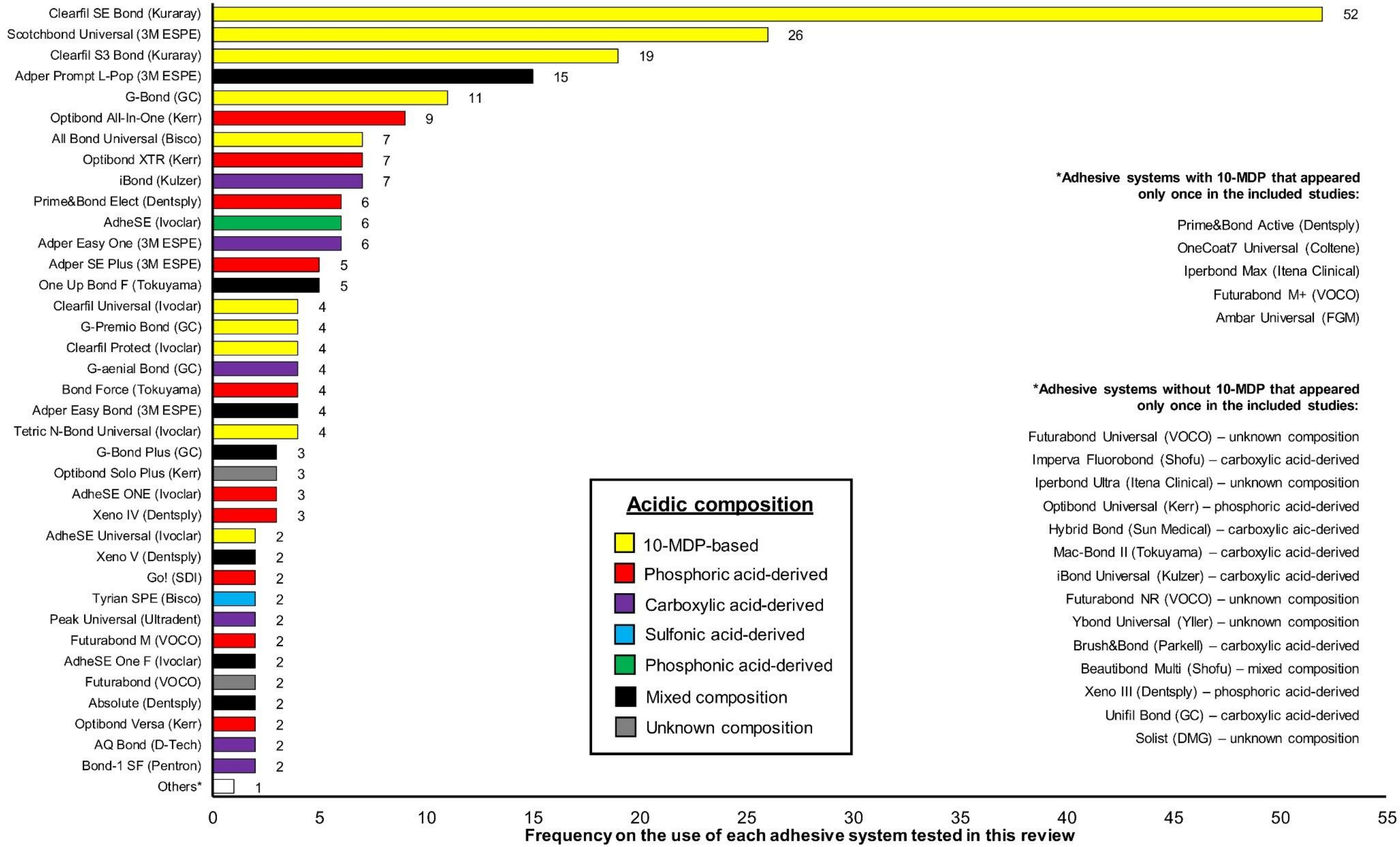


Figure 1. Search flowchart of the study selection according to the PRISMA statement.



***Adhesive systems with 10-MDP that appeared only once in the included studies:**

Prime&Bond Active (Dentsply)
OneCoat7 Universal (Coltene)
Iperbond Max (Itena Clinical)
Futurabond M+ (VOCO)
Ambar Universal (FGM)

***Adhesive systems without 10-MDP that appeared only once in the included studies:**

Futurabond Universal (VOCO) – unknown composition
Imperva Fluorobond (Shofu) – carboxylic acid-derived
Iperbond Ultra (Itena Clinical) – unknown composition
Optibond Universal (Kerr) – phosphoric acid-derived
Hybrid Bond (Sun Medical) – carboxylic aic-derived
Mac-Bond II (Tokuyama) – carboxylic acid-derived
iBond Universal (Kulzer) – carboxylic acid-derived
Futurabond NR (VOCO) – unknown composition
Ybond Universal (Yller) – unknown composition
Brush&Bond (Parkell) – carboxylic acid-derived
Beautibond Multi (Shofu) – mixed composition
Xeno III (Dentsply) – phosphoric acid-derived
Unifil Bond (GC) – carboxylic acid-derived
Solist (DMG) – unknown composition

Figure 2. Graph showing the list and frequency of adhesive systems used in the included studies, allocated by the acidic composition.

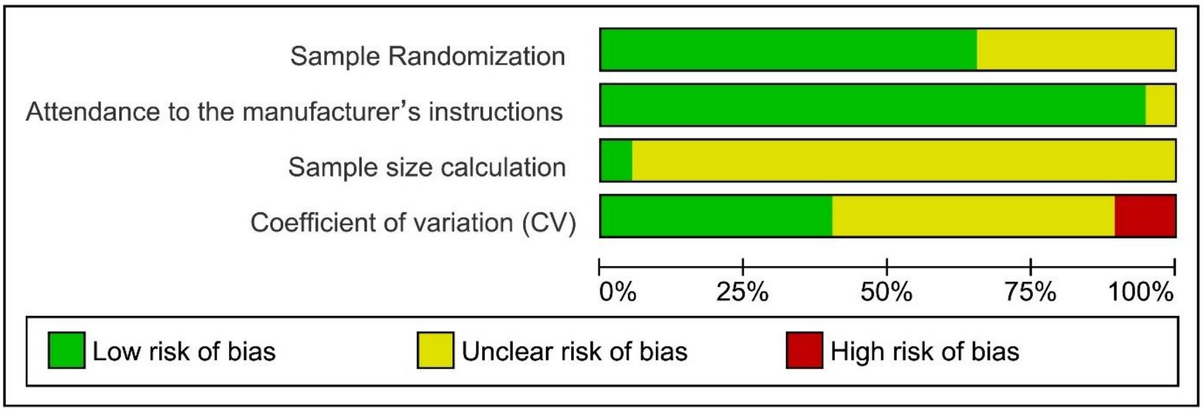


Figure 3. Review authors' judgments about each risk of bias item for each included in vitro study, classified as having low, moderate or high risk of bias.

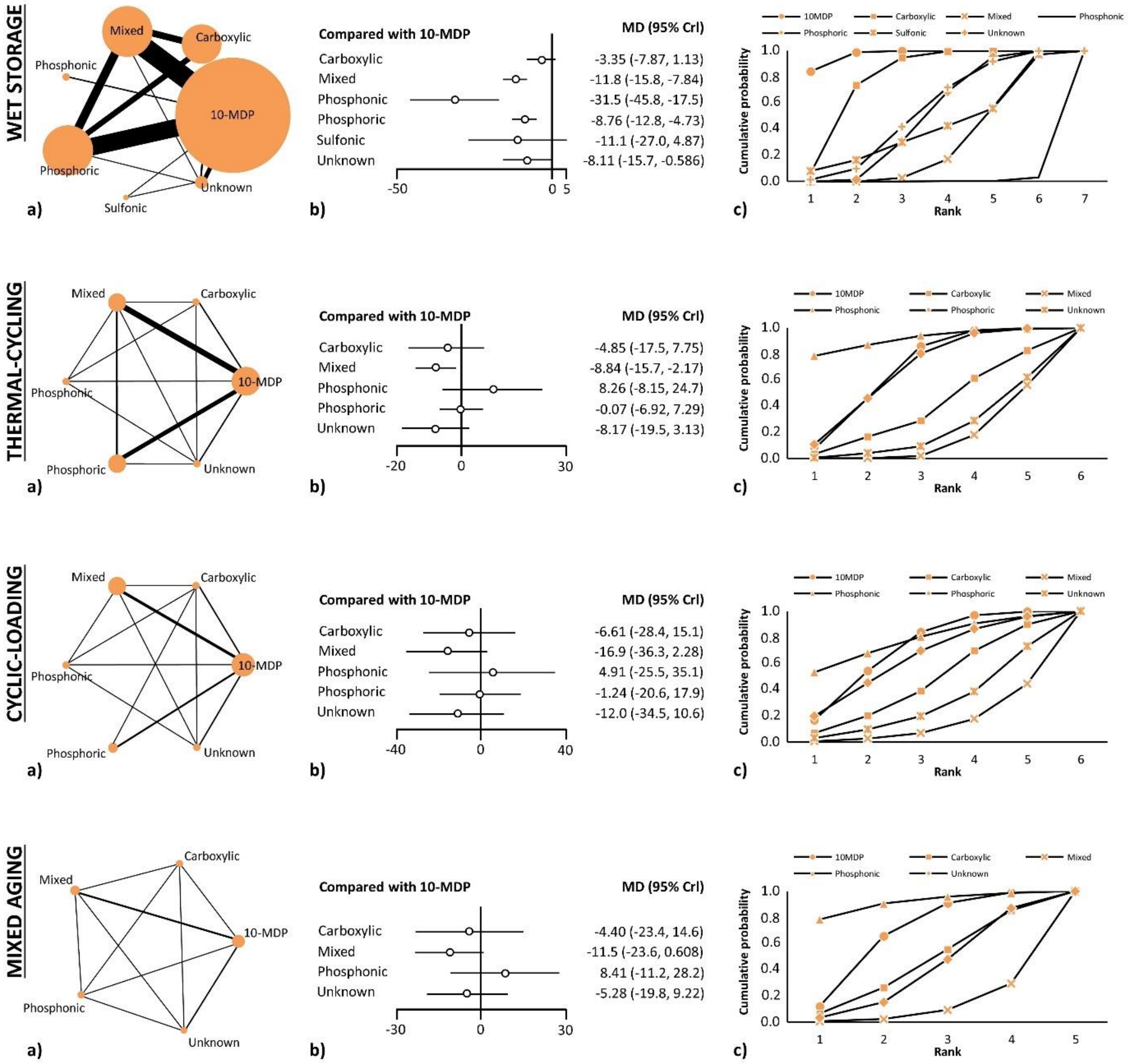
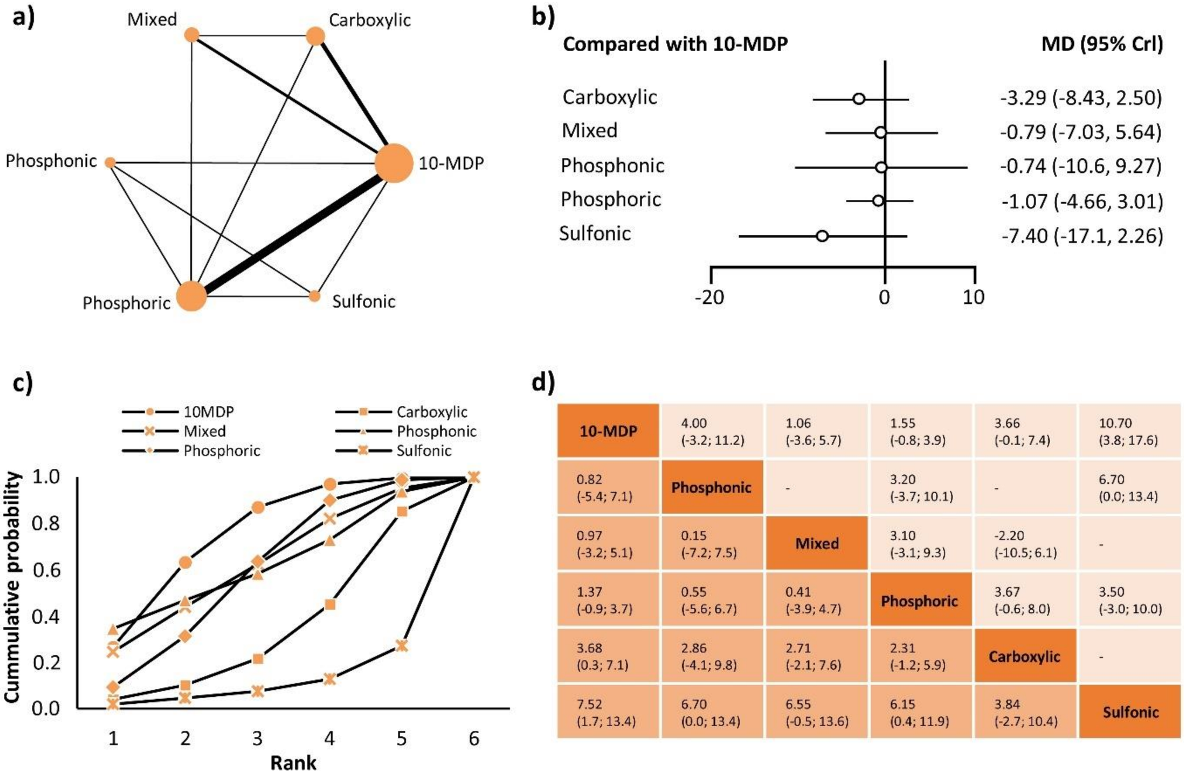


Figure 4. Network meta-analysis comparing the long-term resin-dentin bond strengths obtained with the application of adhesives based on 10-MDP (control) or alternative acidic monomers (carboxylic acids, phosphoric acids, phosphonic acids, sulfonic acids, mixed composition, or an unknown composition). The analyses were separated according to the aging condition as follows: wet storage, thermal-cycling, cyclic-loading, and mixed aging. (a) Graphs showing the network plots where each node indicates a direct comparison with connecting lines between nodes representing the total amount of studies making each comparison; the greater the size of nodes and the thickness of lines indicate that the respective groups are contributing with a higher weight and more direct evidence to the statistical analysis, respectively. (b) Graphs showing the results from the Bayesian random effect consistency model forest plots of the pooled effects estimates of bond strengths expressed in mean difference (MD) and respective 95% credible interval (95% Crl) for different adhesive groups compared with 10-MDP. (c) Graphs showing the ranking of adhesive groups according to their probability of being the best option to resist better to bond strength degradation after aging.



10-MDP	4.00 (-3.2; 11.2)	1.06 (-3.6; 5.7)	1.55 (-0.8; 3.9)	3.66 (-0.1; 7.4)	10.70 (3.8; 17.6)
0.82 (-5.4; 7.1)	**Phosphonic**	-	3.20 (-3.7; 10.1)	-	6.70 (0.0; 13.4)
0.97 (-3.2; 5.1)	0.15 (-7.2; 7.5)	**Mixed**	3.10 (-3.1; 9.3)	-2.20 (-10.5; 6.1)	-
1.37 (-0.9; 3.7)	0.55 (-5.6; 6.7)	0.41 (-3.9; 4.7)	**Phosphoric**	3.67 (-0.6; 8.0)	3.50 (-3.0; 10.0)
3.68 (0.3; 7.1)	2.86 (-4.1; 9.8)	2.71 (-2.1; 7.6)	2.31 (-1.2; 5.9)	**Carboxylic**	-
7.52 (1.7; 13.4)	6.70 (0.0; 13.4)	6.55 (-0.5; 13.6)	6.15 (0.4; 11.9)	3.84 (-2.7; 10.4)	**Sulfonic**

Figure 5. Network meta-analysis comparing the long-term resin-enamel bond strengths obtained with the application of adhesives based on 10-MDP (control) or alternative acidic monomers (carboxylic acids, phosphoric acids, phosphonic acids, sulfonic acids, or mixed composition). The analyses gathered the data regardless of the aging condition. (a) Graph showing the network plots where each node indicates a direct comparison with connecting lines between nodes representing the total amount of studies making each comparison; the greater the size of nodes and the thickness of lines indicate that the respective groups are contributing with a higher weight and more direct evidence to the statistical analysis, respectively. (b) Graph showing the results from the Bayesian random effect consistency model forest plot of the pooled effects estimates of bond strengths expressed in mean difference (MD) and respective 95% credible interval (95% Crl) for different adhesive groups compared with 10-MDP. (c) Graph showing the ranking of adhesive groups according to their probability of being the best option to resist better to bond strength degradation after aging. (d) League table showing Bayesian comparison of all adhesive pairs: the table displays the results for all adhesive pairs in both the upper (direct comparisons) and lower (indirect comparisons) triangles, but with the comparison switched over; for both above and below the leading diagonal, the results are for the adhesive group at the top of the same column vs. adhesive group at the left hand side of the same row.

Supplementary Materials

S1. List of references excluded in the review after full-text reading.

1. Abdalla AI, El Zohairy AA, Aboushelib MMN, Feilzer AJ. Microtensile bond strength of four self-etch adhesives to dentin. *International Journal of Clinical Dentistry* 2010;3(2):91-102.

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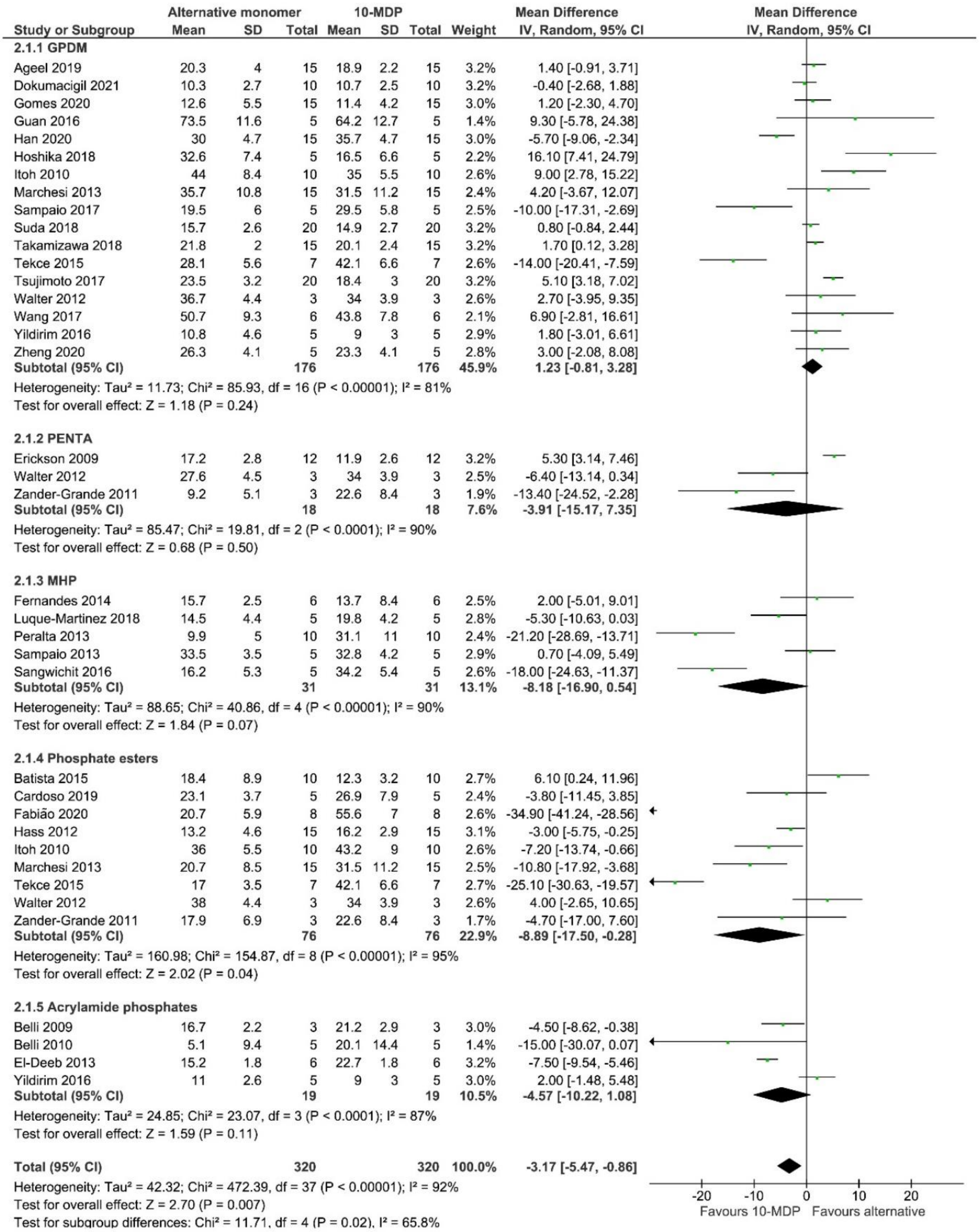
S2. Distribution of each item evaluated during the quality analysis of the included studies and the overall rating of their risk of bias (R), categorized as low (L), moderate (M) or high (H).

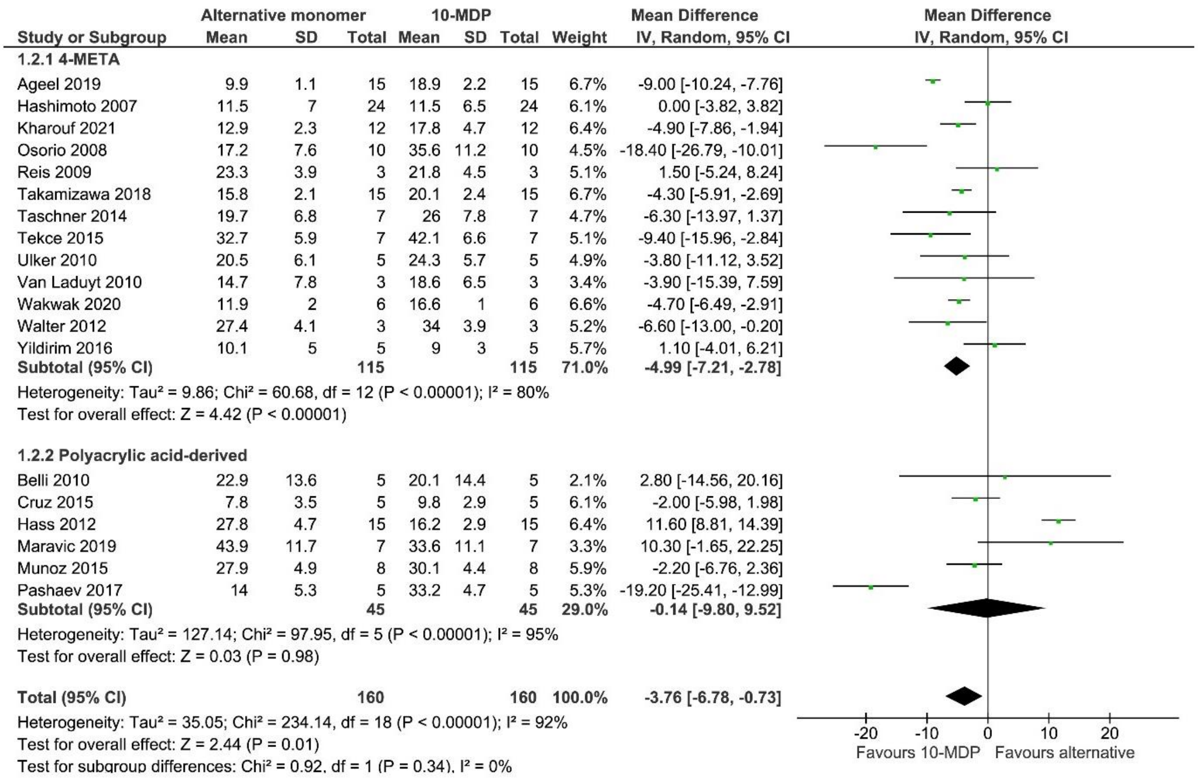
Study	1	2	3	4	R	Study	1	2	3	4	R
Ageel 2019	+	+	+	+	L	Luque-Martinez 2018	+	+	?	~	M
Amaral 2015	+	+	?	~	M	Malaquias 2020	+	+	+	~	L
Batista 2015	?	+	?	~	H	Maravic 2019	?	+	?	~	H
Belli 2009	+	+	?	+	L	Marchesi 2013	+	+	?	~	M
Belli 2010	+	+	?	+	L	Mousavinasab 2009	?	+	?	~	H
Bravo 2017	+	+	?	~	M	Muñoz 2015	+	+	?	+	L
Cardoso 2014	?	?	?	~	H	Osorio 2008	+	+	?	-	M
Cardoso 2019	+	+	?	~	M	Pashaev 2017	+	+	?	+	L
Cavalcanti2008	+	+	?	+	L	Peralta 2013	+	+	?	~	M
Chen 2015	+	+	?	+	L	Reis 2005	+	+	?	+	L
Cruz 2015	+	+	?	~	M	Reis 2008	+	+	+	+	L
Cuevas-Suárez 2019	+	+	?	+	L	Reis 2009	+	+	?	~	M
De Munck 2006	+	+	?	-	M	Roman 2014	+	+	?	-	M
Dokumacigil 2021	+	+	?	~	M	Salz 2005	?	+	?	+	M
El-Deeb 2013	?	+	?	+	M	Sampaio 2013	+	+	?	+	L
Erhardt 2008a	?	+	?	-	H	Sampaio 2017	+	+	?	~	M
Erhardt 2008b	?	+	?	-	H	Sangwichit 2016	+	+	?	~	M
Erhardt 2011	?	+	?	-	H	Sezinando 2015	+	+	?	+	L
Erickson 2011	?	+	?	~	H	Sismanoglu 2019	+	+	?	+	L
Fabião 2020	+	+	?	+	L	Suda 2018	?	+	?	+	M
Farias 2016	+	+	?	~	M	Takamizawa 2018	+	+	?	+	L
Fernandes 2014	+	+	?	-	M	Taschner 2014	?	+	?	~	H
Follak 2018	+	+	?	~	M	Tekce 2015	+	+	?	+	L
França 2007	+	+	?	~	M	Tian 2014	+	+	?	+	L
Fukuoka 2011	?	+	?	~	H	Ting 2018	+	+	?	~	M
Gomes 2020	+	+	+	~	L	Toledano 2007	?	+	?	~	H
Gotti 2015	+	+	?	+	L	Tsujimoto 2017	?	+	?	+	M
Guan 2016	+	+	?	+	L	Ulker 2010	+	+	?	~	M
Han 2020	+	+	?	+	L	Van Laduyt 2010	?	+	?	~	H
Hashimoto 2007	?	+	?	~	H	Wakwak 2020	?	+	?	+	M
Hass 2012	?	+	?	~	H	Walter 2012	+	+	?	+	L
Hoshika 2018	+	+	?	~	M	Wang 2017	+	+	?	+	L
Inoue 2005	?	+	?	~	H	Wong 2020	?	+	?	+	M
Itoh	+	+	?	+	L	Yildirim 2016	+	+	?	~	M
Kharouf 2021	?	+	?	~	H	Zander-Grande 2011	+	+	?	-	M
Li 2019	-	+	?	?	H	Zeidan 2017	?	+	?	~	H
Loguercio 2008	+	+	?	+	L	Zheng 2020	?	+	?	~	H
Loguercio 2011	+	+	?	~	M	Zhou 2015	+	+	?	+	L

Items investigated: #1 – Sample randomization; #2 – Attendance to the manufacturer's instructions; #3 – Sample size calculation; and #4 – Coefficient of variation (CV).
Codes within the items #1, #2, and #3: (+) the item was informed; (?) the item was not informed in the study.
Codes within the item #4: (+) low CV (<20%); (~) moderate CV (20-40%); (–) high CV (≥40%).



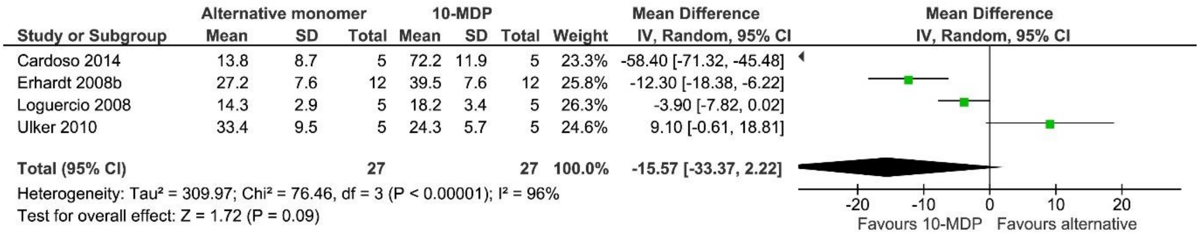
Study or Subgroup	Alternative monomer Mean	SD	Total	10-MDP Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 GPDM								
Ageel 2019	20.3	4	15	18.9	2.2	15	3.2%	1.40 [-0.91, 3.71]
Dokumacigil 2021	10.3	2.7	10	10.7	2.5	10	3.2%	-0.40 [-2.68, 1.88]
Gomes 2020	12.6	5.5	15	11.4	4.2	15	3.0%	1.20 [-2.30, 4.70]
Guan 2016	73.5	11.6	5	64.2	12.7	5	1.4%	9.30 [-5.78, 24.38]
Han 2020	30	4.7	15	35.7	4.7	15	3.0%	-5.70 [-9.06, -2.34]
Hoshika 2018	32.6	7.4	5	16.5	6.6	5	2.2%	16.10 [7.41, 24.79]
Itoh 2010	44	8.4	10	35	5.5	10	2.6%	9.00 [2.78, 15.22]
Marchesi 2013	35.7	10.8	15	31.5	11.2	15	2.4%	4.20 [-3.67, 12.07]
Sampaio 2017	19.5	6	5	29.5	5.8	5	2.5%	-10.00 [-17.31, -2.69]
Suda 2018	15.7	2.6	20	14.9	2.7	20	3.2%	0.80 [-0.84, 2.44]
Takamizawa 2018	21.8	2	15	20.1	2.4	15	3.2%	1.70 [0.12, 3.28]
Tekce 2015	28.1	5.6	7	42.1	6.6	7	2.6%	-14.00 [-20.41, -7.59]
Tsujimoto 2017	23.5	3.2	20	18.4	3	20	3.2%	5.10 [3.18, 7.02]
Walter 2012	36.7	4.4	3	34	3.9	3	2.6%	2.70 [-3.95, 9.35]
Wang 2017	50.7	9.3	6	43.8	7.8	6	2.1%	6.90 [-2.81, 16.61]
Yildirim 2016	10.8	4.6	5	9	3	5	2.9%	1.80 [-3.01, 6.61]
Zheng 2020	26.3	4.1	5	23.3	4.1	5	2.8%	3.00 [-2.08, 8.08]
Subtotal (95% CI)			**176**			**176**	**45.9%**	**1.23 [-0.81, 3.28]**
Heterogeneity: Tau² = 11.73; Chi² = 85.93, df = 16 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 1.18 (P = 0.24)								
2.1.2 PENTA								
Erickson 2009	17.2	2.8	12	11.9	2.6	12	3.2%	5.30 [3.14, 7.46]
Walter 2012	27.6	4.5	3	34	3.9	3	2.5%	-6.40 [-13.14, 0.34]
Zander-Grande 2011	9.2	5.1	3	22.6	8.4	3	1.9%	-13.40 [-24.52, -2.28]
Subtotal (95% CI)			**18**			**18**	**7.6%**	**-3.91 [-15.17, 7.35]**
Heterogeneity: Tau² = 85.47; Chi² = 19.81, df = 2 (P < 0.0001); I² = 90%								
Test for overall effect: Z = 0.68 (P = 0.50)								
2.1.3 MHP								
Fernandes 2014	15.7	2.5	6	13.7	8.4	6	2.5%	2.00 [-5.01, 9.01]
Luque-Martinez 2018	14.5	4.4	5	19.8	4.2	5	2.8%	-5.30 [-10.63, 0.03]
Peralta 2013	9.9	5	10	31.1	11	10	2.4%	-21.20 [-28.69, -13.71]
Sampaio 2013	33.5	3.5	5	32.8	4.2	5	2.9%	0.70 [-4.09, 5.49]
Sangwichit 2016	16.2	5.3	5	34.2	5.4	5	2.6%	-18.00 [-24.63, -11.37]
Subtotal (95% CI)			**31**			**31**	**13.1%**	**-8.18 [-16.90, 0.54]**
Heterogeneity: Tau² = 88.65; Chi² = 40.86, df = 4 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 1.84 (P = 0.07)								
2.1.4 Phosphate esters								
Batista 2015	18.4	8.9	10	12.3	3.2	10	2.7%	6.10 [0.24, 11.96]
Cardoso 2019	23.1	3.7	5	26.9	7.9	5	2.4%	-3.80 [-11.45, 3.85]
Fabião 2020	20.7	5.9	8	55.6	7	8	2.6%	-34.90 [-41.24, -28.56]
Hass 2012	13.2	4.6	15	16.2	2.9	15	3.1%	-3.00 [-5.75, -0.25]
Itoh 2010	36	5.5	10	43.2	9	10	2.6%	-7.20 [-13.74, -0.66]
Marchesi 2013	20.7	8.5	15	31.5	11.2	15	2.5%	-10.80 [-17.92, -3.68]
Tekce 2015	17	3.5	7	42.1	6.6	7	2.7%	-25.10 [-30.63, -19.57]
Walter 2012	38	4.4	3	34	3.9	3	2.6%	4.00 [-2.65, 10.65]
Zander-Grande 2011	17.9	6.9	3	22.6	8.4	3	1.7%	-4.70 [-17.00, 7.60]
Subtotal (95% CI)			**76**			**76**	**22.9%**	**-8.89 [-17.50, -0.28]**
Heterogeneity: Tau² = 160.98; Chi² = 154.87, df = 8 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 2.02 (P = 0.04)								
2.1.5 Acrylamide phosphates								
Belli 2009	16.7	2.2	3	21.2	2.9	3	3.0%	-4.50 [-8.62, -0.38]
Belli 2010	5.1	9.4	5	20.1	14.4	5	1.4%	-15.00 [-30.07, 0.07]
El-Deeb 2013	15.2	1.8	6	22.7	1.8	6	3.2%	-7.50 [-9.54, -5.46]
Yildirim 2016	11	2.6	5	9	3	5	3.0%	2.00 [-1.48, 5.48]
Subtotal (95% CI)			**19**			**19**	**10.5%**	**-4.57 [-10.22, 1.08]**
Heterogeneity: Tau² = 24.85; Chi² = 23.07, df = 3 (P < 0.0001); I² = 87%								
Test for overall effect: Z = 1.59 (P = 0.11)								
Total (95% CI)			**320**			**320**	**100.0%**	**-3.17 [-5.47, -0.86]**
Heterogeneity: Tau² = 42.32; Chi² = 472.39, df = 37 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 2.70 (P = 0.007)								
Test for subgroup differences: Chi² = 11.71, df = 4 (P = 0.02), I² = 65.8%								

S3. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives containing acidic monomers derived from phosphoric acids, allocated by the type of functional monomer. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).



	Alternative monomer			10-MDP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.2.1 4-META								
Ageel 2019	9.9	1.1	15	18.9	2.2	15	6.7%	-9.00 [-10.24, -7.76]
Hashimoto 2007	11.5	7	24	11.5	6.5	24	6.1%	0.00 [-3.82, 3.82]
Kharouf 2021	12.9	2.3	12	17.8	4.7	12	6.4%	-4.90 [-7.86, -1.94]
Osorio 2008	17.2	7.6	10	35.6	11.2	10	4.5%	-18.40 [-26.79, -10.01]
Reis 2009	23.3	3.9	3	21.8	4.5	3	5.1%	1.50 [-5.24, 8.24]
Takamizawa 2018	15.8	2.1	15	20.1	2.4	15	6.7%	-4.30 [-5.91, -2.69]
Taschner 2014	19.7	6.8	7	26	7.8	7	4.7%	-6.30 [-13.97, 1.37]
Tekce 2015	32.7	5.9	7	42.1	6.6	7	5.1%	-9.40 [-15.96, -2.84]
Ulker 2010	20.5	6.1	5	24.3	5.7	5	4.9%	-3.80 [-11.12, 3.52]
Van Laduyt 2010	14.7	7.8	3	18.6	6.5	3	3.4%	-3.90 [-15.39, 7.59]
Wakwak 2020	11.9	2	6	16.6	1	6	6.6%	-4.70 [-6.49, -2.91]
Walter 2012	27.4	4.1	3	34	3.9	3	5.2%	-6.60 [-13.00, -0.20]
Yildirim 2016	10.1	5	5	9	3	5	5.7%	1.10 [-4.01, 6.21]
Subtotal (95% CI)			**115**			**115**	**71.0%**	**-4.99 [-7.21, -2.78]**
Heterogeneity: Tau² = 9.86; Chi² = 60.68, df = 12 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 4.42 (P < 0.00001)								
1.2.2 Polyacrylic acid-derived								
Belli 2010	22.9	13.6	5	20.1	14.4	5	2.1%	2.80 [-14.56, 20.16]
Cruz 2015	7.8	3.5	5	9.8	2.9	5	6.1%	-2.00 [-5.98, 1.98]
Hass 2012	27.8	4.7	15	16.2	2.9	15	6.4%	11.60 [8.81, 14.39]
Maravic 2019	43.9	11.7	7	33.6	11.1	7	3.3%	10.30 [-1.65, 22.25]
Munoz 2015	27.9	4.9	8	30.1	4.4	8	5.9%	-2.20 [-6.76, 2.36]
Pashaev 2017	14	5.3	5	33.2	4.7	5	5.3%	-19.20 [-25.41, -12.99]
Subtotal (95% CI)			**45**			**45**	**29.0%**	**-0.14 [-9.80, 9.52]**
Heterogeneity: Tau² = 127.14; Chi² = 97.95, df = 5 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 0.03 (P = 0.98)								
Total (95% CI)			**160**			**160**	**100.0%**	**-3.76 [-6.78, -0.73]**
Heterogeneity: Tau² = 35.05; Chi² = 234.14, df = 18 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 2.44 (P = 0.01)								
Test for subgroup differences: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%								

S4. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives containing acidic monomers derived from carboxylic acids, allocated by the type of functional monomer. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).

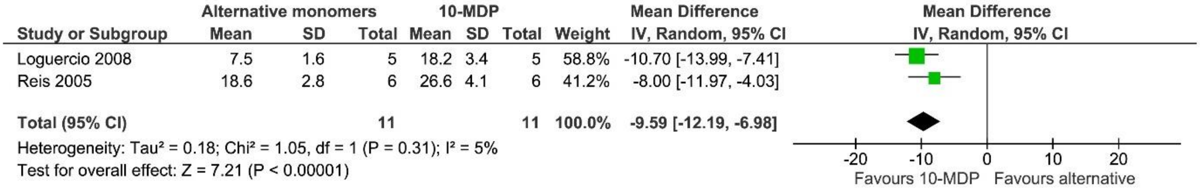


Study or Subgroup	Alternative monomer Mean	SD	Total	10-MDP Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cardoso 2014	13.8	8.7	5	72.2	11.9	5	23.3%	-58.40 [-71.32, -45.48]
Erhardt 2008b	27.2	7.6	12	39.5	7.6	12	25.8%	-12.30 [-18.38, -6.22]
Loguercio 2008	14.3	2.9	5	18.2	3.4	5	26.3%	-3.90 [-7.82, 0.02]
Ulker 2010	33.4	9.5	5	24.3	5.7	5	24.6%	9.10 [-0.61, 18.81]
Total (95% CI)			**27**			**27**	**100.0%**	**-15.57 [-33.37, 2.22]**

Heterogeneity: Tau² = 309.97; Chi² = 76.46, df = 3 (P < 0.00001); I² = 96%

Test for overall effect: Z = 1.72 (P = 0.09)

S5. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives containing acidic monomers derived from phosphonic acids. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).



	Alternative monomers			10-MDP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Loguercio 2008	7.5	1.6	5	18.2	3.4	5	58.8%	-10.70 [-13.99, -7.41]
Reis 2005	18.6	2.8	6	26.6	4.1	6	41.2%	-8.00 [-11.97, -4.03]
Total (95% CI)			**11**			**11**	**100.0%**	**-9.59 [-12.19, -6.98]**

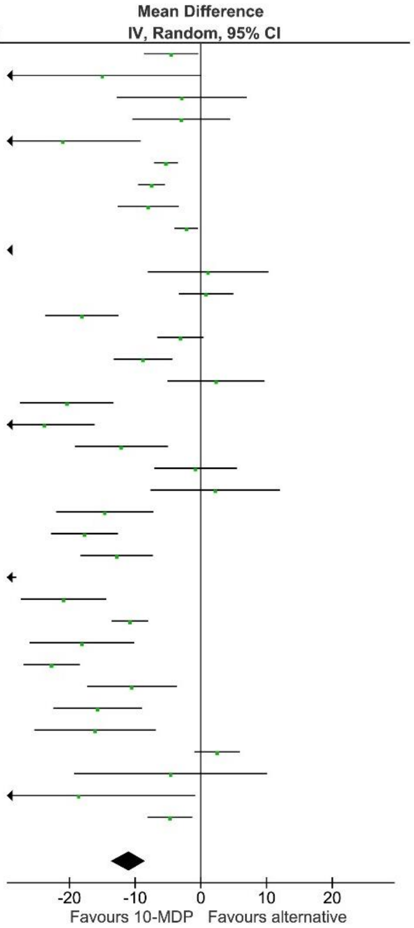
Heterogeneity: Tau² = 0.18; Chi² = 1.05, df = 1 (P = 0.31); I² = 5%
Test for overall effect: Z = 7.21 (P < 0.00001)

S6. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives containing acidic monomers derived from sulfonic acids. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).

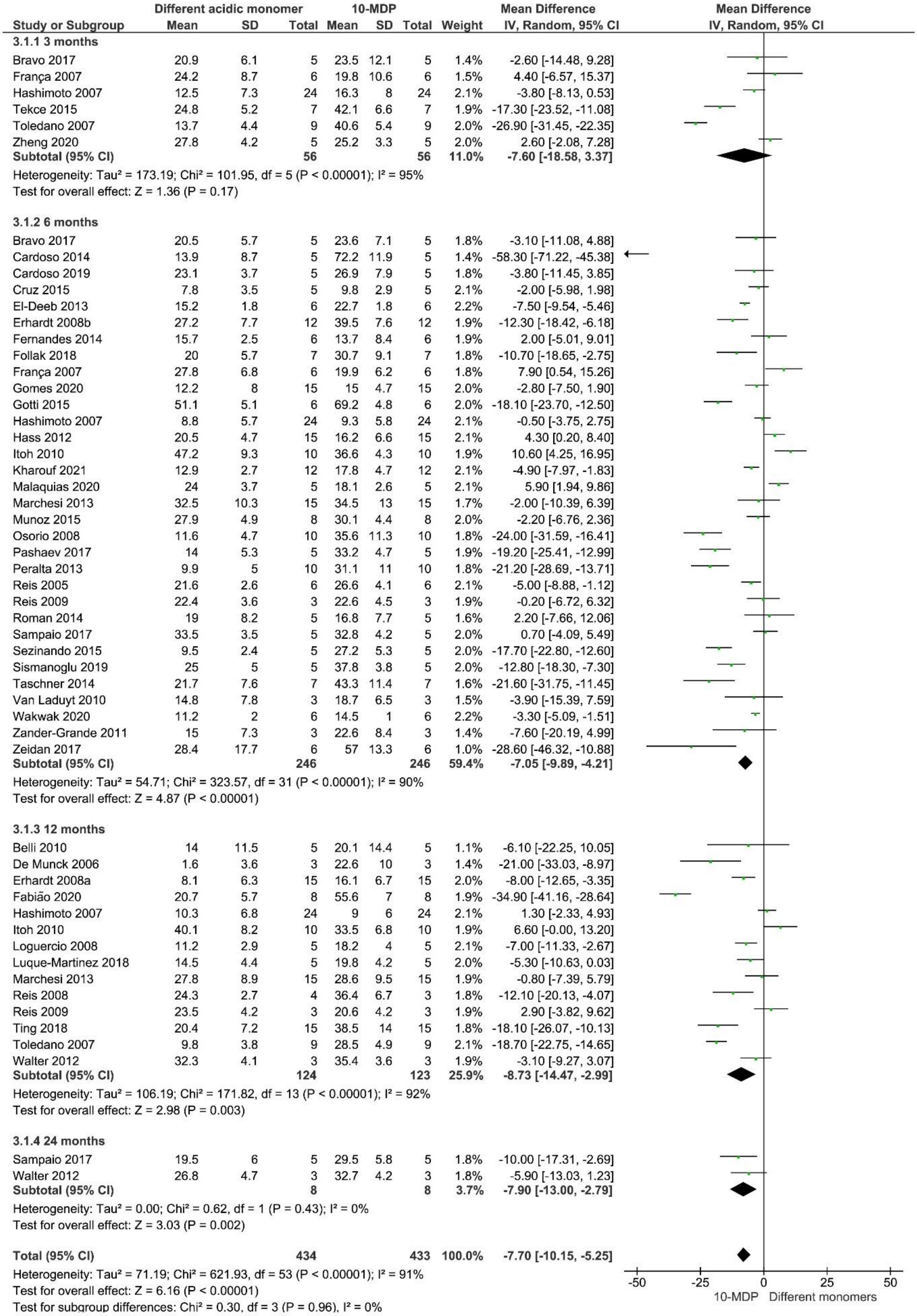
	Alternative monomer			10-MDP				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Belli 2009	16.7	2.2	3	21.2	2.9	3	3.2%	-4.50 [-8.62, -0.38]
Belli 2010	5.1	9.4	5	20.1	14.4	5	1.6%	-15.00 [-30.07, 0.07]
Bravo 2017	20.7	5.9	5	23.6	9.6	5	2.3%	-2.90 [-12.78, 6.98]
Cavalcanti 2008	14.8	5.2	5	17.8	6.7	5	2.7%	-3.00 [-10.43, 4.43]
De Munck 2006	1.6	3.1	3	22.6	10	3	2.0%	-21.00 [-32.85, -9.15]
Dokumacigil 2021	5.4	1.6	10	10.7	2.5	10	3.4%	-5.30 [-7.14, -3.46]
El-Deeb 2013	15.2	1.8	6	22.7	1.8	6	3.4%	-7.50 [-9.54, -5.46]
Erhardt 2008a	8.1	6.3	15	16.1	6.7	15	3.1%	-8.00 [-12.65, -3.35]
Erickson 2009	15	1.4	12	17.2	2.8	12	3.4%	-2.20 [-3.97, -0.43]
Farias 2016	12.7	5	5	52.6	8	5	2.6%	-39.90 [-48.17, -31.63]
França 2007	21	7.8	6	19.9	8.4	6	2.4%	1.10 [-8.07, 10.27]
Fukuoka 2011	13.6	3.4	6	12.8	3.9	6	3.2%	0.80 [-3.34, 4.94]
Gotti 2015	51.1	5.1	6	69.2	4.8	6	3.0%	-18.10 [-23.70, -12.50]
Hashimoto 2007	8.4	5.8	24	11.5	6.6	24	3.3%	-3.10 [-6.62, 0.42]
Loguercio 2011	12.3	4.3	7	21.1	4.2	7	3.2%	-8.80 [-13.25, -4.35]
Marchesi 2013	33.8	9.4	15	31.5	11.2	15	2.7%	2.30 [-5.10, 9.70]
Mousavinasab 2009	11.1	6.8	8	31.5	7.7	8	2.8%	-20.40 [-27.52, -13.28]
Osorio 2008	11.8	5.1	10	35.6	11.2	10	2.7%	-23.80 [-31.43, -16.17]
Reis 2008	24.3	2.7	4	36.4	6.7	4	2.8%	-12.10 [-19.18, -5.02]
Reis 2009	21.1	3.1	3	21.9	4.6	3	2.9%	-0.80 [-7.08, 5.48]
Roman 2014	19	8.2	5	16.8	7.7	5	2.3%	2.20 [-7.66, 12.06]
Sangwichit 2016	19.6	6.5	5	34.2	5.4	5	2.7%	-14.60 [-22.01, -7.19]
Sezinando 2015	9.5	2.4	5	27.2	5.3	5	3.1%	-17.70 [-22.80, -12.60]
Sismanoglu 2019	25	5	5	37.8	3.8	5	3.0%	-12.80 [-18.30, -7.30]
Taschner 2014	6.3	3.8	7	43.3	11.4	7	2.5%	-37.00 [-45.90, -28.10]
Tekce 2015	21.2	5.8	7	42.1	6.6	7	2.9%	-20.90 [-27.41, -14.39]
Tian 2014	12.6	2.1	7	23.4	3.1	7	3.3%	-10.80 [-13.57, -8.03]
Ting 2018	20.4	7.2	15	38.5	14	15	2.6%	-18.10 [-26.07, -10.13]
Toledano 2007	11.7	4.1	9	34.4	5.1	9	3.2%	-22.70 [-26.98, -18.42]
Ulker 2010	13.8	5.3	5	24.3	5.7	5	2.8%	-10.50 [-17.32, -3.68]
Walter 2012	18.3	4.5	3	34	3.9	3	2.8%	-15.70 [-22.44, -8.96]
Wang 2017	27.7	8.5	6	43.8	7.8	6	2.4%	-16.10 [-25.33, -6.87]
Yildirim 2016	11.5	2.6	5	9	3	5	3.3%	2.50 [-0.98, 5.98]
Zander-Grande 2011	18	9.9	3	22.6	8.4	3	1.7%	-4.60 [-19.29, 10.09]
Zeidan 2017	38.4	17.7	6	57	13.3	6	1.3%	-18.60 [-36.32, -0.88]
Zhou 2015	20.6	2.4	7	25.3	3.9	7	3.3%	-4.70 [-8.09, -1.31]
Total (95% CI)			**258**			**258**	**100.0%**	**-11.00 [-13.62, -8.38]**

Heterogeneity: $Tau^2 = 51.40$; $Chi^2 = 381.99$, df = 35 ($P < 0.00001$); $I^2 = 91\%$

Test for overall effect: $Z = 8.23$ ($P < 0.00001$)



S7. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives containing acidic monomers derived from a mixture of distinct functional monomers. The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).



	Different acidic monomer			10-MDP				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
3.1.1 3 months								
Bravo 2017	20.9	6.1	5	23.5	12.1	5	1.4%	-2.60 [-14.48, 9.28]
França 2007	24.2	8.7	6	19.8	10.6	6	1.5%	4.40 [-6.57, 15.37]
Hashimoto 2007	12.5	7.3	24	16.3	8	24	2.1%	-3.80 [-8.13, 0.53]
Tekce 2015	24.8	5.2	7	42.1	6.6	7	1.9%	-17.30 [-23.52, -11.08]
Toledano 2007	13.7	4.4	9	40.6	5.4	9	2.0%	-26.90 [-31.45, -22.35]
Zheng 2020	27.8	4.2	5	25.2	3.3	5	2.0%	2.60 [-2.08, 7.28]
Subtotal (95% CI)			**56**			**56**	**11.0%**	**-7.60 [-18.58, 3.37]**
Heterogeneity: Tau² = 173.19; Chi² = 101.95, df = 5 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 1.36 (P = 0.17)								
3.1.2 6 months								
Bravo 2017	20.5	5.7	5	23.6	7.1	5	1.8%	-3.10 [-11.08, 4.88]
Cardoso 2014	13.9	8.7	5	72.2	11.9	5	1.4%	-58.30 [-71.22, -45.38]
Cardoso 2019	23.1	3.7	5	26.9	7.9	5	1.8%	-3.80 [-11.45, 3.85]
Cruz 2015	7.8	3.5	5	9.8	2.9	5	2.1%	-2.00 [-5.98, 1.98]
El-Deeb 2013	15.2	1.8	6	22.7	1.8	6	2.2%	-7.50 [-9.54, -5.46]
Erhardt 2008b	27.2	7.7	12	39.5	7.6	12	1.9%	-12.30 [-18.42, -6.18]
Fernandes 2014	15.7	2.5	6	13.7	8.4	6	1.9%	2.00 [-5.01, 9.01]
Follak 2018	20	5.7	7	30.7	9.1	7	1.8%	-10.70 [-18.65, -2.75]
França 2007	27.8	6.8	6	19.9	6.2	6	1.8%	7.90 [0.54, 15.26]
Gomes 2020	12.2	8	15	15	4.7	15	2.0%	-2.80 [-7.50, 1.90]
Gotti 2015	51.1	5.1	6	69.2	4.8	6	2.0%	-18.10 [-23.70, -12.50]
Hashimoto 2007	8.8	5.7	24	9.3	5.8	24	2.1%	-0.50 [-3.75, 2.75]
Hass 2012	20.5	4.7	15	16.2	6.6	15	2.1%	4.30 [0.20, 8.40]
Itoh 2010	47.2	9.3	10	36.6	4.3	10	1.9%	10.60 [4.25, 16.95]
Kharouf 2021	12.9	2.7	12	17.8	4.7	12	2.1%	-4.90 [-7.97, -1.83]
Malaquias 2020	24	3.7	5	18.1	2.6	5	2.1%	5.90 [1.94, 9.86]
Marchesi 2013	32.5	10.3	15	34.5	13	15	1.7%	-2.00 [-10.39, 6.39]
Munoz 2015	27.9	4.9	8	30.1	4.4	8	2.0%	-2.20 [-6.76, 2.36]
Osorio 2008	11.6	4.7	10	35.6	11.3	10	1.8%	-24.00 [-31.59, -16.41]
Pashaev 2017	14	5.3	5	33.2	4.7	5	1.9%	-19.20 [-25.41, -12.99]
Peralta 2013	9.9	5	10	31.1	11	10	1.8%	-21.20 [-28.69, -13.71]
Reis 2005	21.6	2.6	6	26.6	4.1	6	2.1%	-5.00 [-8.88, -1.12]
Reis 2009	22.4	3.6	3	22.6	4.5	3	1.9%	-0.20 [-6.72, 6.32]
Roman 2014	19	8.2	5	16.8	7.7	5	1.6%	2.20 [-7.66, 12.06]
Sampaio 2017	33.5	3.5	5	32.8	4.2	5	2.0%	0.70 [-4.09, 5.49]
Sezinando 2015	9.5	2.4	5	27.2	5.3	5	2.0%	-17.70 [-22.80, -12.60]
Sismanoglu 2019	25	5	5	37.8	3.8	5	2.0%	-12.80 [-18.30, -7.30]
Taschner 2014	21.7	7.6	7	43.3	11.4	7	1.6%	-21.60 [-31.75, -11.45]
Van Laduyt 2010	14.8	7.8	3	18.7	6.5	3	1.5%	-3.90 [-15.39, 7.59]
Wakwak 2020	11.2	2	6	14.5	1	6	2.2%	-3.30 [-5.09, -1.51]
Zander-Grande 2011	15	7.3	3	22.6	8.4	3	1.4%	-7.60 [-20.19, 4.99]
Zeidan 2017	28.4	17.7	6	57	13.3	6	1.0%	-28.60 [-46.32, -10.88]
Subtotal (95% CI)			**246**			**246**	**59.4%**	**-7.05 [-9.89, -4.21]**
Heterogeneity: Tau² = 54.71; Chi² = 323.57, df = 31 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 4.87 (P < 0.00001)								
3.1.3 12 months								
Belli 2010	14	11.5	5	20.1	14.4	5	1.1%	-6.10 [-22.25, 10.05]
De Munck 2006	1.6	3.6	3	22.6	10	3	1.4%	-21.00 [-33.03, -8.97]
Erhardt 2008a	8.1	6.3	15	16.1	6.7	15	2.0%	-8.00 [-12.65, -3.35]
Fabião 2020	20.7	5.7	8	55.6	7	8	1.9%	-34.90 [-41.16, -28.64]
Hashimoto 2007	10.3	6.8	24	9	6	24	2.1%	1.30 [-2.33, 4.93]
Itoh 2010	40.1	8.2	10	33.5	6.8	10	1.9%	6.60 [-0.00, 13.20]
Loguercio 2008	11.2	2.9	5	18.2	4	5	2.1%	-7.00 [-11.33, -2.67]
Luque-Martinez 2018	14.5	4.4	5	19.8	4.2	5	2.0%	-5.30 [-10.63, 0.03]
Marchesi 2013	27.8	8.9	15	28.6	9.5	15	1.9%	-0.80 [-7.39, 5.79]
Reis 2008	24.3	2.7	4	36.4	6.7	3	1.8%	-12.10 [-20.13, -4.07]
Reis 2009	23.5	4.2	3	20.6	4.2	3	1.9%	2.90 [-3.82, 9.62]
Ting 2018	20.4	7.2	15	38.5	14	15	1.8%	-18.10 [-26.07, -10.13]
Toledano 2007	9.8	3.8	9	28.5	4.9	9	2.1%	-18.70 [-22.75, -14.65]
Walter 2012	32.3	4.1	3	35.4	3.6	3	1.9%	-3.10 [-9.27, 3.07]
Subtotal (95% CI)			**124**			**123**	**25.9%**	**-8.73 [-14.47, -2.99]**
Heterogeneity: Tau² = 106.19; Chi² = 171.82, df = 13 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 2.98 (P = 0.003)								
3.1.4 24 months								
Sampaio 2017	19.5	6	5	29.5	5.8	5	1.8%	-10.00 [-17.31, -2.69]
Walter 2012	26.8	4.7	3	32.7	4.2	3	1.8%	-5.90 [-13.03, 1.23]
Subtotal (95% CI)			**8**			**8**	**3.7%**	**-7.90 [-13.00, -2.79]**
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%								
Test for overall effect: Z = 3.03 (P = 0.002)								
Total (95% CI)			**434**			**433**	**100.0%**	**-7.70 [-10.15, -5.25]**
Heterogeneity: Tau² = 71.19; Chi² = 621.93, df = 53 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 6.16 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.30, df = 3 (P = 0.96), I² = 0%								

S8. Summary of meta-analysis findings comparing the bond strength of 10-MDP-based and 10-MDP-free adhesives allocated by the period of aging (3, 6, 12, and 24 months). The analyses were conducted using the mean difference (MD) estimate and using random-effects models with 95% confidence intervals (CI).

3. CONSIDERAÇÕES FINAIS

O papel dos sistemas adesivos autocondicionantes e universais é fundamental para os procedimentos de reabilitação oral, sendo o seu desempenho diretamente relacionado com o sucesso das intervenções restauradoras. Portanto, é essencial que o mecanismo de adesão ao dente e a durabilidade obtida com diferentes composições químicas seja melhor elucidados. A partir dos estudos realizados nesta dissertação, foi possível averiguar a influência que o tipo de monômero funcional ácido tem no potencial adesivo imediato e a longo prazo.

O monômero 10-MDP obteve o melhor desempenho adesivo imediato quando comparado aos demais monômeros ácidos utilizados na composição de adesivos autocondicionantes. Isto confirma o que a literatura vem apresentando sobre este monômero em especial, o que é reconhecido como o padrão ouro da adesão odontológica autocondicionante. Por sua vez, os resultados a longo prazo após envelhecimento demonstraram que o 10-MDP teve um efeito menos crucial, apresentando resultados de resistência de união semelhantes às demais composições acídicas. Contudo, o método de envelhecimento parece ter tido um efeito na estabilidade adesivas dos diferentes adesivos, com o armazenamento em água tendo afetado menos significativamente as interfaces adesivas obtidas sob a presença do 10-MDP. Assim, aprece existir uma relação entre a composição acídica dos sistemas adesivos e o tipo/meio de envelhecimento oral simulado, demonstrando que a adesão aos tecidos dentais envolve um mecanismo complexo e que ainda necessita ser melhor elucidado para permitir a utilização do melhor produto para cada situação clínica.

De maneira geral, a presença do monômero 10-MDP pode influenciar positivamente a resistência de união dos adesivos autocondicionantes, principalmente em momentos de avaliação inicial, porém, em relação à durabilidade e estabilidade adesiva, o seu efeito pode ser semelhante ao obtido com outras formulações acídicas, sendo também dependente do método de envelhecimento utilizado.

Embora esta dissertação tenha investigado apenas estudos laboratoriais, o resultado que ela traz é confirmatório acerca do efeito da presença do 10-MDP na adesão aos tecidos dentários. Outros tipos de estudo ainda são necessários, como por exemplo, uma meta-regressão considerando-se os mesmos critérios de elegibilidade aplicados aqui. Sabendo-se que novos sistemas adesivos surgem no mercado a cada novo ano, torna-se importante verificar quais aspectos do protocolo adesivo e combinação de materiais pode resultar em maio potencial adesivo ao dente através da utilização de sistemas adesivos autocondicionantes, cada vez mais populares no meio clínico odontológico.

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