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Meta-analytical Review of Parameters Involved in Dentin Bonding

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Abstract

Bond-strength testing is the most used method to assess bonding effectiveness to enamel and dentin. We aimed to disclose general trends in adhesive performance by collecting dentin bond-strength data systematically. The PubMed and Embase databases were used to identify 2157 bond-strength tests in 298 papers. Most used was the micro-tensile test, which appeared to have a larger discriminative power than the traditional macro-shear test. Because of the huge variability in dentin bond-strength data and the high number of co-variables, a neural network statistical model was constructed. Variables like 'research group' and 'adhesive brand' appeared most determining. Weighted means derived from this analysis confirmed the high sensitivity of current adhesive approaches (especially of all-in-one adhesives) to long-term water-storage and substrate variability.

Key Words

meta-analysis, bond strength, macro-shear, micro-tensile, adhesive, dental materials

Introduction

Worldwide, bond-strength tests are used to measure bonding effectiveness of adhesives to tooth tissue. Such tests serve multiple purposes, ranging from initial screening of new adhesive formulations, testing of various research hypotheses, up to quality control by manufacturers.

Many reviews have focused on bond strength and its predictability of clinical performance (Van Noort *et al.*, 1989; Rueggeberg *et al.*, 1991; Fowler *et al.*, 1992; Pashley *et al.*, 1995; Leloup *et al.*, 2001). The main issues discussed in these reviews deal with the methodology employed and high data variability. The solution proposed was to standardize the bond-strength protocol, hoping for better data interpretation and in particular inter-study comparison (Van Noort *et al.*, 1989; Stanley 1993). Today, the variety in test methodologies has however never been broader, while no consensus exists among researchers regarding the most appropriate use and interpretation of bond-strength data (Armstrong *et al.*, 2010). Nevertheless, the amount of data currently available in literature is so vast that some relevant trends might pop up despite the high variance. This calls, however, for statistical techniques that can deal with such an exponentially growing pool of 'noisy' data (Bishop, 1995).

Therefore, the purpose of this study was to systematically collect dentin bond-strength data, to identify the primary parameters that affect the outcome of bond-strength tests, and to disclose trends in adhesive performance for the different adhesive approaches available today.

Materials & Methods

Systematic Literature Search

By entering the search term '*dentin bond strength AND "published last 5 years"[Filter]*' in PubMed, 1049 studies were identified. The search was conducted on January 17, 2009 and repeated on October 9, 2009. To identify manuscripts not listed in PubMed a similar search covering the same period was conducted using the EMBASE database. Subsequently, all papers, along with the respective identifiers, were inserted in a custom-made relational database. Original articles were retrieved and appraised by 4 calibrated researchers (JDM/AM/AP/AVE). Studies were included when the following criteria were met: (1) bond strength of at least 2 commercial adhesives to dentin was measured; (2) a light-curing composite (no resin cement, nor glass-ionomer) was employed; and (3) for every relevant experimental group in each study at least the following data were recorded: type of test, mean bond strength, standard deviation and number of specimens, teeth and pre-testing failures. Also, parameters regarding the test set-up were recorded, such as substrate origin and preparation, storage time and medium, adhesive and composite brand, light-curing methodology, potential aging procedure and some other test conditions like loading geometry and interface shape (Web appendix Tables 2 and 3).

From the PubMed/Embase identifiers, the number of studies present in the database for every author was calculated. In each study, the author with most studies in the database was identified and served as identifier for the 'research group' that generated the data. All adhesives were categorized according to the classification by Van Meerbeek *et al.* (2003). Additionally, data regarding composition and mechanical properties of adhesives (pH, bonding technique,...) as well as composites (flexural modulus, composite type,...) were retrieved from Van Landuyt *et al.* (2007) and Ilie and Hickel (2009), respectively. Further, to assess the effect of progress in adhesive dentistry, the first appearance in the PubMed database was recorded for each adhesive and is referred to as 'adhesive age'.

To assess publication bias, dentin bond-strength data produced in a single dental materials research lab from the Katholieke Universiteit Leuven (Leuven BIOMAT Research Cluster) during the period 2002-2010 were analyzed, being further referred to as the 'BIOMAT database'.

Descriptive statistics and correlation analyses

The overall mean bond strength (in MPa) and histogram of each bond-strength methodology and adhesive class were calculated. Subsequently, these data were subjected to a first statistical analysis using ANOVA. To assess the importance of several 'continuous' parameters on the outcome of bond-strength tests, correlation analyses were performed on more homogenous subsets. A specific subset of data was therefore prepared, in which only 'control' bond-strength data were included, more specifically representing data derived from specimens that were prepared according to the manufacturers' instructions and tested between 1 day and 1 week, without any artificial aging or mechanical loading imposed, nor involving any modifications to the manufacturer's instructed adhesive procedure. Other subsets included bond-strength data measured upon 'aging by water-storage' or 'thermo-cycling'.

Artificial Neural Networks (ANN)

Next, a subset was prepared containing data of only micro-tensile bond-strength (μ TBS) results (61% of the data: 1314 records). From all parameters registered, 10 clinically and statistically relevant parameters (Table 1) were extracted/calculated to be included in the statistical model. A randomly chosen subset, containing 80% of the dataset, served to create multilayer perceptron neural networks with up to 40 hidden units (Statistica 9.0, StatSoft, Tulsa, OK, USA). The remaining part of the data served to train and test the statistical models by comparing the 'predicted' to the 'actual' reported bond strength. To validate the networks, they were additionally trained on 2 random subsamples. From the 1500 networks that were trained, 8 were retained electronically and from the 8 remaining ones, the 4 providing the most consistent results were retained by hand. Training, testing and validation performance of all retained networks, as measured by correlation between the target and predicted value, was 83%, 75% and 73%, respectively. An important feature of neural networks is generalization, i.e. the ability to predict the outcome of data unknown to the model. If the performance of the network is consistently good on both the test and validation samples, then it is reasonable to assume that the network generalizes well on unseen data. We used this feature to predict the performance of the 10 most common adhesives in the database, as tested by the most prevalent 'research groups'. In this way, a homogenous dataset was created, so that different groups could be compared.

Results

Descriptive Statistics and Correlation Analyses

From the 1049 studies identified, 298 yielded bond-strength data relevant for the current meta-analysis, from which 2157 individual bond-strength tests were extracted (Fig. 1). The two main reasons for exclusion were either that the manuscript contained no bond-strength data or that less than two commercial adhesives were used. Six major bond-strength tests were identified, namely 'tensile', 'shear' and 'push-out', each in a 'micro' and 'macro' variant. The μ TBS and macro-shear bond-strength (MSBS) tests together

represented 83% of all tests (Fig. 1). Therefore, further analysis was limited to these 2 set-ups and was conducted separately, given the considerably different bond strength (Fig. 1) and loading conditions.

Two-way ANOVA indicated that 'adhesive class' as well as 'artificial aging' significantly affected the μ TBS outcome (Fig. 2). For the MSBS, only aging had a significant effect. Consequently, the discriminative power of a micro-tensile test appeared better than that of a macro-shear test. To substantiate this observation further, the 'control' bond strength of 2 frequently tested adhesives (Clearfil SE Bond, Kuraray and Adper Prompt L-Pop, 3M ESPE) was investigated in detail. μ TBS testing revealed a distinct and significant difference between both adhesives ($p < 0.0001$), while for the MSBS test, the relative difference was smaller and non-significant ($p = 0.3716$).

Most correlations observed were low (highest $r = 0.28$) and non-significant (Table 2). For the μ TBS subset, bond strength decreased significantly with increasing water-storage time (Table 2). To assess bond durability water-storage was used in 51 of the 295 retained studies. For the macro-shear subset, bond strength also decreased with storage time but not significantly. Thermo-cycling is the second most-used artificial aging methodology (39 studies), although 16 studies did not have a control group without thermo-cycling. The number of thermo-cycles, varying between 300 and 100,000, did however not affect bond strength (Table 2).

The BIOMAT database contains only μ TBS data, in majority to bur-cut dentin. The methodology varied only slightly over the years and only a limited amount of operators (< 20) were involved. This resulted in a more consistent database than obtained from literature, but less representing the whole spectrum of experimental conditions. As the same inclusion criteria were employed as for the literature review, only 197 out of the 969 records contained relevant data, of which the majority was short-term bond-strength to bur-cut dentin. Some relevant data regarding extended water-storage and thermo-cycling were gathered as well (Fig. 3, web appendix Table 1). Overall a similar trend was observed as in the micro-tensile subset of the literature review (Table 3), though some differences were more pronounced. So is the bond strength of Adper Prompt 37% lower than the three-step gold standard as predicted by the ANN, while in the BIOMAT database it is 48% lower.

Artificial Neural Networks (ANN)

The aim of the sensitivity analysis (Table 1) was to classify the meta-model input parameters according to their influence on the predicted dentin bond strength (the higher the value, the more relevant). The two variables most determining for the bond-strength outcome were the 'research group' and the 'adhesive' (2.9 and 2.81, respectively); both had almost three times more impact on bond strength than the least important variables: 'storage time', 'thermo-cycling' and 'age of the adhesive' (1.07, 1.02 and 1.02 respectively).

Mean bond strength was predicted for the most prevalent adhesives tested in 'control' conditions (per manufacturer's instructions, bonded to SiC-paper ground dentin and tested within 1 week) and as it would be measured by the 7 most productive 'research groups' (Table 3). The mean bond strength of the best performing adhesive was almost twice as high as that of the least performing adhesive. Noteworthy is also that the range of predictions is very wide, as also appears from literature. For example, the 'control' bond strength reported in literature for OptiBond FI (Kerr) and One-up Bond F (Tokuyama) ranges from 33-81 MPa ($n = 31$) and from 11-51 MPa ($n = 20$), respectively. This range is in line with the ANN-predicted range of 39-58 MPa and 14-43 MPa, respectively. Similarly, the bond strength as would be obtained after one-year water storage or when the adhesive was bonded to dentin prepared by a diamond bur (as opposed to SiC-paper), was predicted using ANN. Both consistently resulted in a decrease, ranging from 5 to 39%, in comparison to 'control' bond-strength data (Table 2). The magnitude of this decrease differed for each

adhesive. Some adhesives were more affected by water storage, others more by bur preparation. Noteworthy is that adhesives with a higher 'control' bond strength, appeared less sensitive to aging. From the 10 most frequently tested adhesives, the highest predicted 'control' bond strength was recorded for OptiBond FL (Table 3); it appeared also least affected by aging and bur preparation (10% and 5% decrease, respectively). A little lower 'control' bond strength was recorded for the mild self-etch adhesive Clearfil SE Bond (Kuraray), for which the predicted decreases were 15% after aging and 21% when applied to bur-cut dentin. The lowest 'control' bond strength and highest bond-strength reduction (upon aging and bur-cut preparation) was recorded for One-up Bond F. A similar tendency was noted for other all-in-one adhesives.

When the adhesives that were most frequently tested in literature, were grouped per 'adhesive class' (Van Meerbeek *et al.*, 2003), the highest and most aging-resistant bond strength was found for the 2-step self-etch adhesives, closely followed by the 3-step etch&rinse adhesives (Table 3). Although the 'control' bond strength of the 2-step etch&rinse adhesives were in the same range, they were much more affected by aging. One-step self-etch adhesives were affected considerably by aging as well as by bur-cut preparation.

Discussion

In this review, 295 bond-strength studies were included, considerably more than the 75 studies in a literature review conducted 10 years ago (Leloup *et al.*, 2001, review period 1992 – 1996), even with our stricter inclusion criteria. In this meta-analysis, studies testing only a single commercial adhesive were excluded, while they made up 32% of the data in the previous review. Given the enormous amount of data included, and for instance the fact that 7 out of the 10 most tested adhesives (Table 2) are at this time of publication still commercially available, and that very recent "state-of-the-art" assessments of literature (Pashley *et al.*, 2011; Van Meerbeek *et al.*, 2011) revealed no significant advancement in adhesive technology, nor in bond-strength study design, it is very likely that the outcome of this systematic analysis will remain relevant for quite some time to come. Two major test set-ups were present in literature, of which the micro-tensile test had a higher discriminative power than the macro-shear test. This may explain the current popularity of μ TBS testing in the research community: in the period 1992-1996 macro-shear testing still provided 75% of the data reported (Leloup *et al.*, 2001), while this dropped to 22% in this study (2004-2009). This is substantiated by the observation that macro-shear testing apparently has no value in prediction of clinical performance (Heintze and Rousson, 2011), in contrast to the μ TBS that correlated with the 2-year and 5-year outcome of Class-V clinical studies (Van Meerbeek *et al.*, 2010; Heintze and Rousson, 2011).

Statistical analysis of this meta-analytical review was based on ANN. This methodology is inspired on the working mechanism of the human brain and its principles are based on crude and low-level models of biological neural information processing systems. Neural networks have a remarkable ability to derive and extract meaning, rules, and trends from complicated, noisy, and imprecise data (Bishop, 1995). This neural network model-building technique is an alternative to more traditional statistical methods like general linear models and is getting popular not only in research, but also in fields as engineering and marketing (Paliwal and Kumar, 2009). Recently, ANN has been used to assess meta-analysis data in clinical psychology from 'dot-probe' tests conducted by diverse researchers (Frewen *et al.*, 2008). A similar network-building technique was used to disclose interdependencies between brain regions from functional MRI imaging data collected from more than 500 imaging studies (Neumann *et al.*, 2010). This demonstrates the versatility and wide range of applications for these ANN, especially for the analysis of a large amount of heterogeneous data. Generalization of the results of any of these models, i.e. to predict the outcome of tests not available

in the database, is possible in case a proven methodology is followed (Kleijnen and Sargent, 2000) and when appropriate validation took place. Therefore, in this study, a part of the data (a random subset with 20% of the original data) was masked from the model fitting algorithm and only used to validate the observed data. This also allows controlling over- and under-fitting of the model to some degree.

The most significant parameter identified by ANN was the 'research group', which can be regarded as an aggregate parameter for all variables that are (hopefully more or less) standardized within one testing laboratory. Additionally, parameters included in the current analysis, like composite flexural modulus and substrate origin, are standardized in many research groups, which may reduce the sensitivity of these parameters, hence the reported effect is smaller than their real effect on the bond-strength outcome. This is also the main reason why experimental parameters, such as crosshead speed, clamping method, storage solution, specimen shape, etc. were not recorded; within each research group all these experimental parameters are standardized to enable intra-study comparison. For inter-study comparison, as primarily aimed with this review, test variability induced by specimen preparation and testing protocols cannot be neglected (Rueggeberg *et al.*, 1991; Betamar *et al.*, 2007, Poitevin *et al.*, 2007). Different sources of variability can be identified: biological substrate variability (Shono *et al.*, 1999) and substrate processing-induced differences, as for example different kinds of smear layer, specimen size and preparation (Oliveira *et al.*, 2003; Van Meerbeek *et al.*, 2003; Cardoso *et al.*, 2008; Ermis *et al.*, 2008). Even minute modifications of the test set-up can change the outcome considerably, as suggested by finite element analysis and practical testing (Rueggeberg *et al.*, 1991; Fowler *et al.*, 1992; Betamar *et al.*, 2007; Poitevin *et al.*, 2007). Given the heterogeneity of test results collected worldwide, inter-study comparison may appear useless (Scherrer *et al.*, 2010). However, from this big amount of blurred data we were able to disclose some trends in bonding effectiveness to dentin using an ANN approach. The parameter 'research group' accounted for most of the variability in bonding effectiveness and therefore appeared most determining for the outcome. As a result, our 'predicted' bond-strength values largely varied, similar to bond strengths published in literature (Scherrer *et al.*, 2010). But unlike literature, our 'predicted' bond-strength values are equally distributed and thus mutually comparable, thereby better representing real adhesive performance. An example in the BIOMAT database of this effect is that two-step self-etch adhesives apparently do not degrade by water storage (Web appendix Table 1). This has however partly to be attributed to the fact that in the water storage group, only very few groups, with better performing adhesives (Clearfil SE and Clearfil Protect Bond) are present. Therefore, these grouped performances are less reliable, when analyzed by conventional techniques, while by ANN this poses less of a problem.

A major concern in any meta-analysis is bias of the retrieved data at study level as well as at the outcome level (publication bias). Unlike clinical studies, randomization and blinding is uncommon for bond-strength studies and therefore no measure for the quality of the included studies. Therefore, also a guideline as the PRISMA statement (Moher *et al.*, 2009), which is aimed at clinical interventions, is less applicable to the current review (Web appendix Table 4). Quality of the included studies was preserved by applying strict inclusion criteria. At study level, bias was further minimized by the fact that mostly 'control' data were used and the actual experimental groups (involving experimental compositions/conditions), more prone to reporting bias, were often not included in the database. To assess publication bias, data of the literature review were compared to data obtained in a single research lab. Overall, the similarities are prevailing. The two best performing adhesives are exactly the same; overall one-step self-etch adhesives do underperform and are prone to degradation upon water storage; adhesive performance is affected by water storage, while thermo-cycling has a negligible effect. Noteworthy is that in the BIOMAT database differences induced by experimental conditions are more pronounced (e.g. 1-year water storage induces a decrease of up to 72%, while only up to 36% is predicted by ANN). This must be attributed to the attenuating effect of pooling many

studies and the specific statistics employed that appear to result in a more conservative outcome. So overall, the effect of publication bias is minimal, apart from a publication delay as exemplified by the non-existence of self-adhesive filling materials in literature, while these are already available in the BIOMAT database.

The best performing adhesive at both short and long term was the three-step etch&rinse adhesive OptiBond FL (Kerr). This so-called 'gold standard' adhesive indeed presents with a very favorable laboratory (Peutzfeldt and Asmussen, 2006; Sarr *et al.*, 2009) and clinical (Boghosian *et al.*, 2007; Peumans *et al.*, 2011) performance. The second best performing adhesive in this meta-analysis was the two-step self-etch adhesive Clearfil SE Bond (Kuraray), a mild self-etch adhesive, which is also reputed for its excellent long-term laboratory as well as clinical performance (Peumans *et al.*, 2007; Osorio *et al.*, 2008).

Major clinical concerns regarding today's adhesive technology are technique sensitivity and bond durability (Van Meerbeek *et al.*, 2005), which both were assessed in this meta-analysis. In 16% of the database records, some aspects regarding technique sensitivity of adhesives were tested, such as increased/decreased etching time, adapted hydration state of the etched dentin, application of additional layers, increased/reduced air blowing, etc.. None of these adapted application protocols were, however, consistently applied by multiple authors so that a numerical appreciation was not possible. Pooling of all these modifications revealed only a very small reduction in bond strength, as compared to 'control' data, applied as per manufacturers' instructions (31.3 versus 31.5 MPa, respectively). One specific parameter is related to the way dentin is prepared prior to bonding. Most used preparation methods identified in this review were preparation by either a carbide or diamond dental bur or by silicon-carbide (SiC) paper. Overall, etch&rinse adhesives appeared less affected when prepared by a dental bur (versus SiC-paper), while self-etch adhesives appeared more affected, especially the one-step version. This is not unexpected, because a bur-cut dentin surface is covered with a thicker and more compact smear layer (Oliveira *et al.*, 2003) and thus may impede the bonding effectiveness of especially (ultra)-mild self-etch adhesives (Koshiro *et al.*, 2006). It should be stressed that in simulation of what is clinically done, dentin is best prepared by bur, although in many bond-strength studies adhesives are bonded to SiC-ground dentin.

Regarding bond durability, more consensus in assessment methodology is present in literature. In 92% of the durability data, thermo-cycling or extended water storage was applied. Therefore, both methodologies were included in the ANN analysis as well as in the correlation analysis. Because of methodological issues, the sensitivity of both parameters was not very high in the ANN analysis, but some interesting conclusions can be drawn based upon correlations as well as predictions. First, 'thermo-cycling' did not affect the outcome of bond-strength tests, as was also shown in the previous review (Leloup *et al.*, 2001). Partially, this may be due to the low number of thermo-cycles employed in most studies (mean/median was 6657/1150 cycles). Simple 'water storage' has, however, a clear bond-degrading effect; it mimics the clinically observed restoration degradation very well (Hashimoto *et al.*, 2000; De Munck *et al.*, 2005). Our correlation analysis indicated that μ TBS degrades significantly ($p < 0.0001$) upon water storage. Neural network predictions do however point out that different adhesives degrade differently; bond-strength reductions ranged from 10 to 35% (Table 3). The actual composition of the different adhesives, particularly the monomers, solvents and initiators used, may account for this observed variability. Data in the BIOMAT database appear more affected by water storage (Web appendix Table 1), which is, apart from methodological issues, also related to the storage of micro-specimens (direct exposure to water) instead of the whole restored teeth (indirect exposure) in most literature. Not surprisingly, especially three-step etch&rinse and two-step self-etch adhesives appear most resistant to hydrolytic degradation; they provide a separate, more hydrophobic resin layer as final application step.

In summary, despite the lack of a standard bond-strength protocol, this meta-analysis allowed, thanks to the vast amount of data available, to draw some clear conclusions with regard to the bonding effectiveness of different adhesive approaches to dentin. Moreover, there exists a definite need to measure not only the 'immediate' bond strength, but also 'aged' bond strength in prediction of long-term clinical performance. Finally, in simulation of a clinically produced smear layer, a dental bur should be preferentially used in laboratory bond-strength testing.

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FIGURES

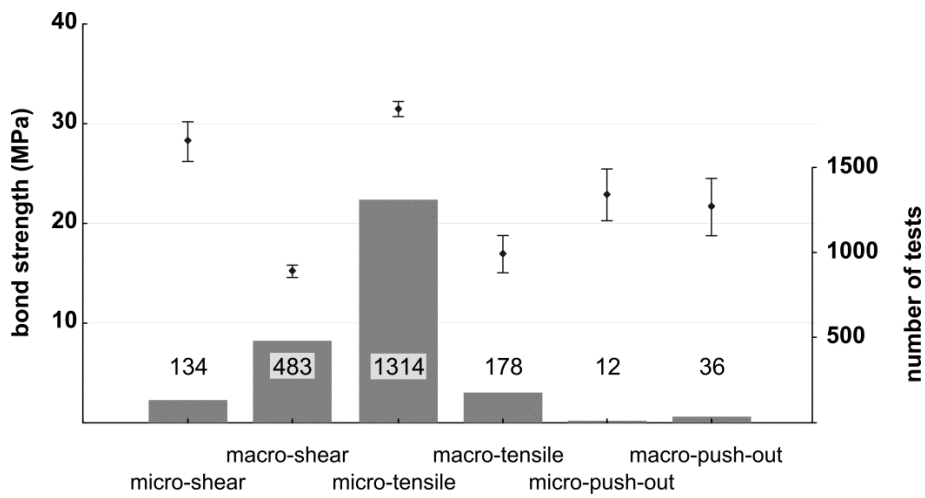


Fig. 1 Mean bond strength in MPa (whiskers denote 95% confidence intervals), categorized for the different test set-ups (left axis), along with a histogram for the same set-ups (right axis).

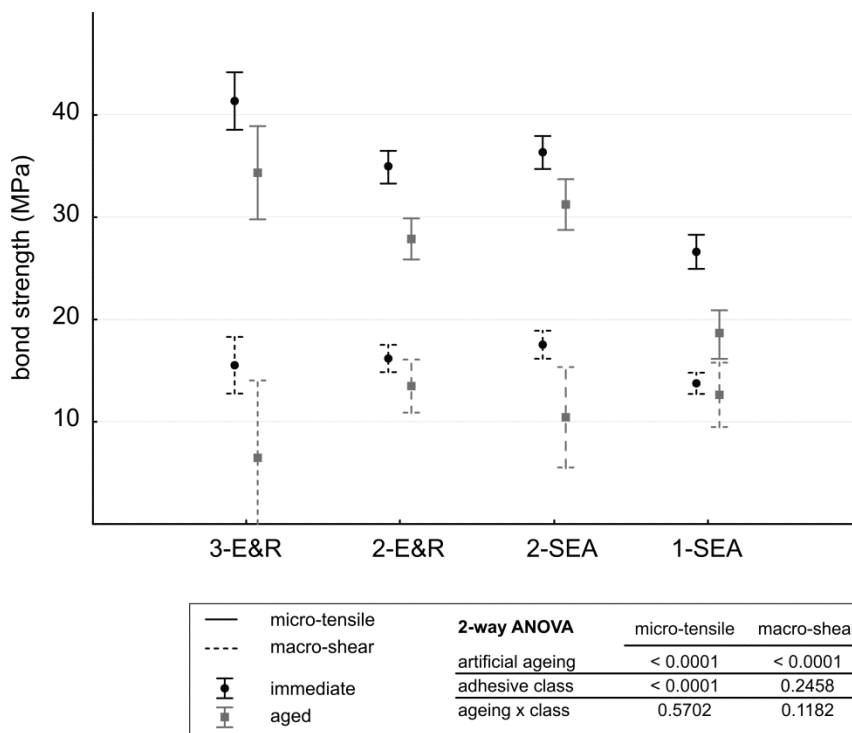


Fig. 2 Mean bond strength in MPa (whiskers denote 95% confidence intervals) and ANOVA analysis for the two most common tests (micro-tensile and macro-shear), categorized per adhesive class (according to Van Meerbeek *et al.*, 2003) and presence of artificial aging. Groups employing an adapted adhesive application were excluded from the analysis.

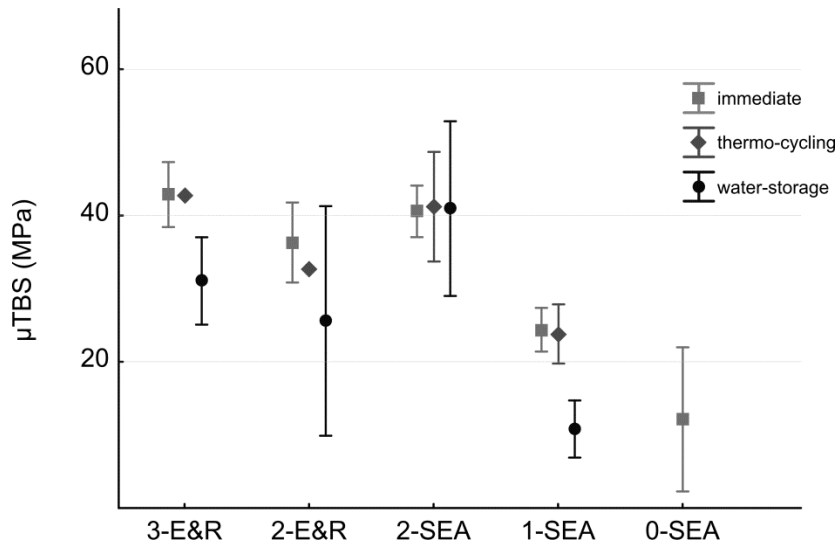


Fig. 3 Mean micro-tensile bond strength (μ TBS) in MPa (whiskers denote 95% confidence intervals) as obtained from the BIOMAT database, categorized by adhesive class (according to Van Meerbeek *et al.*, 2003) and application of artificial aging. *0-SEA = 0-step self-etch adhesives or self-adhesive composite filling materials.

TABLES

Table 1 Artificial network model parameters and average sensitivity of the retained models.

Model parameters	Mean sensitivity*
research group	2.90
adhesive	2.81
control, aging or other	2.16
adhesive classification	2.02
substrate Preparation	1.68
substrate origin	1.48
composite flexural modulus	1.11
storage time	1.07
thermo-cycling	1.02
adhesive age	1.02

*The sensitivity values give an idea of the respective importance of these parameters in the statistical model.

Table 2 Correlation analyses.

	micro-tensile		macro-shear	
	r	p-value	r	p-value
storage time	-0.2793	< 0.0001	-0.2791	0.0772
thermo-cycling	0.1413	0.1742	0.0078	0.9291
composite flexural modulus	0.1640	0.0001	-0.0051	0.9444
age of adhesive	-0.1839	< 0.0001		
age of adhesive – 3-E&R	0.2474	0.0525		
age of adhesive – 2-E&R	0.0199	0.7775		
age of adhesive – 2-SEA	0.0513	0.4832		
age of adhesive – 1-SEA	0.2016	0.0049		

Pearson correlation coefficient and associated p-value of different parameters involved to measure the bond strength to dentin, as measured by a micro-tensile or macro-shear test set-up. correlation analyses for the different subsets of adhesive classes. 3-E&R = 3-step etch&rinse adhesives; 2-E&R = 2-step etch&rinse adhesives; 2-SEA = 2-step self-etch adhesives; 1-SEA = 1-step self-etch adhesives.

Table 3 Bond strength (in MPa) as predicted by the artificial neural networks (ANN)

		SiC 1-day ¹		Bur-cut 1-day ²		SiC 1-year ³	
		n ⁴	μTBS ⁵	μTBS ⁵	decrease ⁶	μTBS ⁵	decrease ⁶
ADHESIVE CLASS	3-E&R	113	41.7 19.1 - 57.6	36.1 5.4 - 60.6	13%	34.6 12 - 54.3	17%
	2-E&R	400	39.1 22.1 - 51.4	34.4 7.2 - 53.9	12%	27.8 2.9 - 57.4	29%
	2-SEA	281	42.7 23.6 - 56	37.9 6 - 60.1	11%	37.1 21 - 51.9	13%
	1-SEA	271	34.4 13.9 - 52.4	25.2 0.7 - 50.3	27%	23.2 5.9 - 42	33%
ADHESIVE							
Optibond FL	3-E&R	45	49.7 39.1 - 57.6	47.3 25.5 - 60.6	5%	44.8 29.6 - 54.3	10%
	Kerr						
Clearfil SE Bond	2-SEA	225	45.4 28.5 - 56	35.8 6.6 - 54.2	21%	38.6 21 - 51.9	15%
	Kuraray						
Scotchbond 1	2-E&R	196	42.2 29.7 - 51.4	34.4 7.5 - 50.5	18%	30.9 4.5 - 57.4	27%
	3M ESPE						
Xeno III	1-SEA	46	38.6 29.1 - 48.3	34.5 11.9 - 50.3	11%	28.6 16.4 - 42	26%
	Dentsply						
Adper Scotchbond Multi	3-E&R	47	38.4 22.5 - 49.2	31.5 5.4 - 49.6	18%	30.3 14.4 - 43	21%
	-Purpose 3M ESPE						
Clearfil S³ Bond	1-SEA	60	37.8 24.6 - 49.9	26.9 2.8 - 44.8	29%	26.1 12.1 - 40.6	31%
	Kuraray						
One-Step	2-E&R	55	36.3 23.3 - 48.8	32.8 7.8 - 45.6	10%	23.2 3.7 - 49.7	36%
	Bisco						
Prime&Bond NT	2-E&R	45	35.9 22.1 - 46.3	30.7 7.2 - 46.2	15%	23.5 2.9 - 44.2	35%
	Dentsply						
Adper Prompt L-Pop	1-SEA	61	31.4 18 - 43.9	20.0 1.3 - 39.6	36%	20.4 8.1 - 34.4	35%
	3M ESPE						
One-up Bond F	1-SEA	44	27.9 13.9 - 42.8	16.9 0.7 - 34.8	39%	18.0 5.9 - 34.9	35%
	Tokuyama						

Mean predicted bond strength in MPa. Values reported for 'adhesive class' are the means pooled for all adhesives tested more than 15 times in the database. ¹'SiC 1-day' = immediate bond strength to SiC-ground dentin after 1-day water storage; ²'Bur-cut 1-day' = immediate bond strength to bur-cut dentin after 1-day water storage; ³'SiC 1-year' = bond strength to SiC-ground dentin after 1-year water storage; ⁴n = times tested in database; ⁵μTBS = mean micro-tensile bond strength in MPa, along with the the lowest and highest prediction for the respective adhesive class/adhesive in any of the 4 models as predicted by any of 7 'research groups'; ⁶Reduction in percentage versus the control (SiC 1-day) bond strength.

WEB APPENDIX

Table 1 Micro-tensile bond-strength data of 'BIOMAT' database.

ADHESIVE CLASS ⁴	Bur-cut short-term ¹			Bur-cut thermo-cycling ²				Bur-cut water storage ³				
	μTBS ⁵	n ⁶	Std. err. ⁷	μTBS	n	Std. err.	% decrease ⁸	μTBS	n	Std. err.	% decrease	
3-E&R	42.9	25	2.2	42.8	2	5.7	0%	31.1	7	2.4	28%	
2-E&R	36.3	16	2.6	32.6	1		10%	25.6	3	3.6	30%	
2-SEA	40.6	48	1.8	41.2	7	3.1	-2%	40.9	9	5.2	-1%	
1-SEA	24.4	47	1.5	23.8	13	1.9	2%	10.8	10	1.7	56%	
0-SEA	12.1	5	3.5									
ADHESIVE												
Optibond FL (Kerr)	3-E&R	43.5	23	2.2	42.8	2	5.7	2%	31.1	7	2.4	29%
Clearfil SE Bond (Kuraray)	2-SEA	43.5	30	2.0	39.0	5	3.9	10%	38.8	6	7.5	11%
Clearfil Protect Bond (Kuraray)	2-SEA	42.6	5	3.4				45.3	3	5.4	-6%	
Adper Scotchbond 1 XT (3M ESPE)	2-E&R	38.6	4	5.0				25.6	3	3.6	34%	
G-Bond (GC)	1-SEA	31.6	13	2.5	27.1	4	5.8	14%	8.7	4	1.8	72%
Bond Force (Tokuyama)	1-SEA	24.2	5	3.8								
Adper Prompt L-Pop (3M ESPE)	1-SEA	22.5	4	4.8	21.2	2	3.0	6%				
iBond (Heraeus)	1-SEA	19.9	6	2.8	18.6	2	0.2	7%	10.9	2	0.8	45%
AdheSE One (Ivoclar-Vivadent)	1-SEA	10.0	5	0.7				9.0	3	1.5	10%	

195 out of 972 tests in the database matched the inclusion criteria. ¹'Bur-cut short-term' = immediate bond strength to diamond bur-cut dentin after 24-hour or 1-week of water storage; ²'Bur-cut thermo-cycling' = bond strength to diamond bur-cut dentin after thermo-cycling for 1800 to 20000 cycles (10991 cycles on average); ³'Bur-cut water storage' = bond strength diamond bur-cut dentin after 6-month or 1-year water storage. ⁴Values reported for 'adhesive class' are the means pooled for all adhesives in the database, adhesives were categorized according to the classification of Van Meerbeek *et al.* (2003): 0-SEA = self-adhesive composites; 1-SEA = 1-step self-etch adhesives; 2-SEA = 2-step self-etch adhesives; 2-E&R = 2-step etch&rinse adhesives; 3-E&R = 3-step etch&rinse adhesives; ⁵Weighted means in MPa; ⁶Times tested in the 'BIOMAT' database; ⁷Standard error of the mean; ⁸Reduction in percentage versus the control (immediate) bond strength.. n = times tested in database.

Table 2 Parameters stored in the database for every manuscript.

Field	example
AB - PubmedID	This study evaluated the effect of 2%,...
AD - PubmedID	Department of Restorative Dentistry, ...
AU - PubmedID	Komori PC, ...
DA - PubmedID	20090414
DCOM - PubmedID	20090812
DP - PubmedID	2009 Mar-Apr
IP - PubmedID	2
IS - PubmedID	0361-7734 (Print)
JID - PubmedID	7605679
Journal - PubmedID	Oper Dent
JT - PubmedID	Operative dentistry
MH - PubmedID	Acid Etching, Dental, ...
OWN - PubmedID	NLM
PG - PubmedID	157-65
PMID - PubmedID	19363971
PT - PubmedID	Research Support, Non-U.S. Gov't
RN - PubmedID	0 (Composite Resins), ...
SB - PubmedID	D
SO - PubmedID	Oper Dent. 2009 Mar-Apr;34(2):157-65.
STAT - PubmedID	MEDLINE
TA - PubmedID	Oper Dent
TI - PubmedID	Effect of 2% chlorhexidine,...
VI - PubmedID	34
ID of the study in the database	Study_ID_1345
Brand name of composite used	Filtek Z250
Type of light-curing unit	halogen
Study involves extended water storage (yes/no)	yes
Study involves thermocycling (yes/no)	no
Study involves some other kind of aging (yes/no)	no
Different storage periods (in months)	week, 6
Origin of the dentin substrate (human / bovine)	human
Type of substrate	caries-affected dentin, dentin
Preparation of the substrate prior to adhesive procedures	SiC paper
Study involves alternative application technique (yes/no)	no
Application techniques used	Instructions of manufacturer
Number of teeth used per experimental group	5
Size of test area in mm ²	0.81
Test area (micro/macro)	micro
Shape of the tested interface (square/round)	square
Test mode (tensile/shear/push-out)	tensile
Author with highest number of citations in the database	Pashley DH
Review_status	reviewed

Table 3 Parameters stored in the database for every experimental group.

field	example
ID of the experimental group in the database	Gr_2111
ID of the study in the database	Study_ID_1345
Size of test area in mm ²	0.81
Size of test area (micro/macro)	micro
Test mode	tensile
Type of test	micro-tensile
Control group (yes/no)	no
Durability group (yes/no)	yes
Storage time in months	6
Number of thermocycles	0
Adhesive brand name	Scotchbond Multi-purpose
Adhesive brand name as looked up in database	Adper Scotchbond Multi-Purpose
Composite brand name	Filtek Z250
Type of light-curing unit	halogen
Adhesive application technique employed	Instructions of manufacturer
Altered application technique employed (yes/no)	no
Mean bond strength in MPa	28.0
Number of specimens in the group	48
Number of pre-testing failures in this group	2
Standard deviation	6
Number of teeth used in this group	5

1.1 Table 4 Prisma 2009 checklist

Section/topic	#	Checklist item	Reported on page #*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	I, §2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	M&M, §1**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	M&M, §1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	M&M, §1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	M&M, §1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	M&M, §1

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	M&M, §1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	WA, p. 3-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	D, §3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	M&M, §4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	M&M, §5

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	D, §3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	M&M, §4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	R, §1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	D, §3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	T3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	D, §3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	WA P 5-8, T2

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	D, §7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	D, §2,3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	D, §7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Ac

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

*A = Abstract; I = Introduction; M&M = Materials and Methods; R = Results; D = Discussion; Ac = Acknowledgements; WA = Web Appendix; T = Table and NA = Not available/applicable; **The PICOS concept focuses on randomized trials and is particularly useful for the evaluation of interventions and is therefore not completely applicable to the current review.

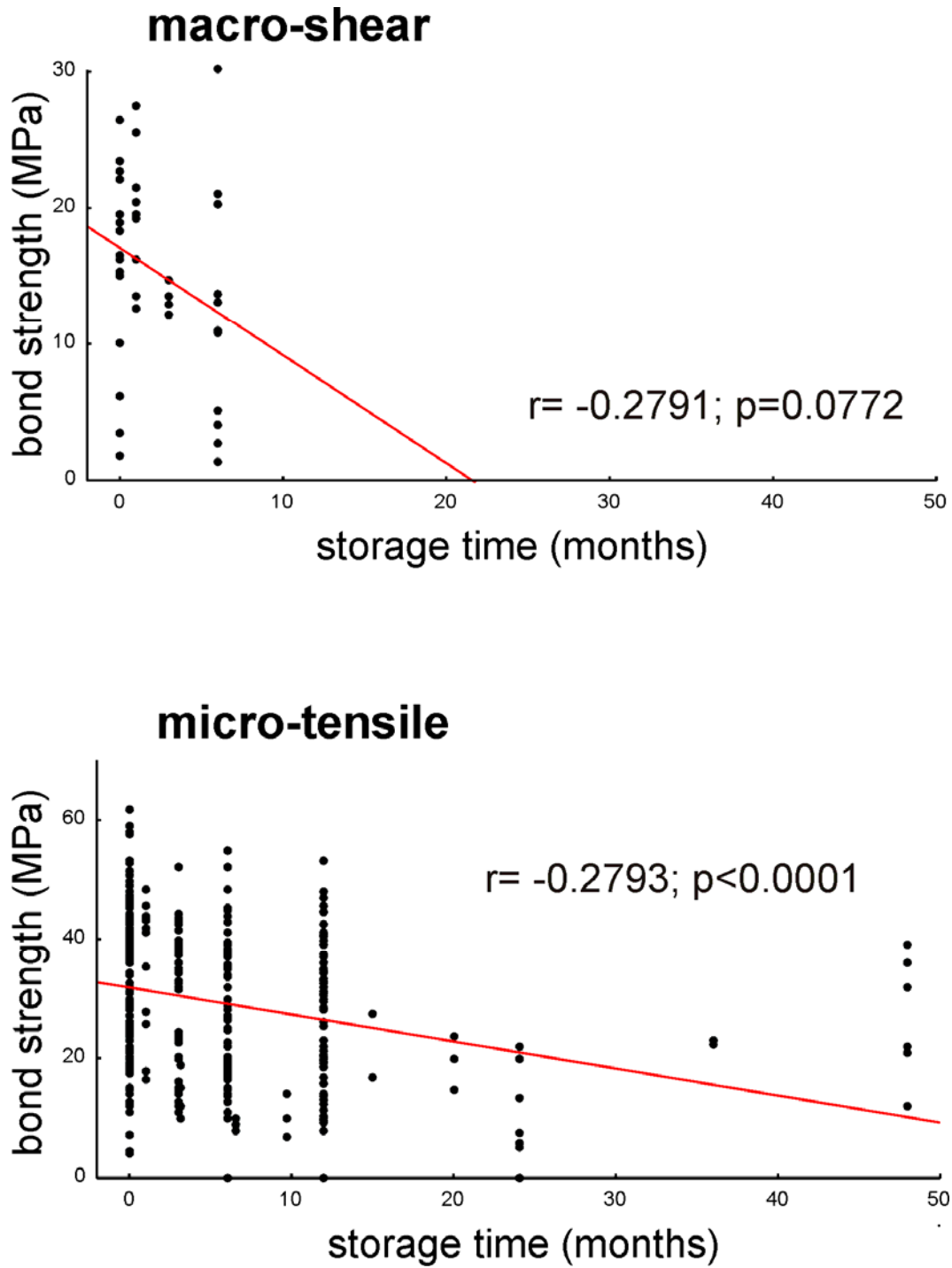


Figure 1 Correlation analysis – effect of water storage. The bond strength measured in studies employing extended water storage was plotted against the storage time used and categorized for the 2 most common tests (micro-tensile and macro-shear).

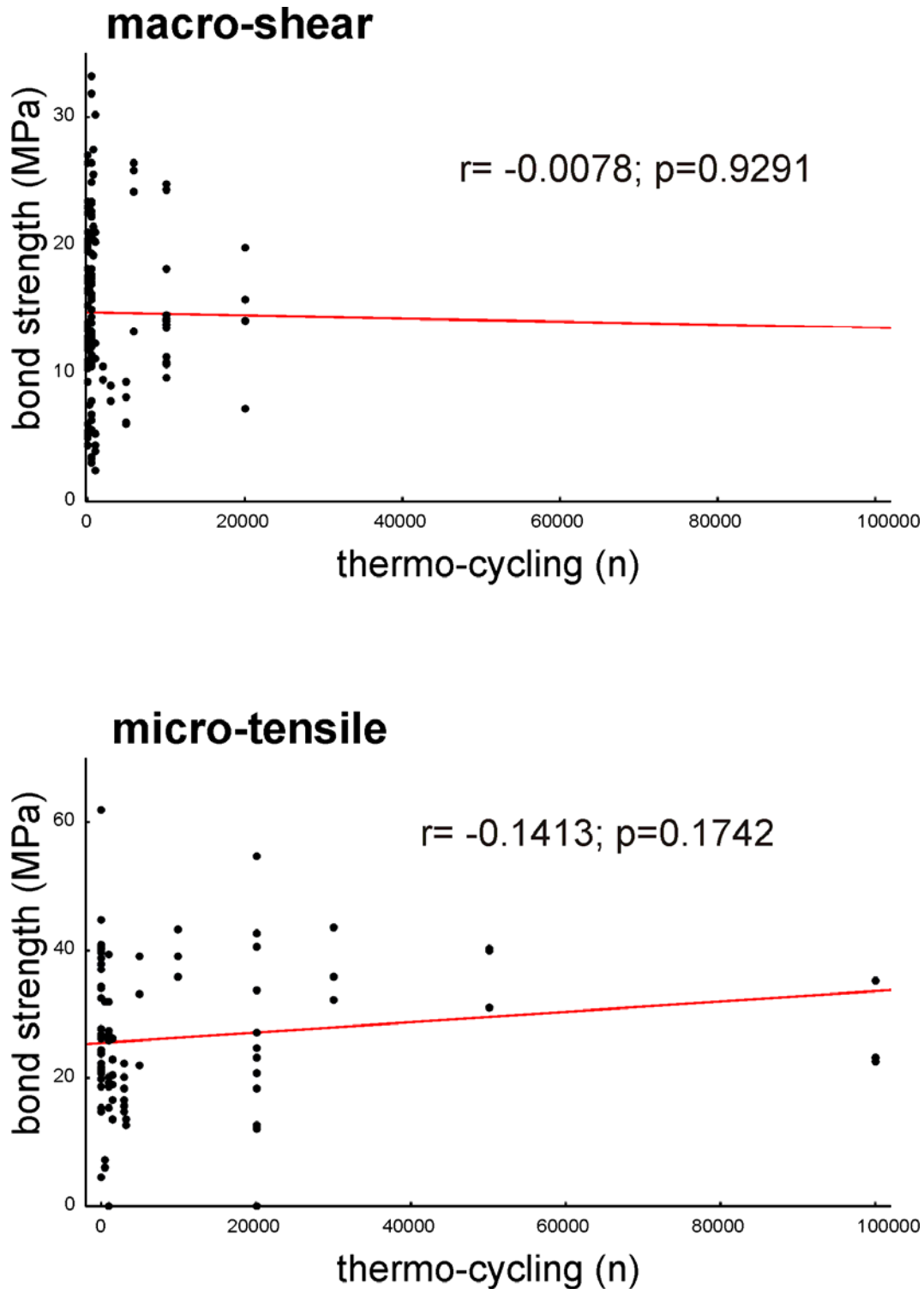


Figure 2 Correlation analysis – effect of thermo-cycling. The bond strength measured in studies employing thermo-cycling was plotted against the number of thermo-cycles used and categorized for the 2 most common tests (micro-tensile and macro-shear). As data for micro-tensile studies were not equally grouped (very few data with very long thermo-cycling), also the non-parametric Spearman rank correlation was calculated, but this correlation was also very small, negative and non-significant (-0.0735).

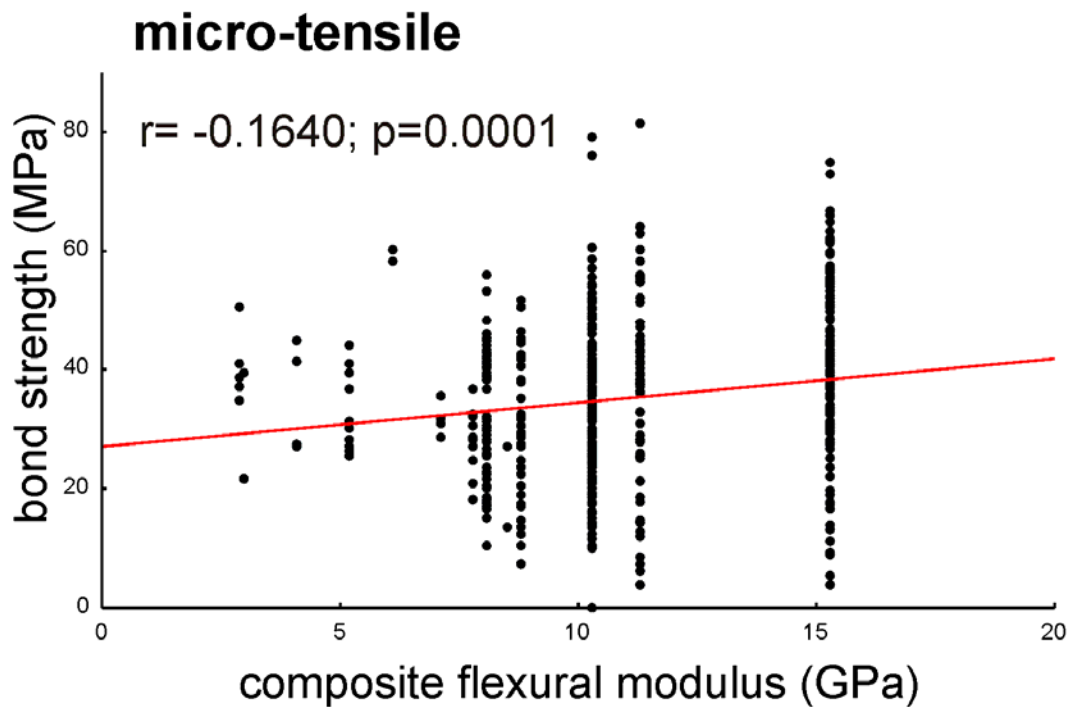
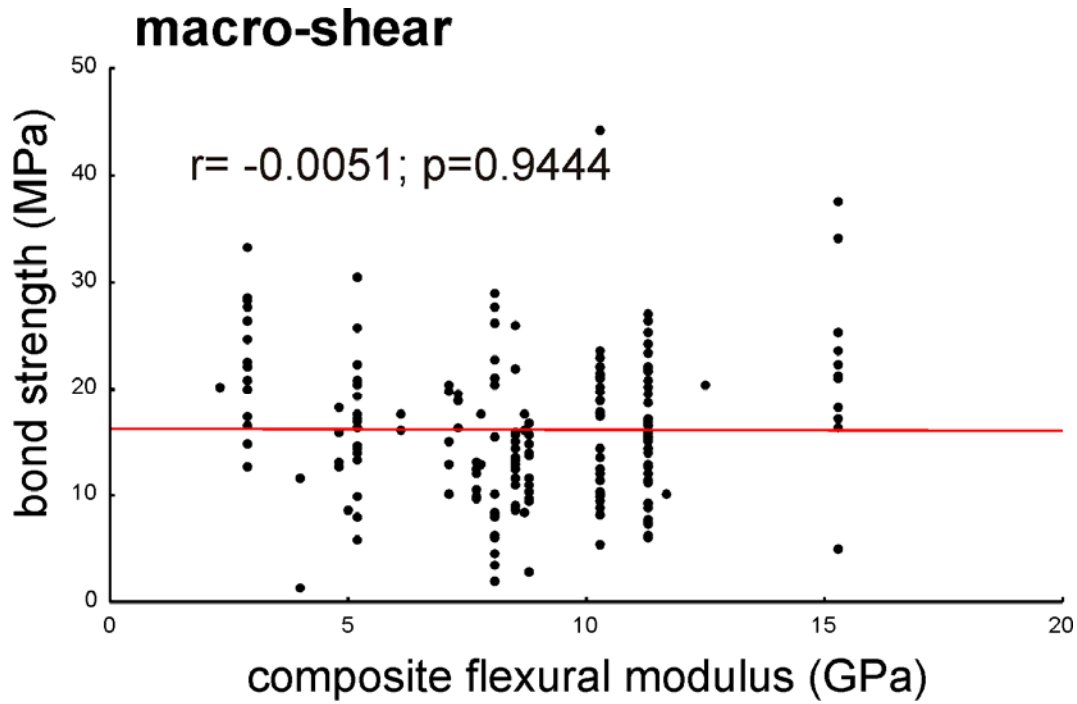


Figure 3 Correlation analysis – effect of composite. The bond strength of control (no aging, no other factors) tests was plotted against the composite flexural modulus (retrieved from Ilie *et al.* 2009) of the resin composite used in GPa and categorized for the 2 most common tests (micro-tensile and macro-shear).

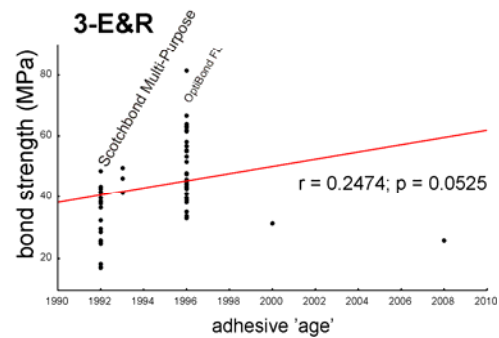
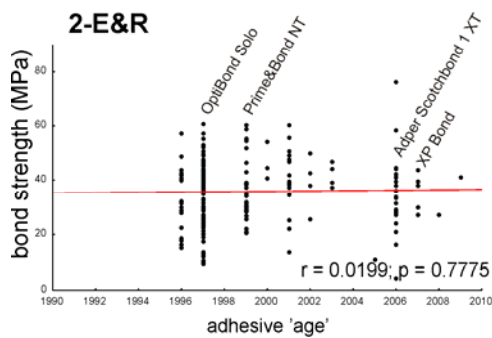
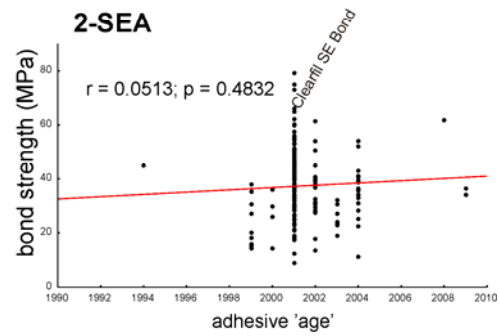
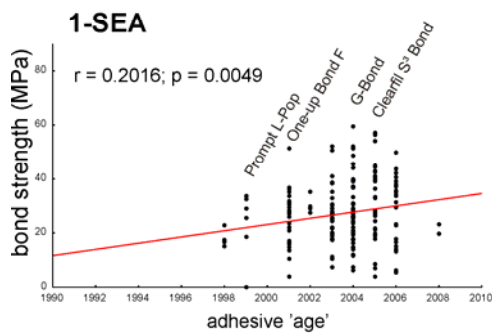
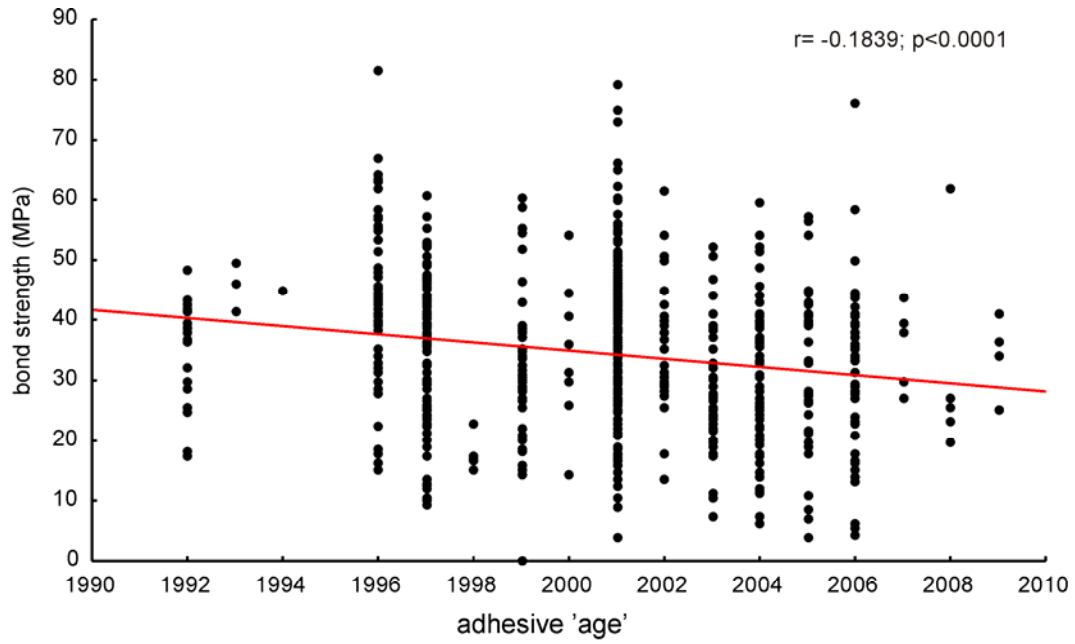


Figure 4 Correlation analysis – effect of adhesive 'age'. The micro-tensile bond strength of control (no aging, no other factors) tests was plotted against the year of first appearance in PubMed of the respective adhesive. Additionally the data were categorized by the adhesive approach (micro-tensile and macro-shear).

List of papers included in the meta-analysis.

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2. Abdalla AI, El Eraki M, Feilzer AJ (2007). The effect of direct and indirect water storage on the microtensile dentin bond strength of a total-etch and two self-etching adhesives. *Am J Dent* 20:370-374.
3. Abdalla AI, El Zohairy AA, Aboushelib MM, Feilzer AJ (2007). Influence of thermal and mechanical load cycling on the microtensile bond strength of self-etching adhesives. *Am J Dent* 20:250-254.
4. Abdalla AI, Elsayed HY, Garcia-Godoy F (2008). Effect of hydrostatic pulpal water pressure on microtensile bond strength of self-etch adhesives to dentin. *Am J Dent* 21:233-238.
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15. Arrais CA, Giannini M, Nakajima M, Tagami J (2004). Effects of additional and extended acid etching on bonding to caries-affected dentine. *Eur J Oral Sci* 112:458-464.
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17. Asaka Y, Miyazaki M, Takamizawa T, Tsubota K, Moore BK (2006). Influence of delayed placement of composites over cured adhesives on dentin bond strength of single-application self-etch systems. *Oper Dent* 31:18-24.
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