Comparator choice in cariology trials limits conclusions on the comparative effectiveness of caries interventions

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Comparator choice in caries prevention and management trials

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Abstract

Comparator choice has been found one major factor impacting on the overall evidence supporting clinical interventions. We performed social network analysis on trials on the prevention/management of caries/carious lesions, hypothesizing that certain comparators are proportionally over-investigated, and others under-investigated, and that comparisons within comparator classes are preferred over comparisons between classes. A systematic review of randomized controlled trials on the prevention/management of caries/existing carious lesions was carried out. All comparators were classified at each of three levels of granularity, becoming more detailed with each level; (a) degree of invasiveness (non-, micro- or invasive), (b) the specific non-invasive, micro-invasive or invasive approach, (c) the actual material or technique used. Social network analysis was used to evaluate trial networks. Searching electronic databases found 4,774 articles of which 765 were relevant and 605 were included. The networks for all levels were polygonal. There was a high degree of separation of comparisons in prevention versus management trials. Invasive comparators were tested most frequently (number of comparators: 611), mainly in management trials. Non-invasive comparators were tested next often (474), mainly in caries prevention. Micro-invasive strategies were tested next often (233), in both prevention and management trials. On more granular levels, few interventions dominated the networks. Regardless of the level, the majority of trials compared within, not between classes. Prevention trials were mainly conducted in children (number of trials in adults/children/both: 37/241/11), while those on managing lesions were conducted in both children and adults (117/179/21). Comparator choice in cariology trials is driven by indication, and limits conclusions on the true comparative effectiveness of all strategies. There are a variety of comparators that have not been, but should be, compared to one another, which should be addressed by future trials. Factors underlying trialists' comparator choice need to be identified.

Keywords

clinical trial; caries prevention; caries treatment; evidence-based dentistry; randomized controlled trial; social networks

Introduction

Dental caries continues to be the most prevalent disease worldwide, burdening billions and generating significant healthcare costs (1-3). There are an increasing number of options for managing caries and carious lesions, fueled by a growing understanding of dental caries as a biofilm disease. Traditionally, invasive treatment strategies (i.e. those breaching the surface of a tooth, removing carious tissue and replacing it using restorations), have been the mainstay of caries lesion management. However, such invasive strategies, which are often required for treating cavitated caries lesions (4), do not manage caries causally, but symptomatically; treating the signs and sequelae of the disease rather than the condition itself. More recently, non-invasive or micro invasive treatment classes have been introduced as options for the management of caries lesions (5). Micro-invasive strategies (i.e. those modifying, but not breaching the surface) can be applied, installing a diffusion barrier against acids and thus protecting the tooth tissue against demineralization. Whereas non-invasive approaches (i.e. those without any operative, surface-modifying or breaching component), aim to control causal factors and avoid lesion progression or even promote lesion remineralization. The latter two strategies are also established for caries prevention, using technically the same approaches as for caries management. A wide variety of non-invasive, micro-invasive and invasive techniques and materials are available for caries control. However, albeit there is an increasing number of trials on caries management and prevention strategies available, the overall evidence on the true comparative effectiveness between these approaches is still unclear. To gain such evidence, it is not only necessary to perform comparative effectiveness research by conventional means (i.e. pairwise comparisons), but also to analyze to which extend comparisons between different interventions for a certain field have actually been made. This will help to inform clinicians and researchers where there might be an absence of evidence rather than evidence of an absence of effect and will help to identify potential promising areas of clinical research.

Much effort and resource has been devoted to improving the conduct and reporting of individual trials and systematic reviews (6, 7), resulting in improved quality of evidence that

can be achieved from recent clinical trials. However, there has been little attention paid as to what these trials have actually compared. This is similar to ensuring that a ship has the best radar, depth gauges and GPS (Global Positioning System) technology but without considering what direction the ship should sail in. The choice of trial comparator affects the value of the collective evidence, and can result in inefficient use of limited research resources (8):

- there may be imbalance in the co-occurrence of comparators, with certain strategies or strategy classes being compared against each other more often, while comparisons against other strategies are avoided (9-11), leaving gaps in the evidence due to the associated segmentation of trials.
- comparisons within the same strategy class instead of across classes might be preferred, a phenomenon called homophily (9-11). This weakens evidence usability and applicability in drawing conclusions about the relative effectiveness between different strategy classes.
- comparisons against less than optimal or weak comparators (so called straw men) or against placebo can lead to overestimation of effectiveness. Ultimately, the effect of including these in a comparison chain, where there has been no head-to-head testing against gold standards or against other treatment comparators where no gold standard is identified, could lead to significantly erroneous conclusions (10-12);

To assess these features, social network analysis (SNA), a mathematical method for evaluating the relationships between actors in the network (9) can be applied (13, 14). SNA has found homophily and co-occurrence of comparators in mycosis (9) and myeloma trials (13). In dentistry, we recently used this technique to analyze networks formed by clinical trials on different dental filling materials and adhesives to assess, if certain material classes were preferred or avoided as a comparators (15).

We aimed to investigate networks of comparators used within clinical trials on caries prevention and management of carious lesions. We hypothesized that certain comparators

are disproportionally investigated, and that comparisons within intervention classes are preferred over comparisons between classes. Our results might support trialists' decision making around comparator choice in future trials in the field.

Methods

Data collection process

This study used a database of trials established to investigate and improve trial methodology for preventing and managing carious lesions, and will also inform the definition of core outcomes sets for managing carious lesions (16).

This review is registered at PROSPERO (CRD42015025310). The Cochrane Central Register of Controlled Trials, MEDLINE (via PubMed) and EMBASE (via OVID) were searched until 25/08/15. The search strategy and screening procedure is shown in Fig 1. Two calibrated reviewers (NI, CL) independently screened titles and abstracts for eligibility. Study inclusion was decided with consensus through discussion.

Data extraction was performed by five calibrated authors independently using a piloted spreadsheet. Given the large number of articles included and the aim of our review, we included each eligible article as a separate entity and data extraction was performed by one of the five authors per study. After the initial phase of data extraction, we performed a duplicative re-extraction on 5% of studies to check for inconsistency of extracted data. This re-extraction was performed by another reviewer than the original reviewer for the different studies. If in a certain item nonconformity was 10% or greater, all entries for this item were re-extracted, again by a different reviewer than during the initial extraction phase. If disagreement occurred, this was resolved by discussion. We found nonconformity in the initially extracted data was greater than 10% for the items setting, the number of participants and whether the focus of the trial was prevention or management. Accordingly, these data were re-extracted for all included studies.

Data were recorded according to Cochrane Collaboration guidelines (17). The following data were extracted:

- Study authors/ years
- Sample size
- Study setting
- Indication (caries disease management through prevention, i.e. no lesion present, or carious lesion management, i.e. lesion present)
- Outcomes assessed (primary, secondary)
- Comparators

Classification of comparators

Comparators were independently allocated to different classes by two reviewers (FS, GG), with consensus reached by discussion. Each comparator was allocated to three different levels. We called these “Invasiveness” at the highest level, then “Approach” and at the most detailed level “Technique/Material” and these terms are used throughout the paper (Appendix Table 1):

Level 1. Invasiveness: The comparators were classified into three different classes according to level of invasiveness (represented by a letter code): non-invasive (NI), micro-invasive (MI) or invasive (I).

Level 2. Approach: Treatments within each class were then categorized based on treatment approach (and a second representative letter code). For example, non-invasive (NI) treatments were categorized into approaches aimed at affecting: the biofilm (NI_B); diet (NI_D) tissue mineralization (NI_M); or combinations of different non-invasive approaches (NI_C).

Level 3. Technique/Material: These approach categorizations were then further classified according to the treatment technique and/or the material class (and a further letter code added). For example, non-invasive treatments affecting biofilm (NI_B) were classified into techniques affecting: oral hygiene (NI_B_H);

application of antibacterial agents (NI_B_A); or other techniques (NI_B_O), including treatments/materials not captured within the other two groups.

Where comparators comprised treatments with different levels of invasiveness, materials, or techniques, these were classified as combinations (C). More details on the classification can be found in the Appendix.

Analysis

In trial networks, network nodes (termed 'vertices') are formed by comparators and connected by edges (trial comparisons), indicating a direct comparison within an RCT. In our network, we color-coded edges for trials which assessed caries prevention as green and carious lesion management as red to further clarify the relationships.

SNA allowed us to statistically evaluate the network properties (Node XL 2014 [www.srmfoundation.org], UCINET 6 [Analytical Technologies, Lexington, USA] and SPSS 22.0 [IBM, Redwood, USA], and to graphically display the created networks to evaluate their structure (Cytoscape 3.4.0 [National Institute of General Medical Sciences, Bethesda, USA].

- Firstly, we evaluated whether particular trial characteristics (e.g. publication year, sample size, setting, dentition, participants) led to different comparators being more commonly tested. Note that in such analysis, one trial can occur several times (one time for each comparator), which inflates the number of trials. We therefore omitted any statistical comparison, and restricted ourselves to a descriptive analysis. We further assessed the influence of publication year of trials on comparator choice and evaluated the association between publication year and different trial properties (sample size, no of arms, participants, setting).
- Secondly, the number of edges (comparisons) and auto-loops comparisons (comparisons within the same comparator class) were assessed. Note that the

number of comparisons is higher than the number of comparators, as (for example) in a four-arm trial, six comparisons are made.

- Thirdly, we evaluated the statistical properties of the networks. (1) Contingency correlation was used to assess if within-class comparisons were favored over between-class comparisons (i.e. if homophily was present). A significant correlation indicated that strategies of the same class were compared against each other more frequently than would be expected. (2) The average number of comparators per node (the degree), the edges needed to connect two nodes (the distance), and number of nodes created per all possible connections (the network density) were assessed (13, 18). (3) The clustering coefficient was used to assess how well connected comparators were. Values of one represented a network where all possible connections are made, and 0, that only the minimum number of connections were made (19). The clustering coefficient is a measure for co-occurrence, i.e. segmentation into “cliques” of comparators. (4) Heterogeneity was assessed, with higher values indicating that only a few nodes dominated the network, serving as hub nodes (20, 21).

Networks were also plotted graphically. Node diameter represented the number of comparator arms forming the node and number of lines connecting nodes (edges) represented the number of direct comparisons.

Results

Search and studies

Searching electronic databases revealed 4774 articles (Figure 1). After screening titles and abstracts, 764 full texts were assessed (retrieval rate 96%), 605 articles (1534 comparators) were included (Appendix Table 2) and 159 articles excluded (Appendix Table 3). 32% of the comparators were tested in studies conducted in secondary care, 31% in a field or school setting, 12% in primary care, 3% in a mixed setting and 22% did not report setting. 58% of

comparators were tested in studies on permanent teeth, 25% primary teeth, 16% both and 1% did not report dentition type.

Figure 1: Flowchart of search strategy and inclusion/exclusion of studies.

Characterization of trials testing different comparators

Overall, invasive comparators were tested most frequently, followed by non-invasive, micro-invasive then combined comparators (Table 1). The date at which the trials were conducted had an influence on comparator choice: Trials employing at least one invasive comparator have been published more recently (median [25th/75th percentiles]: 2006, [1968/2015]) and had a smaller sample size (156 [79/241]). Trials with one or more non-invasive comparator have been conducted earlier (2001 [1991/2009]) and had a higher sample size (453

[368/572]). Trials employing invasive comparators were most frequently set in secondary care, while non-invasive comparators were often tested in field/school settings. Children were mainly the focus regardless of which strategy was assessed; in most trials involving children, interventions were applied to the mixed dentition. The sample size of all included trials was 81 [41/317]. Most trials were conducted in field (188 trials) or secondary (195 trials) setting and on teeth in the secondary dentition (349 trials). 416 trials were conducted in children and 154 trials in adults. The median number of trial arms was 2 [2/3].

Table 1: Overview of characteristics of trials involving different comparators. N number of comparators involved in trials. Abbreviations: I invasive, MI micro-invasive, NI non-invasive, C combinations, P placebo.

Intervention	**N**	**Year of trial publication (median [25th/75th percentiles])**	**Sample size of t (median [25th/75th percentiles])**	**Trial setting (field/primary/secondary/ both or unclear)**	**Trials on primary/secondary /both or unclear dentitions**	**Trials on children/adults/ both or unclear**	**Trial arms (median [range])**
I	611	2006 [2001/2010]	156 [79/241]	48/53/289/221	219/347/45	315/261/35	2 [2/3]
MI	233	2006 [1995/2010]	648 [389/734]	56/53/89/35	6/200/27	184/34/15	2 [2/3]
NI	474	2001 [1991/2009]	453 [368/572]	277/50/84/63	215/98/161	370/83/21	2 [2/3]
C	29	2006 [2002/2010]	240 [146/453]	9/4/5/11	17/7/5	26/2/1	2 [2/4]
P	187	2003 [1992/2010]	464 (326/610)	102/16/32/37	43/102/42	146/31/10	3 [2/3]
Trial level:	**605**	**2005 [1996/2010]**	**98 (41/317)**	**188/73/195/149**	**150/349/106**	**416/154/3**	**2 [2/3]**

The publication year had an impact on sample size (Table 2) with newer trials being significantly associated with having fewer participants than older trials (ß=-11 (95% CI: -18/-5)). No association was found for number of trial arms and publication year. Trials on adults (mean/SD: 2004/9) and trials in primary setting (2005/6) have been published more recently compared to trials on children (2001/11) and trials in mixed settings (1995/12).

Table 2: Association between trial publication year and properties. Linear regression or descriptive subgroup analysis were used to evaluate the association.

Item	**Association** (R^2; ß) or **subgroup finding** (mean; SD; range)
Sample size	R^2=0.02; ß=-11 (95% CI: -18/-5)
No of arms	R^2=0.00; ß=0 (95% CI: 0/0)
Trials on	
children	2001 (11; 1968-2015)
adults	2004 (9; 1973-2015)
both	2002 (10; 1976-2013)
unclear	1988 (4; 1982-1990)
Trial setting	
primary	2005 (6; 1968-2015)
secondary	2003 (9; 1971-2015)
mixed	1995 (12; 1974-2006)
unclear	1994 (8; 1982-2010)

Comparator network analysis at level of “Invasiveness” (Level 1)

Overall, the data showed the network to be densely inter-connected (Figure 2a). However, there was a high degree of segmentation of comparisons depending on whether prevention (green) or management (red) was the trial focus; as would be expected, certain strategies were assessed predominantly in caries prevention trials and others in carious lesion management trials. There was some crossover with micro-invasive strategies “bridging” non-invasive and invasive strategies. There were a high number of auto-loops (Table 3), with a significant contingency correlation (0.76, $p<0.01$) indicating a high number of comparisons within rather than between classes (i.e. high homophily). The average number of comparators per node (the degree), the average number of edges needed to connect two nodes (the distance), and the number of nodes created per all possible connections (the

density) of the network were all high, indicating that most nodes (comparators) were connected not only with themselves, but also with another. This was confirmed by the clustering coefficient value of 1.00. The absence of heterogeneity (0.00) confirmed that no single node acted as a hub node, i.e. dominated the network.

When graphically inspecting the network (Figure 2a), a preponderance of certain comparisons can be seen: non-invasive comparators were often compared with micro-invasive or combination comparators, but rarely against invasive comparators, which in turn were compared against micro-invasive and combined comparators.

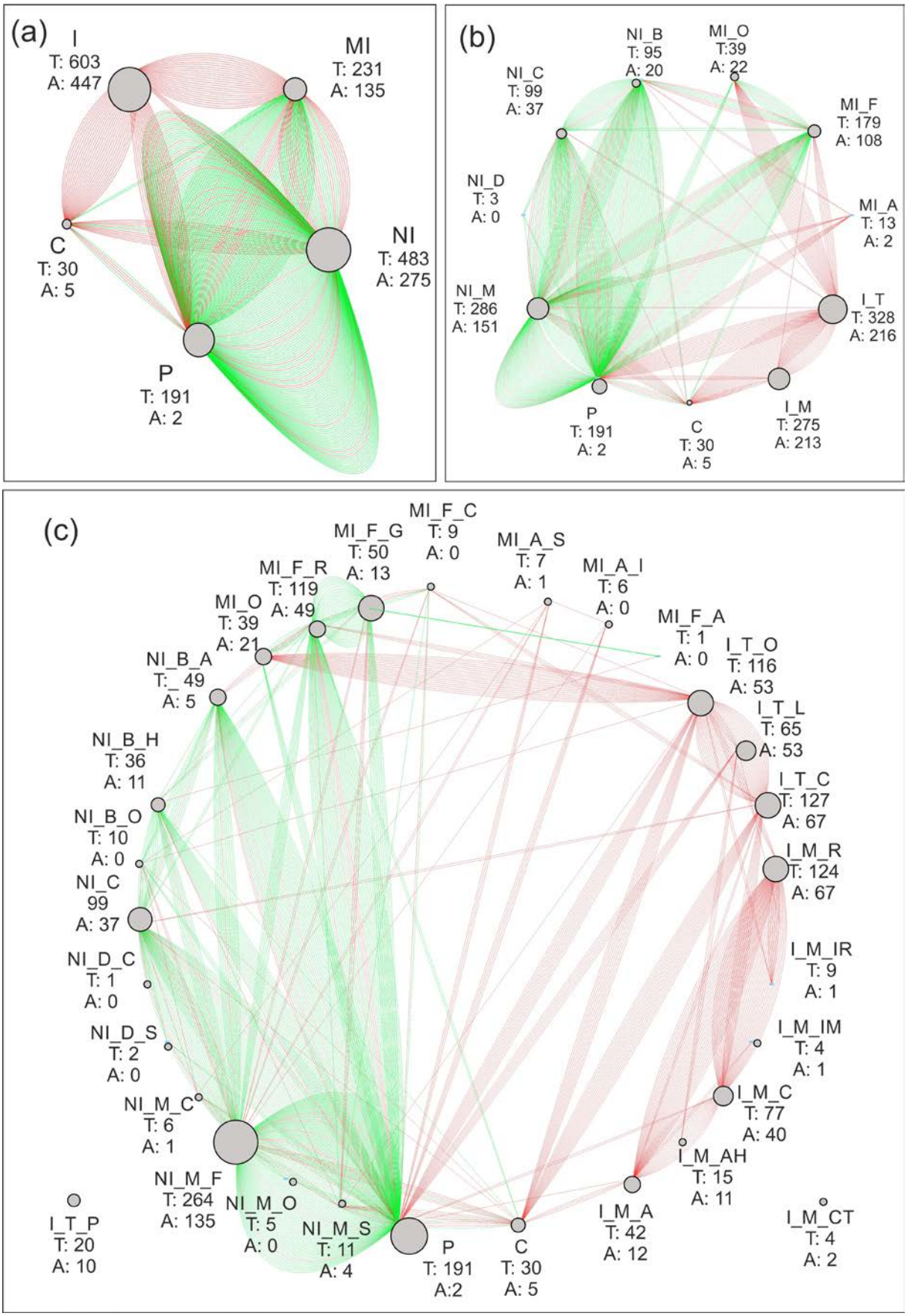

Figure 2: Networks of different comparisons, classified according to (a) invasiveness (Level 1), (b) approaches (Level 2), (c) specific techniques/materials (Level 3). We show how often,

in total, each comparator was employed in a comparison (T, also represented by node diametre), and the number of auto-loop comparisons (A) for each per comparator. Green edges indicate comparisons investigating the prevention of carious lesions and red, the management of existing carious lesions. Abbreviations for the different comparator classes: Invasiveness (letter(s) in first position): NI (non-invasive), MI (micro-invasive), I (invasive), C (combination), P (placebo); Approach (letter in second position): B (biofilm), D (diet), M (mineralization), C (combination), F (fissure) A (proximal); O (other); M (material), T (technique); Specific techniques/materials (final letter-combinations): NI_B_H (oral hygiene), NI_B_A (antibacterial), NI_B_O (others), NI_D_C (counselling), NI_D_S (sugar substitutes), NI_M_F (fluoride), NI_M_C (CPP-ACP), NI_M_S (silver diamine fluoride), NI_M_O (others), NI_C (combination of non-invasive techniques), MI_F_R (resin sealant), MI_F_G (glass-ionomer cement sealant), MI_F_A (amalgam sealant), MI_F_C (sealing over caries), MI_A_S (proximal sealing), MI_A_I (infiltration), MI_O (other micro-invasive techniques), I_M_R (resin based material restoration), I_M_A (amalgam restoration), I_M_C (cement restoration), I_M_IC (indirect restoration with ceramic based material), I_M_IM (indirect restoration with metal based material), I_M_IR (indirect restoration with resin-based material), I_M_CT (cementation of indirect restoration), I_T_C (caries removal), I_T_P (preparation), I_T_L (liner), I_T_O (others invasive treatment techniques)

Table 3: Properties of the constructed networks for all 3 Levels.

Property	**SNA Network Level**		
	Invasiveness (Level 1)	Approach (Level 2)	Technique/ material (Level 3)
Vertices	5	11	30
Edges	1563	1656	1827
Auto-loops	862	769	598
Contingency correlation	0.76	0.88	0.95
(p-value)	(<0.001)	(<0.001)	(<0.001)
Average degree	3.83	7.21	6.21
Density	0.95	0.61	0.18

Average distance	1.05	1.58	2.26
Average clustering coefficient	1.00	0.82	0.50
Heterogeneity	0.00	0.55	0.85

Comparator network at level of “Approach” (Level 2)

The network analysis at the level of “Approach” (Table 3), showed a higher number of classes, with less auto-loops (although still relatively high at 769). Notably, invasive comparators comparing materials or techniques were frequently tested within classes (Figure 2b), reflected by a highly significant contingency correlation (homophily). Given that 11 comparators were available, but only 7.2 comparisons were made on average, the network was less densely connected than that of the first level. This was also reflected by the higher distance (1.58) and the lower clustering coefficient (0.82). The relatively high heterogeneity indicates the presence of hub nodes; certain comparators dominated the network.

As illustrated graphically (Figure 2b), the main comparators were invasive materials and techniques. The next most common were non-invasive approaches to mineralization, frequently compared to placebo, non-invasive approaches to biofilm management, or combinations of non-invasive comparators. Micro-invasive approaches and combinations of comparators were tested less frequently.

Comparator network at level of “Technique/material” (Level 3)

Dividing up comparator comparisons with even more granularity, into the specific techniques and materials used (Figure 2c), resulted in a network consisting of 30 nodes (Table 3). Again, similar to the two higher levels, the number of auto-loops was relatively high (n=598), with a significant contingency correlation (0.95). The network degree was relatively low (each node could have been compared with 30 comparators but was, in fact, only connected to an average of 6 comparators), and the density much lower than that of less granular Level 1 and

2 networks (Figure 2). This was confirmed by a higher distance and a lower clustering coefficient (0.50). Only a few hub nodes served as main connectors within the network, verified by high heterogeneity (0.85).

Inspection of the network graphic (Figure 2c) showed that a few comparators dominated the network: Non-invasive mineralization approaches using fluoride were tested most frequently, regularly against themselves or placebo. The testing of resin-based or cement materials or caries removal techniques was also common. The micro-invasive placement of resin-based fissure sealants was also relatively common. Similar to analyses of the two higher levels, testing within classes was more common than between classes. Two comparator classes (cementation of indirect restorations and different cavity preparations) were only compared within their class and not connected within the network.

Changes in comparator choice over time

The publication year had an influence on comparator choice for some interventions (Table 4). On the approach level, trials on MI_A tended to have been published in more recent years (median [25th/75th percentiles]: 2011 [2009/2012]) compared to NI_M (1997 [1990/2008]) and NI_D (1991 [1976/2015]). On the technique/material level, MI_A_S (2010 [2008/2012]) and MI_A_I (2012 [2012/2013]) had been published in more recent trials. The same could be found for NI_M_S (2009 [2009/2012]) or NI_M_C (2014 [2012/2015]). In contrast, trials on I_M_A (1998 [1992/2004]) trials on MI_F_C (1996 [1993/2012]), trials on MI_F_C (1996 [1993/2012]) and trials on NI_M_F (1995 [1990/2005]) tended to have been published in earlier years.

Table 4: Publication time (median [25th/75th percentiles]) of trials on different interventions.

Individual interventions	Year of trial publication	Individual interventions	Year of trial publication	Individual interventions	Year of trial publication
I	2006 [2001/2010]	I_T	2007 [2003/2010]	I_T_P	2005 [2002/2010]
MI	2006 [1995/2010]	I_M	2004 [1999/2009]	I_T_C	2006 [2003/2009]
NI	2001 [1991/2009]	MI_F	2004 [1993/2010]	I_T_O	2007 [2001/20010]
C	2006 [2002/2010]	MI_A	2011 [2009/2012]	I_M_R	2005 [2000/2010]
P	2003 [1992/2010]	MI_O	2008 [1997/2011]	I_M_IR	2009 [2001/2010]
		NI_M	1997 [1990/2008]	I_M_IM	1995 [1989/2001]
		NI_D	1991 [1976/2015]	I_M_C	2003 [2001/2006]
		NI_C	2007 [1998/2013]	I_M_AH	2007 [2001/2011]
		NI_B	2004 [1999/2008]	I_M_A	1998 [1992/2004]
				I_M_CT	2000 [1995/2005]
				MI_F_A	1998 [1998/1998]
				MI_F_G	2008 [2004/2012]
				MI_F_C	1996 [1993/2012]
				MI_F_R	2001 [1986/2008]
				MI_A_S	2010 [2008/2012]
				MI_A_I	2012 [2012/2013]
				NI_M_C	2014 [2012/2015]
				NI_M_F	1995 [1990/2005]
				NI_M_O	1989 [1979/1996]
				NI_M_S	2009 [2009/2012]
				NI_D_C	2015 [-]
				NI_D_S	1983 [1976/1991]
				NI_B_O	2012 (1995/2015)
				NI_B_A	2003 [2000/2008]
				NI_B_H	2004 [1996/2006]

Discussion

Trial design is often arbitrary, driven by individual preferences or assumed relevance. We have assessed trial comparator choice to evaluate the research agenda underlying trials in cariology. This is relevant, because these choices might introduce bias to the overall

evidence, leading to inaccurate and even incorrect conclusions on the comparative effectiveness of interventions (9-11).

This review showed that a large proportion of trials compared similar, rather than different interventions with each other (significant homophily was present at all levels). Moreover, segmentation (i.e.co-occurrence) of comparator classes was common, and few comparators (namely various restorative materials, mineralization approaches, and fissure sealants) dominated the networks. We therefore accept both our hypotheses: certain comparators are disproportionally investigated whilst others are under-investigated and comparisons within comparator classes are preferred over comparisons between classes.

The segmentation of network, i.e. the preferred comparison of certain comparators, might be mainly driven by specific clinical indications, i.e. not all comparators are appropriate in all situations. However, we found, for example, that carious lesion management using non-invasive strategies was rarely tested, despite being likely to be effective, applicable and efficient (22-24). Instead, invasive comparators for treating carious lesions were commonly investigated, with the majority of invasive trials testing either restorative materials, some of which may have very minor technical improvements, against each other or comparing different invasive techniques (such as different carious tissue removal techniques), while non-invasive strategies tended to be applied to caries prevention. Overall, relatively few trials make any network connection across strategy classes (i.e. comparing invasive, non-invasive, micro-invasive strategies), while clinically, dentists are faced with decisions not only within, but also between comparator classes. For example, should clinicians manage cavitated, possibly cleansable carious lesions in children using a fluoride varnish (non-invasively), a fissure sealant (micro-invasively) or using a restoration (invasively)?

Very few studies compared combinations of comparators, despite this being a common decision in practice: Dentists frequently offer combinations of therapies to a patient. The lack of comparator combinations might be something specific to randomized trials, as trialists aim to understand the efficacy of one specific comparator. Interpreting findings for complex

interventions and their individual component parts is not easily done, while factorial trial designs (which could allow such in-depth component analysis) require often exponentially higher sample sizes and are more difficult to recruit to and costly to conduct.

Placebos were frequent comparators. Testing against placebo is often criticized for overestimating the effectiveness of an intervention (10). In cariology, however, placebo interventions might be justified, as they simulate a conservative approach towards monitoring oral health or a specific carious lesion. This is often acceptable, given the low caries risk in many populations today and low progression rates of (early) carious lesions (25, 26).

Many trial networks show chain-wise, linear geometry, which usually indicates that new comparators are compared with an accepted standard, which in turn has been compared against a formerly accepted standard. This is problematic if the definition of an accepted standard relies on presumed non-inferiority, usually based on insufficiently powered trials (type-II error). Consequently, chain-wise networks are prone to overall evidence distortion (10). However, it was reassuring to find that overall, cariology trials form a polygonal network, indicating the evidence is less prone to such distortion.

We also assessed in what kind of trials different comparators were tested. Invasive strategies were tested in significantly smaller trials, whilst non-invasive comparators were tested in the largest trials. This might be closely linked with trial setting, but also the effort required to provide the intervention. Many preventive intervention trials can be delivered *en masse*, for example, school toothbrushing sessions, whereas invasive trials usually need to be carried out in a dental setting carrying increased time and high costs and therefore often include fewer participants. As non-invasive trials are older and invasive trials tend have been conducted more recently, this might explain the general trend that the sample size of all included trials decreased with time. We also found a time-dependent change of use of some comparators (e.g. proximal sealing/infiltration were published in more recent trials and amalgam fillings or use of fluorides were published in earlier trials). This might reflect the evolution of caries intervention strategies over time: Novel approaches are more likely to be

tested in recent trials and outdated materials/interventions are less likely to be used. Trials employing non-invasive and preventive approaches largely involved children, while those on invasive interventions tended to focus on adults. This is also not surprising as children are often easier to follow-up through schools, increasing the likelihood that the trials will succeed. However, given that emerging evidence finds caries increments per available surface to remain largely constant over life, caries prevention trials are needed in adults (27). This work clearly shows a gap here.

Our study has a number of limitations. Firstly, only randomized trials were included to have a higher internal validity than non-controlled observational trials, but they require more funding and effort and are often conducted under restricted, somewhat artificial settings in selected populations. While they may have lower external validity, they may also investigate different comparators to observational trials. It would be of interest to see if observational studies yield different comparator networks, something which could have relevance for future funding and evidence applicability. Furthermore, we did not assess the quality of included trials as our focus was to assess limitations of evidence due to comparator choice. The quality of studies also is an important factor that shapes the evidence on caries management/prevention approaches and should be assessed in further studies. Secondly, there is no accepted standard of caries preventive/management comparator classification; the one used was devised by us and is only one of many possible. The choice of classification is likely to affect the network analysis outcomes. This was seen when applying classifications at different levels (which serves as a sensitivity analysis in our study); in more granular networks, the number of autoloops (and the resulting homophily) decreased (but remained high). Finally, the review process had limitations; we did not carry out duplicate data extraction, cross- or grey- literature searching. It is agreed that literature identification for methods' analyses is "potentially more resource-intensive than for most reviews of empirical research" (28). We accepted the possible limitations stemming from our pragmatic approach, as having a limited impact on our results.

Conclusions

There are a variety of comparators that have not been, but should be, compared to one another to investigate their comparative efficacy and effectiveness. Factors underlying trialists' comparator choice need to be identified to find ways to strategically guide investigations to add to knowledge fill evidence gaps. Future caries trials should aim for comparing between rather than within different techniques and materiel classes, comparing across invasiveness classes where applicable and testing approaches on different target populations, irrespective of treatment indication.

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