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Substantial findings from two study project popular in cariology and pediatric dentistry

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dedicated to my son, my inspiration and soulmates, my mother, who give me invaluable education opportunities, to the memory of my father for raising me to believe that anything was possible and to my husband for making everything possible

Affidavit

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List of abbreviations

Study project I

STARCARD	STAndard Reporting requirements in CARies Diagnostic Studies
VE	Visual examination
BWR	Bitewing radiography
LF	Laser fluorescence
FOTI	Fiber-optic transillumination
QLF	Quantitative light-induced fluorescence
RoB	Risk of Bias
SE	Sensitivity
SP	Specificity
AUC	Area under curve

Study project II

PMC	Preformed metal crown
SSC	Stainless steel crown
ZC	Zirconia crown
RCTs	Randomized clinical trials
CC	Composite crown
SAC	Self-adhesive cement
SAC-1	Self-adhesive cement 1(SAC-1): RelyX Unicem 2 Automix
SAC-2	Self-adhesive cement 2(SAC-2): NuSmile
RMGIC	Resin modified glass-ionomer cement

List of publications

Authorship:

Publication I. Svetlana Kapor; Mila Janjic Rankovic; Yegane Khazaei; Ina Schüler; Felix Krause; Adrian Lussi; Klaus Neuhaus; Florin Eggmann; Stavroula Michou; Kim Ekstrand; Marie-Charlotte Huysmans; Alexander Crispin; Jan Kühnisch. Systematic review and meta-analysis of diagnostic methods for occlusal surface caries" Clin Oral Investig. 2021 Online

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Publication II. Kessler A*, Kapor S*, Erdelt K, Hickel R, Edelhoff D, Syrek A, Güth JF, Kühnisch J. Two-body wear and fracture behaviour of an experimental paediatric composite crown in comparison to zirconia and stainless steel crowns dependent on the cementation mode. Dent Mater. 2021 Feb;37(2):264-271. https://doi.org/10.1016/j.dental.2020.11.010. Epub 2020 Dec 6. PMID: 33298317

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Jan Kühnisch, Prof. Dr.; Mila Janjic Rankovic, PhD; Svetlana Kapor; Ina Schüler; Felix Krause; Stavroula Michou; Florin Eggmann; Kim Ekstrand; Adrian Lussi, Klaus Neuhaus; Marie-Charlotte Huysmans. “Identifying and avoiding risk of bias in caries diagnostic studies”. Journal of Clinical Medicine 2021 (*under review*)

Jan Kühnisch, Prof. Dr.; Mila Janjic Rankovic, PhD; Svetlana Kapor; Ina Schüler; Felix Krause; Stavroula Michou; Florin Eggmann; Kim Ekstrand; Adrian Lussi,; Klaus Neuhaus; Marie-Charlotte Huysmans. “STAndard Reporting of CAries Detection and Diagnostic Studies (STARCARDDS)”. Clinical Oral Investigations 2021 (*under review*)

Author`s contribution to the publications

The table below gives an overview of the personal contribution which was made to the preparation and publication of the cumulative dissertation.

Svetlana Kapor Ph.D. dissertation	PhD Student	Prof. Dr. Kühnisch	Other scientists
Study project I "Systematic review and meta-analysis of diagnostic methods for occlusal surface caries"			
Idea of project	**-**	100%	-
Study design	**20%**	75%	5% Prof. Hickel
Step 1: Literature search identification	**80%**		20% PhD Mila Janjic Rankovic
Step 2: Hand research of the literature	**80%**		20% PhD Mila Janjic Rankovic
Step 3: Removal of duplications	**80%**	-	20% PhD Mila Janjic Rankovic -
Step 4: Assessment of full text papers	**70%**	20%	10% PhD Mila Janjic Rankovic
Step 5: Extraction of data	**90%**	-	10% PhD Mila Janjic Rankovic
Step 6: Processing data sets	**100%**	-	
Step 7: Descriptive statistical analysis	**100%**	-	-
Step 8: Explorative statistical analysis	**20%**	-	80% Khazaei /Dr. Cris-pin
Step 9: Selection of data worth publishing	**80%**	20%	-
Step 10: Creation of tables & figures	**90%**	10%	-
Step 11: Manuscript preparation & submission	**70%**	20%	10% Co-authors
Study project II "Two body wear and fracture behaviour of paediatric composite crown in comparison to zirconia and stainless-steel crowns dependent on the cementation mode"			
Idea of project	-	100%	-
Study design	**20%**	75%	5% Prof. Hickel
Step 1: Sample collection and crown cementation	**100%**	-	-
Step 2: Specimen preparation	**100%**	-	-
Step 3: Sample ageing	**100%**	-	-
Step 4: SBS test and failure mode analysis	**90%**	-	10% Prof. Ilie
Step 5: Microleakage testing	**100%**	-	-
Step 6: Processing datasets	**70%**	-	30% Dr. Erdelt
Step 7: Descriptive statistical analysis	**80%**	10%	10% Dr Kessler*
Step 8: Explorative statistical analysis	**10%**	-	90% Dr. Erdelt
Step 9: Selection of data worth publishing	**80%**	20%	-
Step 10: Creation of tables & figures	**50%**	10%	40% Dr Kessler*-
Step 11: Manuscript preparation & submission	**70%**	20%	10% Co-authors
Drafting of the cumulative dissertation	**100%**	**-**	**-**

*Dr Kessler contributed equally with Dr Kapor in implementation and realization of experiment results effectively providing ideas during research process, with his experience in digital prosthodontic dentistry

INTRODUCTORY SUMMARY

<u>Name of the study project:</u> Substantial findings from two study projects popular in cariology and pediatric dentistry

The following study projects were performed at the Department of Operative Dentistry and Periodontology, in collaboration with the Department of Prosthodontic Dentistry and the Institute for Medical Information Processing, Biometry, and Epidemiology on Ludwig-Maximilians-Universität München. supervised by Prof. Jan Kühnisch and Prof. Mansmann

The two different study projects were considered as a core topic of the PhD dissertation and includes two published studies applied for accomplishing the requirements for Ph.D. program completement. In period between October 2015 and March 2019, scientific workgroup* compiled of professionals-experts in caries diagnostic and PhD students, were formed with intention to found and acclaim standards for upcoming caries diagnostic studies in a form of a checklist adapted for specific requirements -STAndard Reporting of CAries Detection and Diagnostic Studies-STARCARD checklist (*article under review*). During this period, the scientific workgroup is organized three workshops for discussion, evaluation, and agreement of the results, developed RoB tool-to evaluate internal validity among caries diagnostic studies to be used in meta-analysis and to develop agreements proposals. As result of the first study project, systematic caries diagnostic studies review for caries on occlusal surfaces including meta-analysis (1), systematic review and meta-analysis for caries on proximal surfaces (*article under review*) and one discussion paper on the methodology of caries detection and diagnostic studies (*article under review*) were prepared for publishing.

Second study project were performed in cooperation with Prof. Jan Frederik Güth and

**Members of the scientific workgroup are all co-authors from the 1st publication including me as author*

colleagues from Department of Prosthodontic Dentistry and Operative Dentistry and Periodontology to cover experiment (2D and 3D wear) on nearly developed pediatric composite crown compared to stainless steel and zirconia crown determined on the cementation mode.

Study project I

Systematic review and meta-analysis of caries detection and diagnostic studies on occlusal surfaces

Caries on occlusal surfaces were discovered to be frequent on premolar and molar (2), mostly due to complex morphology of the occlusal surface (3-5). With consideration, that a reproducible and operative caries assessment and detection couldn´t be made only by visual examination (VE), it was a reliable claim that other diagnostic devices are required. Nearby VE, conventional and digital bitewing radiography (conventional and digital BWR), laser fluorescence (LF) measurements, fiber optic transillumination (FOTI) and quantitative light-induced fluorescence (QLF) (6) were established on the marketplace of dentistry to capture the limits of visual inspection and the caries development as well (7). Very lately, systematic reviews and meta-analysis combined the existing records and get assumptions mostly independently for each diagnostic method (8-12). Significant heterogeneity between included caries diagnostic studies is mentioned from the side of these authors and can cause hidden risk of bias (RoB) (9). Briefly here mentioned authors of systematic reviews, defined, and described heterogeneity without to reject the studies with a possibly high RoB (8-12).

Hereby, comprehensive systematic review including meta-analysis was aimed, first, to detect and summarize remaining gaps and to get a clear overview of the so far published knowledge. Special interest was accorded on heterogeneity, to consider possible sources of bias and finally to provide meta-analysis who will compare frequently applied caries diagnostic methods.

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More than a few recommendations and guidelines (13-17) were involved into creating of required methods for systematic review and meta-analysis. enrolled on PROSPERO platform under number: CRD42017069894.(1) Two independently evaluators assessed separately and included only those studies who examined the diagnostic accuracy/reliability of previously described caries diagnostic methods in human premolars and molars. Out of 1090 primarily identified studies using inclusion criteria based on PIRD concept (16),140 studies are examined in detail and finally 37 studies (29 in vitro and 8 in vivo) occurred to be appropriate for the systematic review (1).

RoB: Using the developed tool for RoB assessment (1) all finally included 37 studies have been reexamined and separately reviewed by two other evaluators. Adapted RoB assessment involved individual low RoB studies and ignore possible heterogeneity among studies with high RoB.

Second part of review concentrate on meta-analysis for frequently used thresholds, and all included diagnostic methods. Only two identified studies used FOTI as diagnostic methods, none used QLF as diagnostic method.(1)

Meta-analysis of in vitro studies. Nearly all studies (29 from 37) were examined the diagnostic accuracy under dentin caries detection level (18) and were performed under laboratory terms. Additionally, for overall caries detection level and for all diagnostic methods were characteristically recognized a higher specificity (SP) then sensitivity (SE). At the 1/3 dentin detection level(19) was detected the highest area under curve (AUC) for VE, but typically were higher to other diagnostic methods e.g., LF or radiography. So far, most commonly used further diagnostic methods were VE, BWR and LF measurements (1). It became clear that the methodology of numerous caries diagnostic studies is heterogeneous and therefore, the comparability of their outcomes is reduced.

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Meta-analysis of in vivo studies. Only 8 from 37 studies were included into meta-analysis. The meta-analysis of VE at the caries detection level showed higher SE than SP (1). Exceptional results were found for LF and conventional BWR as well.

Difference between in vitro and in vivo studies. Because of inequality of included studies, complete assessment could not be made, and few trends were stated(1). Under laboratory terms VE (diagnostic performance) tend to be higher than in clinical terms, on the other side, we observe lower VE (diagnostic performance), other diagnostic methods like conventional BWR and LF showed better diagnostic performance under clinical terms. (1, 8, 9). Still, it looked to stay on a predisposition for all methods and SE was found higher in studies under clinical terms. SP was registered higher only in the case of VE under laboratory terms. Huge SE difference was found for VE under clinical and laboratory terms (11). Consequently, VE results to higher SP under laboratory terms.

Strengths and limitations. As far as we know, this is the first systematic review that examined together nearly all frequently used diagnostic methods for occlusal caries in one meta-analysis. Review followed strictly study selection protocol and considered different caries detection level individually for laboratory and clinical terms. Only one limitation was observed that other colleague did not exclude studies with a high RoB like we did and that need to be discussed in future(1). This review confirmed that VE alone is not ideal for caries detection on occlusal surfaces and is essential to be complemented by further diagnostic methods. (1, 11, 12). Moreover, identified heterogeneity can be valuable for studies under clinical terms. The result of this study suggests necessary for standardization and need for the future to conduct well powered and good designed caries detection and diagnostic studies who will utilize distinct caries levels and various diagnostic methods. Due to the limitation of present data in several diagnostic methods the existing meta-analysis outcomes should be concern with caution (1).

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Study project II

Two-body wear and fracture behavior of an experimental pediatric composite crown in comparison to zirconia and stainless-steel crowns dependent on the cementation mode

Initial introduced and described manufactured crown for primary molars teeth were preformed metal crowns (PMC) in 1950 year. (20, 21) Standard recommendations in pediatric dentistry usually propose the usage of manufactured pediatric stainless-steel crowns (SSCs) (22). This clinical restorative option is safe and effective, although commonly declined from parents' aesthetic point of view (23). Lately, manufacturers have proposed aesthetic preformed pediatric zirconia crowns (ZCs) or veneers stainless steel on the dental marketplace (24), only evaluated in a few randomized clinical trials (RCTs) (25-27).To avoid following limitation manufactured company 3M recently developed composite crowns (CC) due to aesthetic reasons by parents (23). The main benefits to apply CC on primary molars could be bonding to the composite established luting agents. Therefore, easy occlusal adjustments and material weakness by veneered SSC can be accepted to difference of other available preformed crowns (SSC, ZSC).

So far as we know there are no available published studies about the in vitro and clinical implementation of this recently developed composite crown. The second study in our project is only published study that preclinical used this brand-new composite crowns. (28) Subsequently, the main aim of second study project occurred to estimate fracture performance and two-body wear of preformed CCs preclinical, in comparison with other preformed crowns and luting techniques.

Following standardization and requirements, (28) overall 56 tooth stumps were duplicated from primary molar (75) and prepared for two body wear simulation. Three types of preformed crowns were included and divided into three groups. In the first group, 16 from 56 tooth stumps were prepared and used for cementation of CC-composite crowns (based on methacrylate resin matrix along with zirconia/silica nanocluster). In the second group we used 16 tooth stumps for cementation of SSC -stainless steel crowns. Nevertheless, in the last group finally 24 tooth stumps were cemented with ZC-zirconia crowns (consisted of around 90% ZrO_2).(28) Following manufactured instructions for cementation protocol, the described preformed crowns were cemented using three different cement types: self-adhesive cement 1(SAC-1): RelyX Unicem 2 Automix (3M ESPE Dental Products, St. Paul, MN, USA), self-adhesive cement 2(SAC-2) NuSmile BioCem NuSmile (Houston, TX, USA and the third were the experimental resin-modified glass ionomer cement (Exp. RMGIC, 3M).

Two-body wear testing and descriptive wear evaluation: Chewing simulations were performed together with thermocycling, using applied force of 50 N with frequency of 1.2Hz for a million and two hundred cycles. (Chewing simulator-CS-4, SD Mechatronic, Feldkirchen-Westerham, Germany). After chewing simulations all specimens were storage in water and scanned for failure analysis. (28). Established on our results, the initial aim of the present study was declined due to the lower 2D wear after cementation with SAC compared to RMGIC between the preformed crowns groups. CCs in combination with SAC (1 or 2) showed the lowest failure ratio then cemented with RMGIC, they increased the breakdowns. (28). SSC in combination with SAC indicated longer survey and only some widespread gaps parallel to RMGIC. Therefore, important difference featured to the mechanical properties between cement and the crown. We found significant material loss in CCs because of combination of weakness on mechanism wear (29). Difference on the damaged sides were demonstrated on the SEM images like occlusal perforation (30-32), especially for SSCs. (28). Opposite to this, by ZCs cemented with SAC, soft gaps were found, like in the former published study(33) the reason were that occlusal surface of ZC require to be polished (32). Former studies (34) confirmed that polishing improved lower wear of the antagonistic enamel (34). In our study all crowns were fabricable already polished. We presumed, that hardness has significant influence on study results. Based on results of wear testing all SSCs endured chewing simulation. Occlusal perforations, on the other hand, were described just in 0.2% in period of 5 years (35). Descriptive findings confirmed by CCs the greatest 2D and 3D wear described by the assets of material needed for composite manufacture (31). CCs cemented with RMGIC showed significantly further widespread wear. Identical was obtained for SSC. ZC indicated to the lowest 2D and 3D wear. One crown from ZCs were lost during the wear simulation. (28). Influence of cementation were stated on the fracture and 2D wear, related to the preformed pediatric crowns due to the small level of changes in difference to indirect tailored restoration in permanent dentition. That is the reason of demand for more resilient cement material (36). Our results showed that SAC demonstrates well quality improvements execute in comparison with composite or stainless steels (28). SAC has much better strength/fracture toughness in comparison to RMGIC, it was intended like significant issue to influence of various values of wear. Fracture toughness of ZCs until now do not show impact of the cementation.

Strength and limitations. In our study we used usually testing protocol applied for restorative materials on adults (33, 37-39) and verified to complete maintenance period for the preformed pediatric crowns as well. To eliminate heterogeneity of preparation for every tooth stump we used analogous material and form individually. (40, 41) Because of enamel morphology and structure differences can be a challenge for tooth stumps and chewing simulation protocol (42). Therefore, for appropriate chewing simulation we used uniformly designed and shaped antagonist (43, 44). It should be underlined that our crowns are cemented below ultimate laboratory circumstances and that disagreements among the protocol of cementation must be understood with concern for the reason of enhanced adhesive bonding among SAC and composite as material. Furthermore, we suppose that disagreements among cementations in vivo may not be so manifest like in our study. Under regular in vitro specifications the current study with limits has identified, distinct break forms for preformed pediatrics crowns (SSCs, ZCs and CCs). The lowest total number of breaks was observed for the CCs and ZCs. The 2D- and 3D-wear testing was assessed like the lowest for the ZCs. Cementation protocol was detected to has a major influence on the consumption of SAC in CC and SSC following in a considerably lower wear. Established on our in vitro records for the CC, before general use from clinicians, the in vivo implementation is mandatory.

Publication I

Systematic review and meta-analysis of caries detection and diagnostic studies on occlusal surfaces

Svetlana Kapor; Mila Janjic Rankovic; Yegane Khazaei; Ina Schüler; Felix Krause; Adrian Lussi; Klaus Neuhaus; Florin Eggmann; Stavroula Michou; Kim Ekstrand; Marie-Charlotte Huysmans; Alexander Crispin; Jan Kühnisch

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REVIEW

Systematic review and meta-analysis of diagnostic methods for occlusal surface caries

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Abstract

Aim This systematic review and meta-analysis aimed to assess the diagnostic performance of commonly used methods for occlusal caries diagnostics, such as visual examination (VE), bitewing radiography (BW) and laser fluorescence (LF), in relation to their ability to detect (dentin) caries under clinical and laboratory conditions.

Materials and methods A systematic search of the literature was performed to identify studies meeting the inclusion criteria using the PIRDS concept ($N=1090$). A risk of bias (RoB) assessment tool was used for quality evaluation. Reports with low/moderate RoB, well-matching thresholds for index and reference tests and appropriate reporting were included in the meta-analysis ($N=37$; 29 in vivo/8 in vitro). The pooled sensitivity (SE), specificity (SP), diagnostic odds ratio (DOR) and areas under ROC curves (AUCs) were computed.

Results SP ranged from 0.50 (fibre-optic transillumination/caries detection level) to 0.97 (conventional BW/dentine detection level) in vitro. AUCs were typically higher for BW or LF than for VE. The highest AUC of 0.89 was observed for VE at the 1/3 dentin caries detection level; SE (0.70) was registered to be higher than SP (0.47) for VE at the caries detection level in vivo.

Conclusion The number of included studies was found to be low. This underlines the need for high-quality caries diagnostic studies that further provide data in relation to multiple caries thresholds.

Clinical relevance VE, BW and LF provide acceptable measures for their diagnostic performance on occlusal surfaces, but the results should be interpreted with caution due to the limited data in many categories.

Keywords Occlusal caries · Pit and fissure caries · Caries detection · Caries diagnostics · Visual examination · Bitewing radiography · Laser fluorescence measurements · Fibre-optic transillumination · Systematic review · Meta-analysis · Diagnostic performance · Accuracy · Sensitivity · Specificity

Introduction

Over the last several decades, occlusal surfaces have been found to be one of the most prevalent sites for caries development in children and adolescents, mainly due to their anatomical susceptibility [1–6]. Because a valid and reproducible caries diagnosis and assessment could not be made by visual examination (VE) alone, there was a consistent demand for additional diagnostic devices for caries detection and diagnostics in pits and fissures. In addition to VE, conventional bitewing radiography (conventional BWR), digital bitewing radiography (digital BWR) and laser fluorescence (LF) measurements [7] were used in clinical practice or specifically introduced on the dental market in order to overcome the limitations of visual and/or tactile examination as well as to image and/or quantify the caries process to a certain degree [8]. On the basis of the acquired diagnostic information, the clinician should be enabled to make individual decisions about caries monitoring, prevention and/or operative intervention [9–11].

Numerous in vitro and in vivo caries detection, diagnostic, assessment and/or monitoring studies have been designed, conducted and published during the last few decades to describe the diagnostic performance of test methods

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in terms of validity (the diagnostic accuracy in relation to a reference standard) and intra-/inter-examiner reliability (the reproducibility of a diagnosis between different time points and examiners). Most recently, systematic reviews and meta-analyses have merged the available data and drawn conclusions mainly separately for each diagnostic method [12–16]. In addition, this author group [13–15] has mentioned substantial heterogeneity between the included diagnostic studies, and problematically, little attention has been paid to this important methodological issue so far; therefore, potential methodological sources of bias might be undetected and, furthermore, may also potentially skew meta-analysis data. Regarding this aspect, each diagnostic trial should ideally be designed similarly and should use equal scientific standards and protocols to generate comparable results that decrease the risk of bias (RoB) as much as possible. In contrast, previously published systematic reviews describe and report heterogeneity but do not exclude studies with a potentially high RoB. Therefore, this systematic review of the literature and meta-analysis was aimed, first, to identify caries diagnostic studies on pits and fissures that are tested with commonly used diagnostic methods, second, to evaluate study quality and identify only those studies with low/moderate RoB and, finally, to provide meta-analytic data on the diagnostic performance of clinically relevant detection and diagnostic methods.

Material and methods

The methodology of this systematic review was influenced by several recommendations or guidelines. The QUADAS 2 tool [17, 18], which was designed for the quality assessment of diagnostic accuracy studies, provided the basis for the RoB assessment. Here, the most recently published draft of the 'Cochrane Handbook for Diagnostic Test Accuracy Reviews' was also used [19]. The writing of this systematic review strictly followed the PRISMA-DTA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies) for diagnostic studies in its latest version [20]. The PRISMA-DTA group developed criteria to evaluate the validity and applicability of diagnostic studies and to enhance the replicability of systematic reviews in this area. The present systematic review was registered on the PROSPERO platform (CRD42017069894).

Search strategy

The research question, inclusion and exclusion criteria and search strategy were conducted on the basis of the PIRD concept [21]. Basically, this systematic review of the literature included in vitro and in vivo diagnostic studies that tested the diagnostic accuracy and/or reliability of different diagnostic methods for primary caries detection and assessment in human permanent posterior teeth (premolars and molars). In vivo studies were included regardless of the age of the population and the number of included patients or teeth. Studies containing information on primary teeth or teeth with restorations, secondary caries or artificially induced caries lesions were excluded. With respect to its clinical relevance, the following index tests were included in the search: VE, conventional BWR, digital BWR, LF measurements (DIAGNOdent 2095 or 2190, KaVo, Biberach, Germany), fibre-optic transillumination (FOTI, IC Lercher, Stockach, Germany) and quantitative light-induced fluorescence (QLF, Inspektor Research Systems, Amsterdam, The Netherlands). Other index test methods were not considered in this review. An essential characteristic of studies on diagnostic accuracy was the inclusion of a reference test, frequently also named the 'gold standard' or 'reference standard'. The included in vitro studies had to use any histological technique to validate the 'true' caries extension; otherwise, the studies were excluded. Under in vitro conditions, several histological techniques, e.g. slices, grinding, hemisection or microradiography, are well-established which fulfil the before-mentioned prerequisite. In clinical studies, cavity preparation or biopsy can be considered equivalent to provide proof about the presence of any (dentin) caries [22]. As dental radiography was commonly applied under clinical conditions as well, it was, therefore, also included [23, 24]. In relation to the previously formulated aims and the corresponding inclusion and exclusion criteria, a structured search of the literature was initiated in accordance with the mnemonic PIRD recommendations [21]. This concept included information about the study material or population, the selected index tests, possible reference tests and diagnoses of interest (outcomes). The final consented search items are shown in Table 1.

Basic literature search and study selection according to PRISMA recommendations

The systematic search of the literature was performed in the MEDLINE (via PubMed) and EMBASE (via Ovid) electronic literature databases using the consented search terms (Table 1) according to standard procedures [20, 25]. The search included all publications that were listed until 31 December 2018 in the databases and were written in English. Grey literature was not included. Additionally, reference lists of included studies and reviews were screened to identify any studies that may have been missed. A few studies ($N=4$) were found in result of manual searches.

Table 1 Documentation of keywords according to the PIRDS concept (Campbell et al. 2015)

Population/problem (P)		Index test (I)		Reference test (R)		Diagnose and study type (D/S)
Caries	AND	Visual	AND	Validity	AND	Systemati* Review
Decay		Clinical		Validation		Meta-Analysis
AND		Clinically		Valid*		Diagnos*
Occlusal		Inspect*		Accuracy		Diagnost*
Fissure		ICDAS		Sensitivity		Detection
		Bitewing		Specificity		Detect
		Conventional Radiography		SE		Detect*
		Digital Radiography		SP		Assessm*
		Radiogra*		ROC		Vivo
		Film		Az		Vitro
		Analo*		Reproducibility		Study
		X ray		Reproducib*		Studies
		Xray		Reliab*		
		Speed		Reliability		
		Roentge*		Kappa		
		Radiology		Threshold		
		Radiol*		Cut off		
		Laser fluorescence		Performance		
		Diagnodent		Histolog*		
		FOTI		Micro		
		DiFOTI		Micro computed		
		Di(FOTI)		CT		
		Fiber		*CT		
		Fibre				
		Transillumination				
		Optic				
		Opti*				
		QLF				
		Quantit*				
		Laser				
		Light				
		Induced				

MeSH terms which were used to search the PubMed and EMBASE databases: ((Caries or Decay) AND (Occlusal or Fissure) AND (Visual or Clinical or Clinically or Inspect* or ICDAS or Ekstrand or Bitewing or Conventional or Digital or Radiography or Film or Radiogra* or Analo* or Speed* or X Ray or Xray or Radiology or Radiol* or Roentge* or Laser or Fluorescence or Diagnodent or FOTI or DiFOTI or Fiber or Fibre or Transillumination or Optic or Opti* or QLF or Quantit* or Laser or Light or Induced) AND (Validity or Validation or Valid* or Accuracy or Sensitivity or Specificity or SE or SP or ROC or Az or Reproducib* or Reproducibility or Reliability or Reliab* or Kappa or Threshold or Cutoff or Performance or Histolog* or Micro or Micro-computed or CT or *CT) AND (Systemat* or Review or Meta-Analysis or Diagnos* or Diagnost* or Detection or Detect or Detect* or Assessm* or Vivo or Vitro or Study or Studies))

Identification of the relevant literature

All identified bibliographies (PubMed $N=946$, EMBASE $N=836$), including titles and abstracts, were exported to a bibliographic software package (X7.8 for Windows, Thomson Reuters). The imported set of records from each database, including hand searches, was merged into one core database to remove duplicate records and to facilitate retrieval of relevant articles. In the next step, duplicates ($N=696$) were removed, and the title (and, if needed, the abstract of each bibliography) was checked as to whether it met the inclusion criteria; otherwise, the study was excluded. After the primary identification of includable studies and the removal of duplicates, 1090 records were identified.

Screening and eligibility check

The titles and abstracts were screened by two reviewers (SK, MJR) independently. The reviewers were not blinded to the names of the authors, institutions, journal or results of each publication. All records were counterchecked in relation to the initially consented inclusion and exclusion criteria. If papers met the inclusion criteria completely or partially, their full-text documents were obtained. Doubts or disagreements were continuously resolved by discussion with an experienced researcher (JK). After review of the titles and abstracts, records that were found to be irrelevant were excluded from further proceedings ($N=894$). At this step, 196 records were identified for full-text reading. Studies ($N=56$) that were found to be irrelevant after their full texts were read were excluded from further analysis (supplemental Table S0). Finally, 140 studies met the inclusion criteria and were read in detail.

Data collection from the selected studies

Following the recommendation for diagnostic test accuracy [26], the following relevant items were extracted: study type (in vivo or in vitro studies), study population and teeth (number and age of patients, type and number of permanent teeth used in the study), index test methods (methods, scoring criteria and cut-offs), reference standard method (type of histological validation method, scoring criteria and cut-offs), validity and/or intra- and inter-examiner reliability data for the overall caries detection level (D0 versus D1-D4; Marthaler 1966), dentin caries detection level (D0-2 versus D3-4, Marthaler 1966) [27] and 1/3 dentin caries detection level (D0-2 versus D3-4, Ekstrand et al. 1997) [28]. Two reviewers (SK, MJR) independently extracted the required data from all primary studies. Any doubts or disagreements were continuously resolved by discussion with an experienced researcher (JK) until a consensus was reached. All data were systematically entered into an EpiData database [29] (EpiData software version 2.0.9.57, EpiData Association, Denmark).

RoB assessment

To date, no suitable set of criteria exists for assessing RoB among caries diagnostic studies. Therefore, existing checklists and proposals [21, 30–32] were analysed and adapted to clinical/laboratory caries diagnostic studies. The developed set of criteria includes 16 signalling questions divided into four main domains used for RoB assessments during the review (supplemental Table S7). Using the RoB assessment tool, all included studies were re-evaluated and assessed independently by two reviewers (SK, MJR). An additional and blind assessment was performed by two other colleagues from the workgroup (FE, SM). All RoB assessments are listed in supplemental Tables S8a/b–S13a/b.

In addition to the initially performed systematic search and selection of the literature, all identified papers were further selected according to their RoB status. Here, seven core domains were selected (tooth selection, index test criteria, reference test criteria, incorporation bias, partial verification bias, differential verification bias, bias in the analysis), and each study had to show a low or moderate inclusion in these domains; otherwise, the study was excluded from further analysis. In the next step, the remaining studies were crosschecked for the availability of sufficient validity data reporting cross-tabulation, sensitivity (SE), specificity (SP), positive predictive (PPV), negative predictive values (NPV) or areas under the receiver operating characteristic curve (AUC).

Data handling, statistical procedures and meta-analysis

All data were entered into a database and later exported to an Excel spreadsheet (Excel 2010, Microsoft Corporation, Redmond, WA, USA). Descriptive analyses were performed using Microsoft Excel 2010 and the statistical package mada version 0.5.9. [33] for RStudio [34]. If the included studies provided contingency tables, the data were used directly. If not, true positives (SE), true negatives (SP), PPV and NPV were calculated from the results in the original publication. If this calculation was not possible, the corresponding study was excluded. Corrections of tables with zero cells were also made; when, for example, the value for the true positives is zero, *R* itself makes a correction by changing the zero to 0.5 (a very small number) because RStudio cannot deal with zero cells. In some reports, statistical information was given for more than one examiner. However, in those cases, a mean was calculated by logit transformation.

Meta-analytic statistics were calculated for all included diagnostic test methods and commonly used diagnostic thresholds. Diagnostic accuracy and their 95% confidence intervals (95% CI) were calculated from the pooled data from all included studies, in terms of SE, SP and the diagnostic odds ratio (DOR). A bivariate diagnostic random-effects meta-analysis suggested by Reitsma et al. [35] was used to provide pooled estimates of SE and SP for the respective subgroups along with their 95% CI. This method can take the heterogeneity between studies into account by jointly analysing the logit transformation of SEs and SPs [36]. Finally, the pooled DOR was calculated using a random-effects model following the approach by DerSimonian and Laird [37] and aimed at describing the performance of the included diagnostic tests. An uninformative test shows a DOR value of 1; as the DOR increases, the test has more discriminatory power [38]. The area under the curve (AUC) of summary receiver operating characteristics (sROC) was reported to create an overview of the results within each subgroup. The AUC value quantifies the overall ability of a diagnostic test to discriminate between individuals with the disease and those without the disease [39]. The ideal test would have an AUC value of 1, whereas a random guess would have an AUC of 0.5; the larger the area under the ROC curve, the more accurate the diagnostic test. In addition, sROC plots and forest plots were computed to illustrate the diagnostic performance and heterogeneity, respectively [39].

Results

According to the workflow recommended by the PRISMA guidelines, 140 (108 in vitro and 32 in vivo) studies were initially identified (Fig. 1). After further consideration of the results from the RoB assessment (supplemental Tables S8a/b–S13a/b), an additional 103 publications needed to be excluded due to high RoB or insufficient data reporting (supplemental Tables S8c/d–S13c/d); the summary graphs from the RoB assessment are depicted in Fig. 2. Finally, 29 in vitro and 8 in vivo studies [40–76] were selected according to the described stepwise process and were found to fulfil the inclusion criteria for meta-analysis (Fig. 1, Table 2). Only two studies were identified to use FOTI, and none used QLF.

Meta-analytic validity data are presented for all included caries detection and diagnostic methods in relation to the three chosen caries detection levels for laboratory and clinical studies in Tables 3 and 4, respectively. Most data sets originated from in vitro studies ($N=29$, Table 3) rather than clinical investigations ($N=8$, Table 4). In the in vitro results for all diagnostic methods at the caries detection and dentin caries level, a higher SP than SE value was typically found (Table 3). AUCs were characteristically higher for additional diagnostic methods, e.g. radiography or LF, than for VE. The highest diagnostic performance was observed for VE at the 1/3 dentin caries detection level (AUC = 0.89). The DOR values ranged from 1.94 to 37.77 (dentin caries detection level/in vitro, Table 3), 2.14 to 60.37 (caries detection level/in vivo, Table 4) and 11.79 to 127.56 (dentin caries detection level/in vivo, Table 4).

A meta-analysis was conducted for in vivo studies as well (Table 4). Here, SE (0.70) was registered to be higher than SP (0.47) for VE at the caries detection level. The SE (0.72) and SP (0.77) were higher at the 1/3 dentin caries detection level. The meta-analytic diagnostic performance of conventional bitewing radiography (F-speed) and LF was found to be excellent.

In addition to the fact that comparisons between in vitro and in vivo studies should be performed with caution with respect to the imbalance of included studies, a few trends were observed. While on the one hand, the diagnostic performance of VE tended to be higher under laboratory conditions than in clinical settings, on the other hand, the diagnostic performance of VE was not perfect and was lower than that of additional diagnostic methods. Here, conventional radiography (E-speed) and LF measurements showed higher performance data under clinical conditions. Furthermore, for all methods, there seemed to be a tendency towards a higher SE in clinical studies. SP was found to be comparable under laboratory and clinical conditions; only in the case of VE were higher values registered in vitro. Again, full comparisons could not be made due to incompleteness of the data (Tables 3 and 4). In addition, SROC curves and forest plots were computed and are presented in the additional online material (supplemental Tables S14–S17).

Discussion

This study project summarized the diagnostic accuracy of occlusal caries lesion detection, diagnostic, assessment and/or monitoring methods that were investigated under in vitro and in vivo conditions in permanent, posterior teeth. Therefore, a systematic search of the literature was conducted; potential sources of bias were considered; and finally, a meta-analysis was performed to compare commonly used caries diagnostic methods instead of analysing each method separately [12–16, 77–81]. When considering the quantity and quality of the systematically searched literature, it should be noted that there was a remarkable reduction in includable studies with each additional selection step (Fig. 1). Finally, 37 studies were included in the meta-analysis [40–76], and unfortunately, these studies were not equally distributed over all test methods, study setups and considered thresholds (Tables 2, 3 and 4). Most studies were conducted under laboratory conditions (Fig. 1, Table 2) and investigated the diagnostic accuracy using the dentin caries detection threshold (Tables 3 and 4). VE, BWR and LF were tested most frequently than other additional diagnostic methods. This heterogenetic information pattern suggests that it is substantially necessary to conduct caries diagnostic studies that include different test methods and thresholds on pits and fissures. This demand is even more crucial for clinical studies.

The diverging methodology of each trial—technologies, thresholds, index and reference test criteria (supplemental Tables S1–S6)–and several sources of bias (Fig. 2, supplemental Tables S7–S13b) resulted in the exclusion of numerous studies, which ultimately lowered the number of includable studies and illustrated the heterogeneity between studies. This fact underlines the need for standardization and the necessity to conduct well-designed and well-powered caries diagnostic and detection studies in the future.

Regarding the meta-analytic diagnostic performance of the included diagnostic methods (Tables 3 and 4), it must be emphasized that for some methods, only a limited number of studies were identified. Exceptions were VE, BWR and LF (Tables 3 and 4). When viewing these data, a few trends can be discussed, but it should be mentioned from the outset that the results of this meta-analysis should not be overrated due to the limited number of includable studies for each of the relevant caries detection categories (Table 2). Nevertheless,

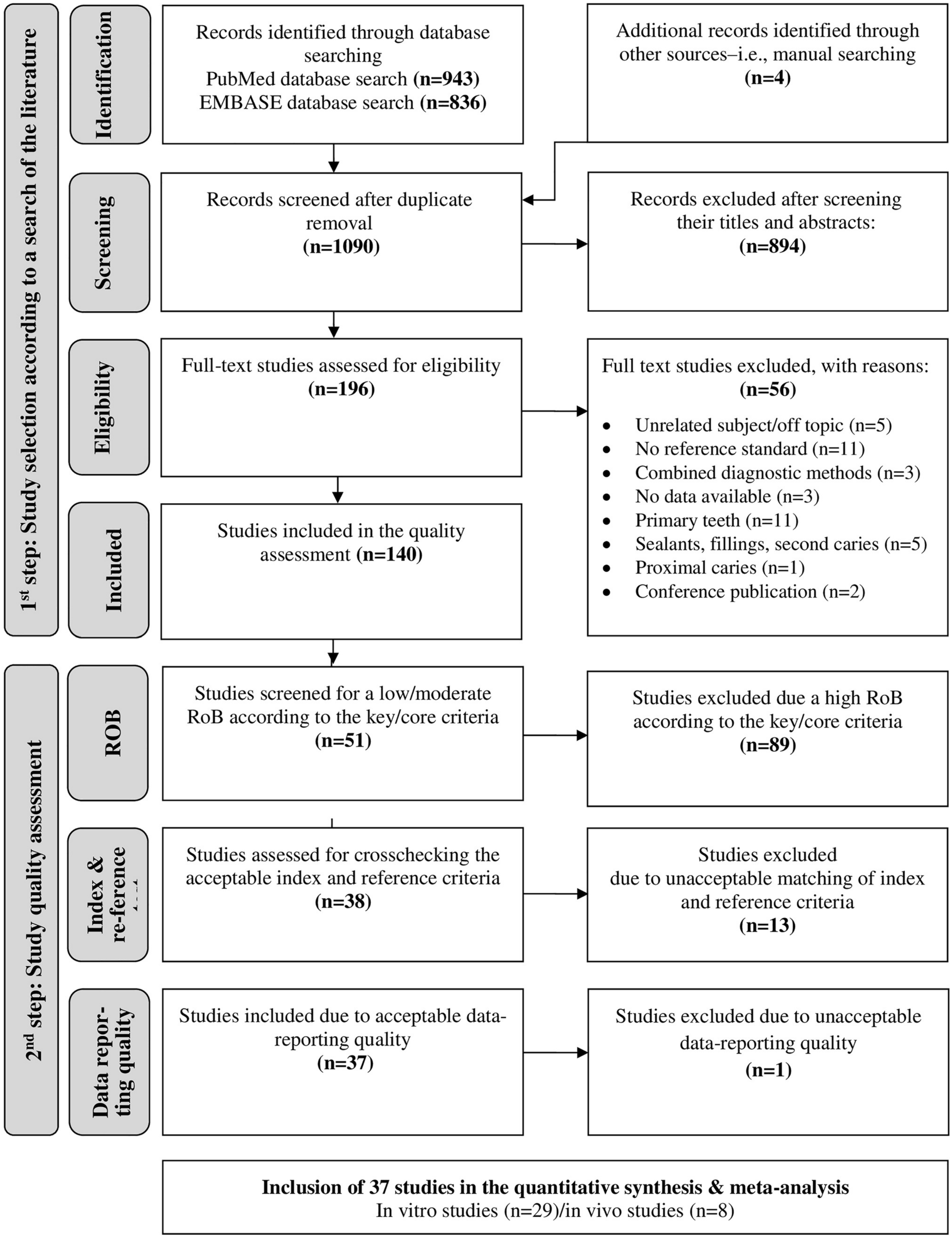

Fig. 1 Flow diagram detailing our search and study selection process applied during the systematic literature search (*1st step*) and study quality assessment (*2nd step*)

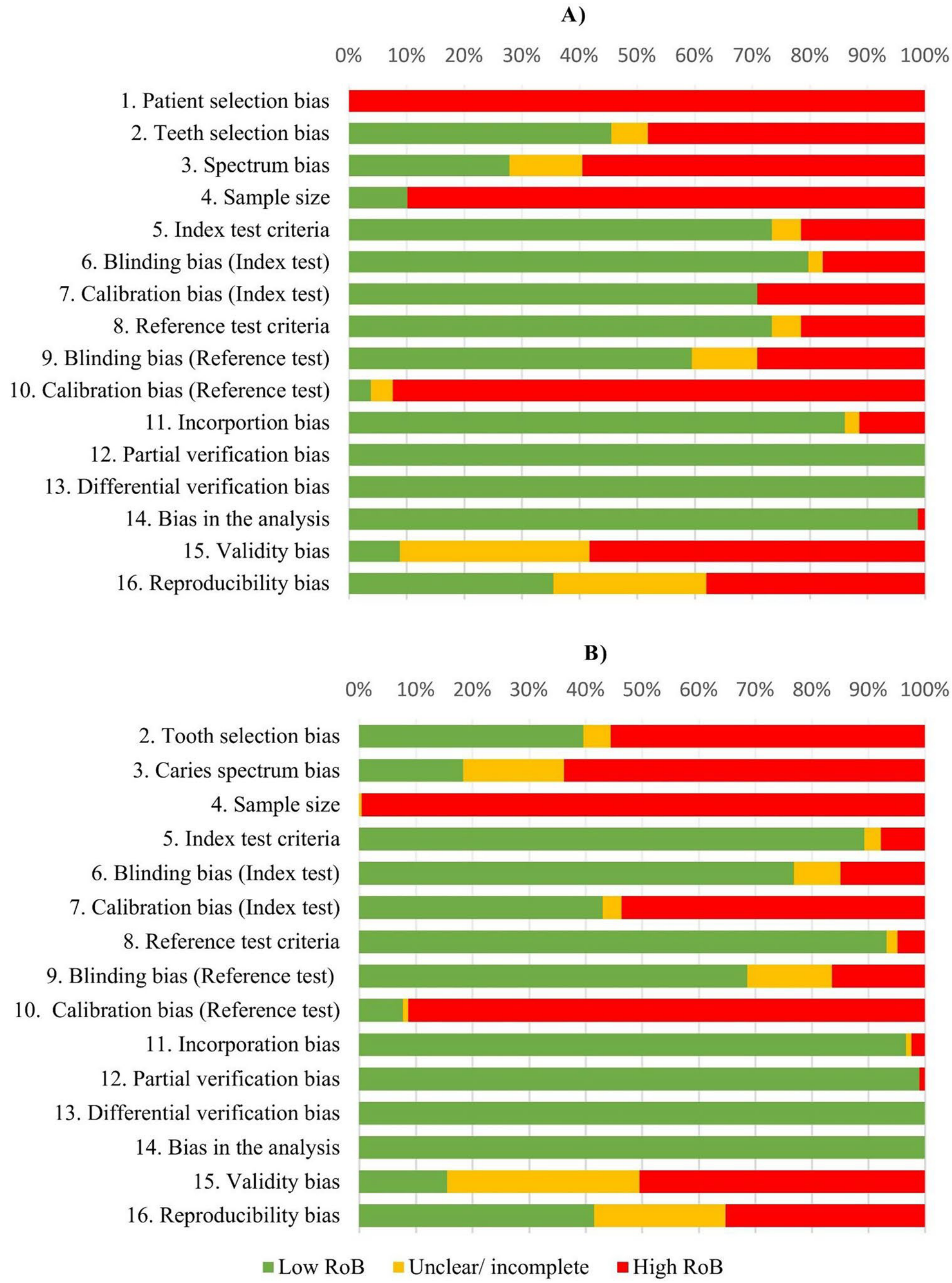

Fig. 2 RoB graph across included in vivo (**A**) and in vitro (**B**) caries diagnostic studies for occlusal surfaces. Item no 1 (*patient selection bias)* is only available for clinical diagnostic studies

a few conclusions can be drawn from the available data. The data support the generally and repeatedly published assumption that VE of pits and fissures is not perfect and needs to be accompanied by additional diagnostic methods. Nevertheless, more recently published criteria (ICDAS, UniViSS) that summarize the whole spectrum of non-cavitated caries lesions may help to overcome this drawback [16, 82–84]. Under in vitro conditions, VE showed mostly high SP values, while SE varied between the different methods and thresholds. A large difference between SE values was registered for VE under in vitro and in vivo conditions (Tables 3 and 4), which was also reported by Gimenez et al. [15]. Therefore, VE under in vitro conditions results in higher SP values. Vice versa, clinical evaluations probably include more details, which may result in higher diagnostic SE values especially for enamel caries.

It should be further noted that VE is the method that enables the clinician to collect important diagnostic covariables, e.g. presence of biofilm or lesion appearance, enables differential diagnoses and provides finally information about the caries lesions activity [85, 86]. The latter aspect potentially influences the individual caries management strategy and it's consideration has become mandatory in clinical practice [87–89]. Contrary, with respect to the

Table 2 Overview of the identified diagnostic studies in relation to the method used and characteristics of the study set-up with stepwise included studies for meta-analysis

1st step			2nd step		
Study inclusion according to the systematic search of the literature			Study inclusion according to the quality assessment		
Studies on diagnostic methods	Study set-up	Specification (N according to PRISMA)	Low/ moderate RoB	Acceptable index and reference test	Acceptable data reporting quality
VE (*N*=106)	In vivo (*N*=27)	Without a probe (*N*=22)	10	4	3
		With a probe (N=5)			
	In vitro (*N*=79)	Without a probe (*N*=66)	23	14	13
		With a probe (*N*=13)			
Conventional bitewing radiography (*N*=63)	In vivo (*N*=18)	D-speed (*N*=10)	3	2	1
		E-speed (*N*=3)	2	2	2
		F-speed (*N*=1)	-	-	-
		Not specified (*N*=4)	1	-	-
	In vitro (*N*=45)	D-speed (*N*=13)	4	3	3
		E-speed (*N*=24)	5	2	2
		F-speed (*N*=6)	2	2	2
		Not specified (*N*=7)	1	1	1
Digital bitewing radiography (*N*=19)	In vivo (*N*=3)	Sensor (*N*=0)	-	-	-
		Phosphor plate (*N*=1)	-	-	-
		Not specified (*N*=2)	1	-	-
	In vitro (*N*=16)	Sensor (*N*=9)	3	2	2
		Phosphor plate (*N*=8)	2	1	1
		Not specified (*N*=0)	-	-	-
LF measurement (*N*=68)	In vivo (*N*=22)	DIAGNOcam 2095 (*N*=22)	9	3	3
		DIAGNOcam 2190/Pen (*N*=5)	2	-	-
	In vitro (*N*=46)	DIAGNOcam 2095 (*N*=38)	18	10	10
		DIAGNOcam 2190/Pen (*N*=12)	7	6	5
Fibre-optic transillumination (*N*=8)	In vivo (*N*=1)		-	-	-
	In vitro (*N*=7)		3	3	3
Quantitative light-induced fluorescence (*N*=7)	In vivo (*N*=1)		1	-	-
	In vitro (*N*=6)		2	-	-

methodological difficulties and missing standards to validate caries activity, it was decided to exclude the activity assessment from the present systematic search of literature and meta-analysis.

In vitro data from Ekstrand and co-workers [28, 90, 91] pointed to the fact that non-cavitated occlusal lesions depth (histological assessed), either, was restricted to the enamel or penetrated the dentin, but then restricted to the outer 1/3 towards the pulp. To raise the accuracy, e.g. in terms of SE and SP, Ekstrand et al. [28] suggested to move the standard thresholds - enamel versus dentin caries - to lesions reaching the middle or inner 1/3 of the dentin. Thus, combined SP and SP values amounted to 175 [91]. The new threshold is much more relevant to the clinicians than the old one, as non-cavitated lesions without an obvious shadow should receive non-operative care if the lesions are assessed as active, while more mature active lesions should receive operative [16].

BWR is the most commonly used additional caries lesion detection method in daily dental practice. However, its validity on occlusal surfaces is often questioned, especially in the early stages of caries [92]. Here, the anatomy of the tooth crown results in superimposed images on the two-dimensional (bitewing) radiographs, making the detection of early dentin caries lesions harder in comparison to that on proximal sides [93]. Surprisingly, the results of the present meta-analysis did not show a striking difference in SE and SP values between different X-ray types assessed in this review. However, the difference in accuracy parameters was obvious compared to those of LF. However, due to the limited number of studies belonging to each BWR category,

Table 3 Bivariate diagnostic random-effects meta-analysis for the finally included in vitro studies for all diagnostic methods at different caries detection levels

Meta-analytical diagnostic performance		In vitro		
		Caries detection level	Dentin detection level	1/3 dentin detection level
VE	N	3	8	2
	SE (95% CI)	0.59 (0.52–0.67)	0.46 (0.20–0.73)	0.69 (0.51–0.82)
	SP (95% CI)	0.83 (0.70–0.92)	0.87 (0.72–0.95)	0.88 (0.83–0.92)
	AUC (Reitsma)	0.59	0.79	0.89
	DOR	5.55 (1.88–16.38)	5.93 (3.11–11.31)	16.6 (4.85–56.79)
Conventional bitewing radiography (D-speed)	N	-	1	-
	SE (95% CI)		0.42 (0.18–0.69)	
	SP (95% CI)		0.73 (0.53–0.87)	
	AUC (Reitsma)		0.60	
	DOR		1.94 (0.46–8.17)	
Conventional bitewing radiography (E-speed)	N	-	2	-
	SE (95% CI)		0.48 (0.21–0.77)	
	SP (95% CI)		0.95 (0.53–0.997)	
	AUC (Reitsma)		0.75	
	DOR		10.69 (3.67–31.15)	
Conventional bitewing radiography (F-speed)	N	-	2	-
	SE (95% CI)		0.50 (0.22–0.79)	
	SP (95% CI)		0.97 (0.71–0.998)	
	AUC (Reitsma)		0.82	
	DOR		23.60 (8.28–67.24)	
Digital bitewing radiography (phosphor plates)	N	-	2	-
	SE (95% CI)		0.48 (0.24–0.73)	
	SP (95% CI)		0.95 (0.59–0.995)	
	AUC (Reitsma)		0.73	
	DOR		15.57 (0.47–515.27)	
LF 2095	N	6	7	-
	SE (95% CI)	0.75 (0.58–0.86)	0.68 (0.54–0.79)	
	SP (95% CI)	0.76 (0.60–0.87)	0.78 (0.68–0.85)	
	AUC (Reitsma)	0.81	0.79	
	DOR	10.28 (4.35–24.28)	8.01 (4.04–15.88)	
LF pen 2190	N	2	4	-
	SE (95% CI)	0.78 (0.44–0.94)	0.63 (0.37–0.83)	
	SP (95% CI)	0.77 (0.62–0.87)	0.77 (0.62–0.88)	
	AUC (Reitsma)	0.77	0.78	
	DOR	11.83 (2.66–52.63)	5.85 (1.77–19.30)	
Fibre-optic transillumination FOTI	N	1	2	-
	SE (95% CI)	0.97 (−0.92–0.99)	0.49 (0.20–0.79)	
	SP (95% CI)	0.50 (0.34–0.66)	0.97 (0.89–0.994)	
	AUC (Reitsma)	0.92	0.92	
	DOR	38.33 (10.15–144.77)	37.77 (13.69–104.19)	

these results should be interpreted with caution. Unlike previously published reviews [13], this review considered separate studies using conventional film-based BWR and digital BWR (including their different modalities) with the aim of reducing bias. Unfortunately, this approach resulted in a low number of includable studies in each category.

LF has been used as an adjunct caries detection method for incipient lesions that otherwise could not be detected by VE alone [94]. The results of our study revealed high SE and SP values for LF under in vitro conditions, which is in line with previously reported findings by Gimenez et al. [14] and Rosa et al. [12]. When considering the small number of includable data from in vivo studies (Table 4), these data should be treated with caution, but they are still comparable to previous findings from Pinheiro et al. [94]. In contrast to these reassuring results, LF alone is not sufficient for the correct diagnosis of caries and good standardization is essential to avoid overtreatment and false-positive readings due to other fluorescence sources [12, 14, 81, 84, 94].

The present study has strengths and limitations. First, one strength is that commonly used diagnostic methods for occlusal caries detection and diagnostics were analysed in one meta-analysis. Second, there was a strict study selection protocol, which was based on principles

Table 4 Bivariate diagnostic random-effects meta-analysis for the finally included in vivo studies for all diagnostic methods at different caries detection levels

Meta-analytical diagnostic performance		In vivo		
		Caries detection level	Dentin detection level	1/3 dentin detection level
VE	N SE (95% CI) SP (95% CI) AUC (Reitsma) DOR	2 0.70 (0.59 – 0.80) 0.47 (0.26 – 0.70) 0.70 2.14 (0.73 – 6.28)	-	3 0.72 (0.52 – 0.86) 0.77 (0.67 – 0.85) 0.77 10.18 (3.94 – 26.29)
Conventional bitewing radiography (D-speed)	N SE (95% CI) SP (95% CI) AUC (Reitsma) DOR	1 0.65 (0.57 – 0.73) 0.58 (0.42 – 0.72) 0.65 2.59 (1.24 – 5.44)	2 0.79 (0.41 – 0.96) 0.75 (0.68 – 0.82) 0.77 11.79 (2.43 – 57.24)	-
Conventional bitewing radiography (E-speed)	N SE (95% CI) SP (95% CI) AUC (Reitsma) DOR	1 0.80 (0.71 – 0.87) 0.94 (0.46 – 0.996) 0.94 60.37 (3.31v1100.70)	2 0.76 (0.61 – 0.87) 0.98 (0.79 – 0.998) 0.90 127.56 (7.38 – 2203.70)	-
Conventional bitewing radiography (F-speed)	N SE (95% CI) SP (95% CI) AUC (Reitsma) DOR	-	-	-
Digital bitewing radiography	N SE (95% CI) SP (95% CI) AUC (Reitsma) DOR	-	-	-
LF 2095	N SE (95% CI) SP (95% CI) AUC (Reitsma) DOR	1 0.88 (0.81 – 0.93) 0.71 (0.55 – 0.83) 0.88 18.33 (7.57 – 44.37)	2 0.91 (0.86 – 0.95) 0.78 (0.46 – 0.94) 0.92 35.90 (13.43 – 96.00)	-
LF pen 2190	N SE (95% CI) SP (95% CI) AUC (Reitsma) DOR	-	-	-
Fibre-optic transillumination FOTI	N SE (95% CI) SP (95% CI) AUC (Reitsma) DOR	-	-	-

for performing systematic reviews and, in addition, a tailored RoB assessment that included only studies with a low RoB and excluded probable heterogenic publications. Third, the present study considered different thresholds independently for in vitro and in vivo studies. As a main limitation of the study selection process used, the exclusion of reports with a potentially high RoB from the meta-analysis and feasibly subjectivity of included selection criteria might be discussed for very low number of the included studies, especially in the clinical research. To our knowledge, such strict selection has not previously been performed because it is not part of the current recommendations for conducting a meta-analysis. While this step may result in the analysis of a homogenous pool of studies, it resulted, by contrast, in a substantial reduction in includable studies. It is further worth mentioning that several reports needed extensive discussion with respect to missing data or information. Therefore, the inclusion or exclusion of a single study remained in some cases a subjective procedure that could not be fully objectified. Because of the limited number of includable studies and the low sample size, the results from this meta-analysis should be interpreted with caution. This fact underlines the urgent need for well-designed and well-powered diagnostic studies that use multiple diagnostic procedures and different caries thresholds.

Conclusions

There is an overall need for high-quality, well-designed and standardized studies on the detection, diagnosis, assessment and/or monitoring of occlusal surface caries. This need must be emphasized for diagnostic studies under in vivo conditions due to the limited number of clinical trials and the documented heterogeneity between published reports. When considering the meta-analytic results, VE, BWR and LF provide acceptable measures for their diagnostic performance on occlusal surfaces. Again, the present results should be interpreted with caution with respect to the limited data in many diagnostic categories.

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Declarations

Ethics approval This article does not contain any animal or human studies performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

Conflicts of interest Svetlana Kapor declares that she has no conflicts of interest. Mila Janic Rankovic declares that she has no conflicts of interest. Alexander Crispin declares that he has no conflicts of interest. Yegane Khazaei declares that she has no conflicts of interest. Ina Schüler declares that she has no conflicts of interest. Felix Krause declares that he has no conflicts of interest. Kim Ekstrand declares that he has no conflicts of interest. Stavroula Michou declares that she has no conflicts of interest. Klaus Neuhaus declares that he has no conflicts of interest. Florin Eggmann declares that he has no conflicts of interest. Adrian Lussi declares that he has no conflicts of interest. Marie-Charlotte Huysmans declares that she has no conflicts of interest. Jan Kühnisch declares that he has no conflicts of interest. All applicable international, national and/or institutional recommendations for conducting systematic revisions were followed.

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Publication II

Two-body wear and fracture behaviour of an experimental paediatric composite crown in comparison to zirconia and stainless-steel crowns dependent on the cementation mode

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Two-body wear and fracture behaviour of an experimental paediatric composite crown in comparison to zirconia and stainless steel crowns dependent on the cementation mode

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ABSTRACT

Objectives. The purpose of this in vitro study was to assess the two-body wear and fracture behaviour of an experimental additive manufactured composite crown in comparison to zirconia and stainless steel crowns and its cementation protocol for primary molars.
Material and methods. Three different paediatric crowns – experimental composite crowns (CCs, 3M), zirconia crowns (ZCs, NuSmile), and stainless steel crowns (SSCs, 3M)–were cemented with an experimental resin-modified glass ionomer cement (RMGIC, 3M) and two self-adhesive cements (SACs; RelyX Unicem Automix 2, 3M; BioCem, NuSmile). Seven groups, each with eight specimens, were thermally cycled (55 °C/50 °C) and dynamically loaded (50N/ 1.2Hz) in a masticatory simulator with steatite antagonists. The areal and volumetric material loss of all specimens before and after 1,200,000 masticatory cycles was evaluated with a 3D profilometer. Light and scanning electron microscopy were used for qualitative analysis. Pairwise comparisons between all the groups were performed using the Mann–Whitney *U* test ($p < 0.05$).
Results. Microscopic imaging revealed different wear patterns for each material. Lowest fracture rates were documented for the CCs. In contrast, all the SSCs showed perforations. The CCs cemented with RMGIC showed the highest significant volumetric wear (6.3 ± 0.72 mm^3), followed by the SSCs cemented with RMGIC (3.6 ± 1.79 mm^3) and CCs cemented with SAC (3.5 ± 1.92 mm^3). No significant differences were found in terms of the wear among all the other groups, ranging between 0.4 ± 0.25 and 0.6 ± 0.32 mm^3.
Conclusion. The volume loss of the tested crowns differed for each material and was dependent on the type of cementation. With regard to in vitro wear and fracture patterns, cementation with SAC may increase the clinical performance of CC paediatric crowns.

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1. Introduction

Prefabricated paediatric crowns are frequently used to restore primary molars with severe carious destruction due to their less technique-sensitive clinical application technique and excellent longevity [1–4]. The documented annual failure rates for stainless steel crowns (SSCs) were found to be in the range of 0–14%, which was lower than most other restorative techniques [5,6]. While the success of prefabricated SSC is well shown, the lack of aesthetics has been increasingly questioned by caregivers in daily dental practice. Therefore, veneered stainless steel or full zirconia crowns were introduced in the dental market. However, veneered SSCs have the disadvantage that ceramic veneers may chip off or, in the case of zirconia crowns, tooth preparation prior to crown placement is much more invasive than that required for placing SSCs [7]. Nevertheless, aesthetic paediatric crowns also show high 3-year retention rates of 76–94% [3,4,8]. Aiming to overcome the above mentioned limitations, a new experimental composite crown (CC) based on a homogeneous methacrylate resin matrix with silica/ zirconia nanocluster filler particles was recently developed (3M, Seefeld, Germany) due to parental request for tooth-coloured restorations [9]. The major advantage of using CC might be the beneficial bonding to the composite-based luting cements. Further, an easier dental handling in terms of occlusal corrections and no material chip-off can be assumed compared to that of conventional SSCs, pre-veneered paediatric crowns or Zirconia crowns (ZC).

Crowns are industrially manufactured in additive technology, which has recently gained importance alongside subtractive manufacturing due to the feasibility of efficiently fabricating complex geometries in a minimum amount of time and saving material [10]. Until recently, there have been no scientific data available about the laboratory and clinical performance of this new and innovative paediatric crown. Therefore, the primary objective of this in vitro study was to preclinically evaluate the two-body wear and fracture behaviour of additively manufactured CCs in comparison with different available paediatric crowns and cementation procedures. The initially formulated null hypothesis was that there would be no difference in terms of the fracture and wear resistance for the chosen paediatric crowns and their cementation protocols.

2. Materials and methods

2.1. Study design

This in vitro study on the two-body wear and fracture behaviour included three different pre-fabricated, paediatric crowns (CC, SSC, ZC) which were not individualised during cementation.

Composite crown (3M): methacrylate based resin matrix with silicia/zirconia nanocluster)

Zirconia crown (Nusmile): 80–96% ZrO_2, 4–10% Y2O3, <5% HfO2, <5% organic binder, 1–4% pigments) = Y-TZP dental Zirconia.

Stainless steel crown (3M): Fe-Ni-Cr

which were cemented using two self-adhesive cements (SAC) and a resin modified glass-ionomer cement (RMGIC) on standardized tooth stumps.

2.1.1. *Standardization and fabrication of standardized test dies*

Considering the non-availability of appropriate and sufficient material for human teeth, a cavitated primary molar (tooth 75) was reconstructed initially and a 3D scan of a natural human tooth was preformed afterwards, which was later digitally optimized. Subsequently, three duplicates of this primary molar were milled from a composite resin Lava Ultimate block (3M) due to the material properties which are comparable to dentin [11,12]. Next, each of these fabricated duplicates were prepared according to requirements for the included crown types. In detail, CC and ZC needed an occlusal reduction of approximately 1.5 mm, proximal separation (~1.5 mm), circumferential reduction of approximately 1 mm and shaping/ bevelling of all the edges until the selected crown passively fitted exactly over the prepared duplicate tooth stump. SSC required an occlusal reduction (~1.5 mm) and proximal separation (~1.5 mm). Following this, the prepared tooth stumps for each crown type were also reproduced using the previously mentioned CAD/CAM-based workflow. In total, 56 standardized tooth stumps (CCs = 16, ZCs = 24, SSCs = 16) were milled from Lava Ultimate blocks (3M), and each specimen was embedded in cold-curing methyl methacrylate resin (Technovit 4004, Heraeus Kulzer, Wehrheim, Germany) which was chosen because of its module of elasticity (2.000–2.300 N/mm^2) closely to human bone (spongiosa: 1.000 N/mm^2; corticalis: 10.000 N/mm^2), according to the mounting requirements for the two-body wear simulation [13]. Before crown cementation, each tooth stump was cleaned with airborne particles with aluminium oxide (<1 bar and particle size ≤50 μm), steamed off and the specimens were dried with compressed water- and oil-free air. Finally, all tooth stumps were degreased with iso-propanol before cementation.

2.1.2. *Cementation of crowns using self-adhesive cement 1 (SAC-1; RelyX Unicem 2 Automix)*

Then, the crown was cemented as follows: (1) excess material was removed; (2) the crown was cured for 5 s (s) after it was installed and excess material was removed from each crown; and (3) the crown was light cured for 10 s on each of the buccal, oral and occlusal surfaces (Elipar S10, 3M). Immediately after polymerization, all the specimens were stored in distilled water at 37 °C for 24 h (Jouan EU3, innovens Ovens, ThermoFisher Scientific Inc., Waltham, MA, USA).

2.1.3. *Cementation of the zirconia crowns using self-adhesive cement 2 (SAC-2; NuSmile BioCem. NuSmile)*

In addition, zirconia crowns were cemented with the specifically recommended luting cement according to the manufacturer's instructions. In detail, excess material was removed after flash curing (<5 s), then the crowns were additionally light cured for 10 s on the buccal and oral surfaces, and all the specimens were also stored in distilled water at 37 °C for 24 h.

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2.1.4. *Cementation of the crowns using experimental resin-modified glass ionomer cement (Exp. RMGIC, 3M)*

The experimental RMGIC is composed of methacrylated polycarboxylic acid, HEMA, ethyl acetate, FAS glass, non-reactive zirconia silica filler, titanium dioxide, potassium persulfate and a photoinitiator. Subsequently to automixing each crown was filled with the experimental RMGIC and fixed over the tooth stump. Light curing and removal of excess material was performed similar to the SAC-1 group.

2.1.5. *Two-body wear testing*

Specimens and antagonists were mounted in a chewing simulator (CS-4, SD Mechatronic, Feldkirchen-Westerham, Germany). The cyclic fatigue test was applied to each crown with a round steatite sphere with a diameter of 4 mm. The sphere was placed onto the vestibular cusp, and the dynamic loading contained an additional horizontal shift of 2 mm in the central direction of the abutment. A force of 50 N was applied for 1,200,000 cycles at a frequency of 1.2 Hz. The loading speed was 20 mm/s, and the lifting speed was 60 mm/s. Cyclic loading was examined every ~100,000 cycles to evaluate the possible destruction or failure of the specimen. While the mechanical force was applied, thermocycling was simultaneously conducted by changing the water temperature every 30 s from 5 °C to 55 °C.

2.1.6. *Evaluation of wear*

After cementation, water storage for 24 h at 37 °C and before artificial ageing, all the specimens were optically scanned (baseline scan, Laser scanner LAS-20, SD Mechatronic). A second scan was applied after artificial ageing (test scan). Both datasets were superimposed (Geomagic Qualify 2012, Morrisville, USA) with a best-fit algorithm in an iterative approach using the equator and non-abraded areas as a reference to analyse the quantity of wear. The parameters were the volume of wear, surface of wear and maximum and mean wear depth. Failure analysis was performed with a light microscope (BMS 74956, Breukoven, Essebann, The Netherlands) to detect and verify the crack lines, (micro)perforations, fractures and/or loss. In addition, specimens were further examined with a scanning electron microscope (SEM, DSM 982, Zeiss, Oberkochen, Germany) for obtaining images of the fracture pattern. To investigate the filler dimension and distribution of the CC material, five samples were observed by SEM sputtering and after heat exposure for one minute in a flame.

2.1.7. *Statistical evaluation*

The descriptive and explorative analysis of the data was undertaken with Microsoft Excel and SPSS Statistics for Windows, Version 21.0.1 (SPSS Inc., an IBM Company, Armonk, NY, USA). The significance level was set at $p < 0.05$. Pairwise comparisons between all the groups were performed using the Mann–Whitney *U* test.

3. Results

The two-body wear analysis showed divergent outcomes for each of the included types of crowns and their cementation. When considering first SSCs as the most frequently used paediatric crowns, gross perforations in the occlusal contact areas were the commonly observed form of failure independent of the cement type (Table 1, Fig. 2); none of the SSCs were lost. SSCs that were cemented with SAC showed, first, less extensive perforations and, second, survived longer until perforation of all the specimens (~700,000 cycles before perforation) in comparison to the RMGIC (~300,000). Contrary to the previously mentioned observation, brittle fractures were found to be the common fracture mode for SAC cemented ZCs (Table 1, Fig. 2); only one ZC (SAC-2 cementation) fractured in full. Perforations were mostly observed in the group for RMGIC fixed ZCs. The lowest failure rate was documented for the CCs in combination with SAC. When using the experimental RMGIC, the failures of the CCs increased (Table 1 and Fig. 2).

The descriptive findings from the extensive 3D- and 2D-wear analysis can be taken from Fig. 1. ZC showed the lowest volumetric (0.40 ± 0.25 mm^3) and two-dimensional (0.09 ± 0.01 mm^2) wear. Similar numeric data with insignificant differences were observed for the SSCs, which were cemented with SAC (0.5 ± 0.31 mm^3, 0.10 ± 0.06 mm^2). Substantially more extensive wear – in terms of the volume and area – was documented for CCs cemented with RMGIC (6.3 ± 0.72 mm^3, 0.39 ± 0.06 mm^2); the wear was found to be lower in cases with SAC (3.5 ± 1.92 mm^3, 0.27 ± 0.10 mm^2). The same relationship was found in the case with SSC (Fig. 1).

SEM images displayed differences on the worn surfaces (Fig. 2). All SSCs showed limited wear traces with the presence of occlusal perforation. Serrated metal edges and small crack lines surround the perforations. On the CCs, a large and deep indentation produced by localized wear was observed. In addition, wear traces showed scratches in the direction of sliding interrupted by some cracks. The evaluation of the ZC showed deep cracks and chipping in the area of vertical loading of the antagonist (Fig. 3).

The SEM images that show the filler composition of the CC material are shown in Fig. 4. A variety of fillers were observed, and regarding particle dimensions, the largest particles observed were nonuniform fillers in the range of seven microns and less. The shapes of the submicron particles were round and irregular, and the interspaces were filled with smaller particles.

4. Discussion

The present study primarily investigated the fracture pattern and wear behaviour of prefabricated paediatric crowns with different cementation modes. Based on our findings, the initially formulated hypothesis was rejected due to the documented differences between the test groups (Table 1 and Fig. 1). Here, two-body wear was shown to be lower when prefabricated paediatric crowns were cemented with SAC compared to RMGIC. When comparing the crown types, it became evident that each material showed its own wear pattern. The hardness and surface texture of the restoration were known as relevant influencing criteria on the wear of the material [14–16]. For most materials, metals in particular, the wear resistance was believed to be directly proportional to the hardness, as expressed in Archard's theory [17]. However,

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Table 1 – Quantitative fracture pattern analysis of different crown materials and cementation strategies after testing.

Crown type	Cementation	Light microscopic evaluation (4.5 fold) after testing				
		Intact	Crack lines	Micro-perforation	Perforation	Fracture & Loss
Stainless steel crowns (SSCs)	RelyX Unicem 2 Automix (SAC-1)	–	–	–	8[a]	–
	Experimental RMGIC	–	–	–	8[b]	–
Zirconia crowns (ZCs)	RelyX Unicem 2 Automix (SAC-1)	5	3	–	–	–
	BioCem (SAC-2)[c]	3	3	–	–	1
	Experimental RMGIC*	–	2	–	6	–
Exp. Composite crowns (CCs)	RelyX Unicem 2 Automix (SAC-1)	8	–	–	–	–
	Experimental RMGIC	1	2	4	–	1

[a] Perforation of all the specimen after ~700.000 cycles.
[b] Perforation of all the specimen after ~300.000 cycles.
[c] One specimen showed loss of retention during testing.

this relationship did not seem to apply to materials such as ceramics, where the hardness is more likely to be determined by microstructural inhomogeneities. Therefore, the surface of ZC must be well-polished if occlusal adjustments with coarse rotating instruments are performed [16]. It was shown in previous studies that the polishing step reduces the wear of the opposing enamel and can reduce it to a level of SSC [18].

In our study, all the crowns were fabricated and polished industrially, and we assumed, therefore, that hardness may have had an overriding significance on the results. The hardness of the included crowns could be ranked as follows: zirconia > metal > composite [19,20] and corresponded well to the abrasion data in this study (Fig. 1)

Considering the results from wear testing, all the SSCs survived. Nevertheless, localized perforations of different sizes were documented on the wear traces. During testing, the steatite antagonist occluded against the ductile metal surface, and wear was initially caused by plastic deformation. Due to the repeating sliding force impact, wear proceeded, and characteristic metal perforations appeared (Fig. 2). In vivo perforations, however, were reported in only 0.2% after 5 years [1]. The surfaces of the adhesively cemented SSC perforation endured twice as long as conventional cemented SSC before perforations were observed referring to the material properties of the cement [21]. In addition to this, the crown thickness (CC ~550 μm; ZR ~750 μm; SSC ~200 μm) might be considered as another reasonable factor.

In addition to the full loss of one ZC, the frequent failure pattern was perforation by collapse of the surface, which was preceded by micro-fractures. The wear behaviour of the ZC was therefore different from that of the others. Here, the vertical load results in material fatigue on the initially touched contact area, and the lateral movement of the steatite antagonists remained without detectable abrasion. Therefore, brittle fractures were found to be the dominating wear mechanism (Fig. 2), which is in line with previously published reports [22]. In the case of ZC, neither a significant influence of the different SACs nor RMGIC was observed.

CCs cemented with SAC showed a success rate of 100% without any surface defects. In contrast, in the RMGIC group, one composite crown fractured, and six showed surface insufficiencies. The significant difference might be attributable to the mechanical properties of the crown and cement. In the CCs, a combination of abrasion and fatigue seemed to be the dominating wear mechanism [23], which resulted in a substantial loss of material. Cyclic loading caused vertical cracks when the tensile strength of the material was exceeded due to shear stress. In addition, horizontal cracks were formed by compressive and tensile stresses, which were initiated on the filler matrix interface attributed to the different elastic moduli of the inorganic fillers and organic matrix [24]. The remaining particles on the surface or on the steatite antagonist might act as abrasives on the material's surface, although simultaneous thermocycling would likely rinse off such abrasives from the crown surface. The scratches observed from the SEM images in the sliding direction (Fig. 2) supported this assumption.

When considering the quantitative analyses of wear, it was found that CCs showed the significantly highest 2D- and 3D-material loss in each cementation group in comparison to the other crown types (Fig. 1). This could be easily explained by the material properties, which were needed for additive manufacturing of the composite materials [25]. Here, the basic requirement was an adapted viscosity of the non-polymerized resin which should not exceed 5 Pas prerequisite in SLA and DLP printing at present to ensure satisfactory layer recoating [26,27]. This requirement is mainly achieved by a low filler content and adapted filler size [28], which is illustrated in Fig. 4. While the additively manufactured composites had a volumetric filler content of approximately 30 volume percent as shown for the material 3Delta temp in the study of Kessler et al. [28], conventional dental composites reach up to ~80 volume percent by use of fillers with a comparable size and dimensions [29]. Finally, the lowered filler content did explain the substantial wear of the prefabricated CCs.

A substantial impact of cementation was observed on the two-body wear and fracture behaviour, which seemed to be

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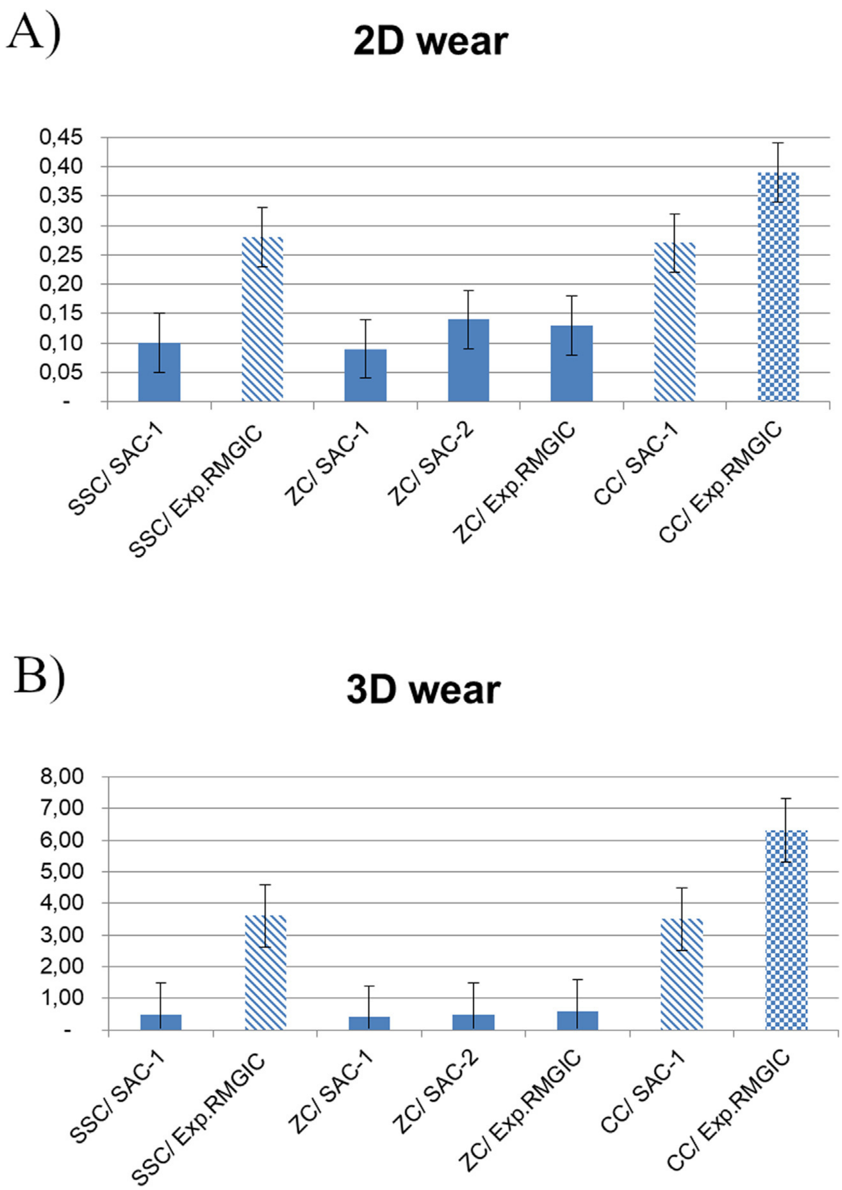

Fig. 1 – Means and standard deviations of the two (A) [mm^2] and three (B) [mm^3] dimensional maximum depth of wear after 1,200,000 loading cycles. The bars (mean ± 1 standard deviation) and same bar patterns represent the homogeneous subgroups (α = 0.05).

relevant in paediatric crowns due to the low level of individualization in comparison to customized indirect restorations in permanent teeth. In prefabricated crowns, cement gaps up to 0.38 mm could be expected, which required a resistant cement material [30]. In this context, the lower wear of the SSC and CC should be first discussed, which were fixed with SAC in comparison to the corresponding groups with the RMGIC protocol (Fig. 2). The SAC acted as a solid intermediate layer and influenced the wear of the crowns due to its material properties, such as the elastic modulus, hardness, compressive strength and adhesion to dies [21]. As shown in the present study, SAC exhibited advantages, which resulted in better performance in relation to ductile stainless steels or elastic composites (Fig. 2). A reduction in the stiffness of the crown material would transfer the stress more prominently to the cement layer and act, therefore, as an intermediate buffer zone compared with the behaviour of other materials [31]. In this context, the resin-based cements possessed a significantly higher compressive strength than the RMGIC, which was supposed to be one of the important factors that affected the different wear values [21]. Finally, the system became stiffer, acted as a "mono-block" and was able to compensate for more stress in comparison to the RMGIC [31].

The strength of the ZC might outweigh the influence of certain cement properties, such as the low compressive strength and increased cement film thickness of the monolithic ZC. Corresponding results are observed in previous studies showing no influence of the cementation of zirconia on the fracture toughness [8,32].

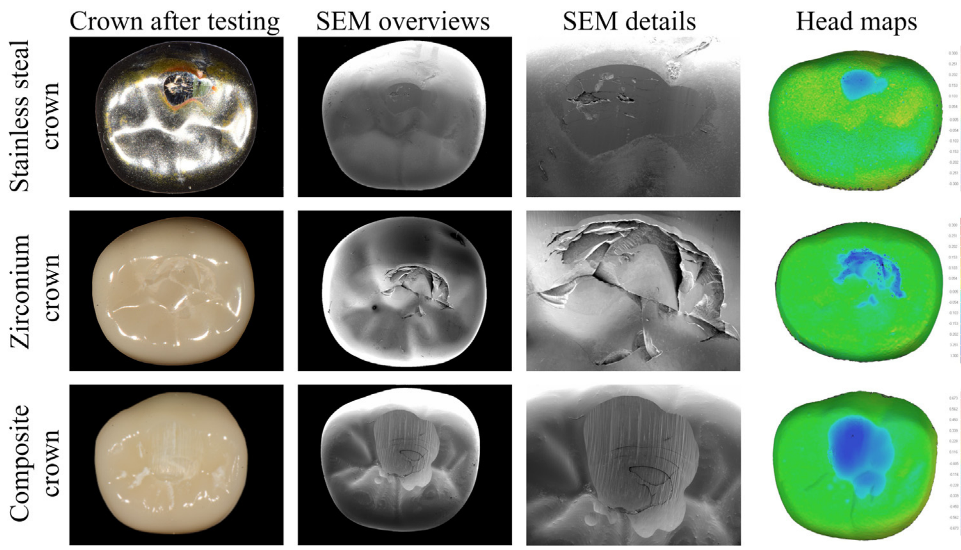

Fig. 2 – Representative photographs, SEM micrographs (magnification 8× and 15×) and head maps after superimposition of the baseline and test scan for stainless steel crowns, zirconia crowns and composite crowns showing indentation produced by localized wear of the crown material, perforations, surface and chipping fractures.

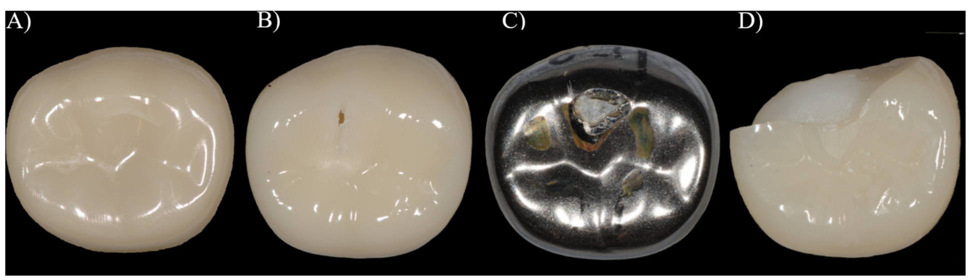

Fig. 3 – Representative photographs of fracture patterns (A) crack lines (B) micro perforation (C) perforation (D) fracture & loss.

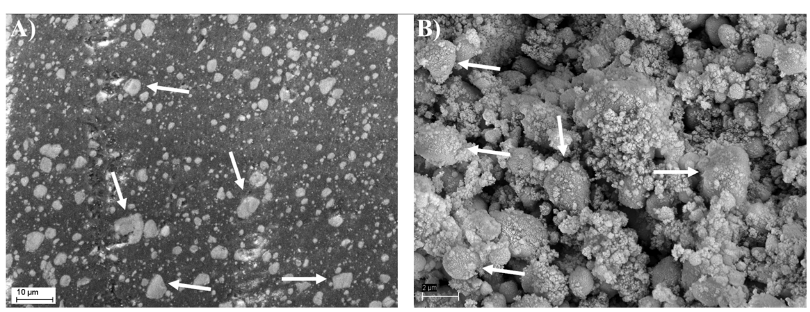

Fig. 4 – SEM micrographs of sputted (A) and burned (B) CC samples investigated with a magnification of 5,000×.White arrows mark larges inorganic fillers.

In the case of zirconia-based restorations, it is considered that conventional cementation is acceptable, although SAC might be preferred when adhesive cementation is required. Bearing in mind the challenges of using SAC in (paediatric) clinical practice, e.g., bleeding and moisture control as well as correct removal of excess material, it should be noted that SAC is linked with a technique-sensitive clinical workflow, which could potentially limit the use of SAC in paediatric dentistry. This relationship was shown in a 3-year longitudinal study in paediatric ZC performed significantly different in relation to the used cement (Biocem: 44%; RMGIC: 88%) [8].

When considering the methodology of the study, the following strengths and limitations need to be discussed. The chewing simulation allows a comparative evaluation and ranking of different materials under standardized in vitro conditions. In this study, a worst-case scenario is chosen by testing the materials with a protocol that is commonly used for adult restorative materials [22,33–35]. Therefore, a chewing force of 50 N, with a frequency of 1.2 Hz, 1,200,000 mastication cycles and simultaneous thermocycling is applied. In the literature, 120,000 cycles are often compared with an in vivo time of 6 months up to 1 year [36,37], and the chosen protocol, therefore, covers the entire service time of the paediatric crowns. Thermocycling as an ageing method takes into account the water uptake and hydrolyses in methacrylate based materials [38]. The wear of restorative materials is further dependent on the tooth stump. The present study uses standardized dies of similar form and material to eliminate potential bias from preparation of individual teeth.The dies are milled from a composite resin material with a similar flexural strength (196 ± 10 MPa), E-modulus (10.7 ± 0.3 GPa) and Poisson's ratio (0.43 ± 0.03) to those of human dentin [11,12].

It should be noted that there are limitations in terms of clinical relevance in this study. Enamel as an antagonist represents regular clinical situations. However, it is accompanied by morphological and structural differences and complicates standardized wear testing [39]. Therefore, in this study, equally shaped and structured steatite antagonists were used, which are supposed to be suitable for wear tests [40,41]. In this context it should be mentioned that we didn't analyse the wear of the antagonist. Considering the impact of cementation, it must be emphasized that the crowns are cemented under optimal in vitro conditions without the influence of humidity and potential bleeding on the hydrophobic composite resin material. In addition, the documented differences between the cementation protocols should be interpreted with caution because of the optimized adhesive bonding between the composite resin material and SAC. Furthermore, tooth stumps are abraded by airborne particles and aluminium oxide before cementation with SAC. Therefore, we assume that the differences due to cementation under clinical circumstances might not be as pronounced as shown in this study.

5. Conclusion

Within the limitations of the present study, it can be concluded that under standardized laboratory conditions, different failure patterns for paediatric SSCs, ZCs and CCs were detected. The overall number of failures was found to be the lowest for the CCs and ZCs. The lowest 2D- and 3D-wear was evaluated for the ZCs. The cementation protocol was observed to have a significant impact on the use of SAC in composite and stainless crowns resulting in a significant lower wear. Based on the laboratory data for the experimental CC, it needs to be emphasized that clinical testing is required before widespread use.

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