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Screening for dysglycaemia in dental primary care practice settings: systematic review of the evidence

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Introduction: Increasing prevalence of diabetes and periodontal disease is prompting identification of additional clinical settings to identify patients at risk for dysglycaemia. A systematic review of studies that have examined feasibility of screening for at-risk patients in general dentistry settings at point-of-care (POC) was undertaken. Materials and methods: Systematic review of pragmatic clinical field trials piloting POC screening for dysglycaemia risk in dental settings was undertaken in studies whose primary objective was to explore rates of dysglycaemia among undiagnosed patient populations. Results: Among 17 dental clinical field trials identified, 10 were systematically reviewed. High rates of undiagnosed dysglycaemia were detected among dental patients by biological screening in all trials. Notably, substantive differences in study design and population characteristics were identified, precluding meta-analysis. Conclusion: Screening for dysglycaemia in dental offices effectively identified high-risk patients requiring triage for glycaemic management. Considerations for future clinical trial design were advanced to establish an evidence base amenable to meta-analysis of the relative translational value of glycaemic screening in dental settings.

Key words: Diabetes, dental office, screening, pragmatic clinical trials, oral health

INTRODUCTION

Overview

The primary objective of this study was to conduct a systematic review of clinical and field trials in the past 10 years that examined dysglycaemia screening at point-of-care (POC) in dental practices. The primary outcome was rate of dysglycaemia reported in the dental setting. Triage for medical evaluation and compliance were examined as secondary outcomes. Further, study design, glycaemic measure evaluated and instrumentation employed for glycaemic assessment were compared across studies.

Epidemiology of dysglycaemia and periodontitis

Epidemiological surveys have indicated that the rate of both type 2 diabetes (T2DM) and periodontal disease (PD) have achieved epidemic proportions in many countries worldwide. In the USA, 30.2 (9.4%)

and 84.1 (33.9%) million people are impacted by diabetes (diagnosed and undiagnosed) and prediabetes, respectively¹. Diabetes ranks seventh among the top 10 causes of mortality in the USA, as the principal driver of renal failure, amputations, and a clinically significant contributor to cardio/cerebrovascular diseases². Prevalence rates in the USA for diabetes/prediabetes in adults are projected to achieve 21-33% by 2050, contingent on mortality rate³. The USA ranked third in the world for the largest number of affected adults in 2014, with China (18.9%) and India (11%) ranking first and second, respectively⁴. Between 1980 and 2014, substantive increases in diabetes have been seen in countries with predominantly Black (Egypt), Asian (Indonesia, Pakistan, Japan) and Hispanic (Brazil, Mexico) populations, causing these countries to displace European populations previously ranked among the top 10 countries contributing to the global burden associated with diabetes. Shifts in prevalence are especially striking in Africa and South East Asia⁴. The projected direct annual cost globally for diabetes

is estimated at international (Intl)\$825 billion, with 60% of the cost of care borne by low-to-middle-income countries and the substantial cost burden directly impacting affected individuals as out-of-pocket expense⁵.

Recent surveillance data, refined assessment approaches and updated definitions of PD collectively point to an underestimation of historic disease prevalence of $\geq 30\%^{6,7}$. Nearly 65 million Americans (46%) of the population) are impacted by PD, with higher rates observed in Hispanic and Black populations⁷. In European countries, periodontitis prevalence of > 50% is projected, with 70-85% prevalence in populations > 60 years old8. While PD prevalence varies by country, substantive increases from 10-15% global prevalence in 1997 to rates of 58% and 77% in Southeast Asia and Western Pacific, respectively, in 2010 were noted, mainly in developing and low-tomiddle-income countries. Increased prevalence was attributed to socio-environmental shifts, aging populations, increased burden of diabetes, detrimental dietary changes promoting obesity, sedentary lifestyle, increased tobacco use, and limited access to oral healthcare⁹.

Oral consequences of two interactive chronic conditions

Diabetes progression is characterised by adverse microand macro-vascular processes driven by inflammatory processes. Diabetic progression contributes to co-morbid complications, including PD, which further contribute to a decline in quality of life, increase morbidity and mortality, and associated healthcare cost. PD simultaneously contributes to systemic inflammation.

A growing evidence base supports that underlying pathological processes common to PD and T2DM potentiate disease progression in a bidirectional manner. Bidirectional interaction is supported by a meta-analysis 10 (2014) and review 11 (2014) that reported reductions in haemoglobin A1C (HbA1C) measures following periodontal treatment. Moreover, sustained dysglycaemia in association with unresolved PD has been reported 10,12,13. Clinical consequences associated with dysglycaemia may include persistence of PD. Underlying infectious and inflammatory processes have been posited to contribute to the pathophysiology of both chronic conditions 14-16.

An estimated 25% and 90% of individuals with diabetes and prediabetes, respectively, remain unaware of their dysglycaemic status¹⁷. Such a high prevalence of undiagnosed dysglycaemia in dental settings imposes on dentists the often-unachievable task of controlling PD in affected patients, trapping them in a cycle of PD and unresolved dysglycaemia, and putting them at risk for oral and systemic disease

progression. Patients with undiagnosed or poorly managed diabetes and diabetes-associated complications seen in the dental setting may exhibit other oral pathology, including root caries, xerostomia (dry mouth), oral mucosal disease including increased candidiasis susceptibility, oral neurosensory disorders¹⁸, and implant complications¹⁹. A modest association between diabetes history and head and neck cancers has been reported^{20,21}, but remains controversial due to confounding factors such as environmental exposures (smoking).

Status of screening for dysglycaemia in the dental setting

Historical perspective

Importantly, both conditions represent potentially modifiable diseases responsive to available, evidencebased, relatively low-cost interventions if the at-risk population is identified, ideally in early stages of disease to stem progression and onset of co-morbid complications. In 2008, the US Preventive Services Task Force (USPSTF) recommendations were advanced for population-based screening for diabetes in asymptomatic patients diagnosed with, or under pharmacological management for, hypertension (defined as 135/ $80 \text{ mmHg})^{22}$, in internal medicine However, screening in dental settings was precluded pending achievement of evidence to support recommendation for screening as set forth by the 2013 National Screening Committee²⁴. A systematic review of clinical trials conducted to inform further updates to USPSTF recommendations concluded that screening contributed to delayed disease progression²⁵. Challenges in defining optimal screening criteria were captured by Bullard et al. 17, who compared 2008 USPSTF criteria with the expanded criteria set by the American Diabetes Association (ADA) screening guidelines that include: body mass index (BMI) > 25 kg/m²; physical inactivity; race/ethnicity; hypertension (> 140/90 mmHg); gestational diabetes or birth weight ≥ 4,000 g; self-reported prediabetes; or cardiovascular disease. Applying both sets of guidelines to National Health and Nutrition Survey Examination Survey (NHANES) data of ~5,800 participants (2007–2012) to project screening rates, considerable variability in sensitivity across ADA and USPSTF criteria for detection of dysglycaemia in individuals with no diabetes diagnosis (88.8% and 31%, respectively) was noted. The authors noted that incorporating additional risk assessment to mitigate over-screening introduced new challenges in the absence of optimised risk assessment tools to identify high-risk candidates, and emphasised the need to validate tool performance in a populationcentric manner. Authors identified urgency in defining

best practices surrounding screening in light of high rates of co-morbid complications already present in patients newly diagnosed with diabetes and prediabetes, and escalating disease prevalence¹⁷. USPSTF recommendations amended in 2015 included hypertension, age range 40–70 years, and obese status²³. ADA screening criteria updated in 2017 currently include: age ≥ 45 years; testing in patients who meet overweight or obesity criteria with one or more of the following risk factors: (i) first-degree relative with diabetes; (ii) high-risk ethnicity; (iii) women with history of gestational DM; (iv) cardiovascular disease history; (v) hypertension or pharmaceutically managed hypertension; (vi) high-density lipoprotein (HDL) cholesterol < 35 mg/dL and/or triglyceride > 250 mg/dL; (vii) polycystic ovary syndrome in women; and (viii) physical inactivity; other clinical conditions associated with insulin resistance²⁶.

Gestational birth weight of ≥ 9 pounds has been removed as a risk factor for T2DM²⁶. Guidelines still lack uniform standard definitions and include some overlap. USPSTF guidelines are generally applied for population-based screening, whereas ADA criteria recommendations are applied for clinical care and assessing risk factor profiles.

Screening for dysglycaemia in the dental setting: clinical and field trials

This review focused on systematic examination of the cumulative evidence emerging from clinical/field trials conducted to date that examined the feasibility of glycaemic screening at POC in the dental setting to define the prevalence of dysglycaemia in order to test alternative approaches to interdisciplinary care delivery for patients impacted by these conditions. The goal is to improve patient outcomes. Implications of the current evidence were reviewed.

MATERIALS AND METHODS

Systematic review approach

Systematic review was conducted on studies investigating the feasibility of conducting POC biological

glycaemic screening in clinical dental settings to detect undiagnosed dysglycaemia. Key word searches were conducted by study investigators and the institutional reference librarian, who has extensive experience in performing literature searches to support systematic reviews. No language exclusion was applied if English abstracts were available to assess eligibility for inclusion. *Table 1* summarises search strategies, terms, and databases or other resources queried. Additional relevant literature was identified by reviewing citations of relevant articles.

High-level screening inclusion criteria were:

- Articles published within the last 10 years whose aims included conduct of chair-side POC glycaemic evaluation in a clinical dental setting representing clinical trials, pilot studies or field reports
- Articles published within the last 10 years reporting rates of dysglycaemia detected in the dental setting among patients with no historical diabetes/prediabetes diagnoses or recent glycaemic evaluations.

A flow diagram adapted from Moher *et al.*²⁷ (*Figure 1*) illustrates the vetting process applied for identifying articles eligible for inclusion in systematic analyses.

RESULTS

Systematic review

Of 135 articles identified by the search strategy, 21 qualified for further screening for potential inclusion. Two studies were reviews, and were excluded based on publication type. While two relevant press releases were excluded, publications cited therein were considered for inclusion. Four of 21 articles²⁸⁻³¹ focused on dysglycaemia risk prediction modelling in the dental setting utilising prospectively-acquired, self-reported data or retrospective analyses of historical data in the absence of biological testing, and were excluded from review. However, the relative merits of risk modelling were discussed with comparisons to the gold standard of biological screening as undertaken in the systematically reviewed studies (Table S1). Seven studies 32-38 were excluded based on justifications presented in Table 2.

Table 1 Search strategy overview

Search terms Search targets

Prediabetic state* OR prediabet* OR dysglycem* AND Dental* or dentist*, AND Risk* OR assess* OR model* OR screen* OR algorithm* AND Risk assessment OR risk factors; Glucose* OR hemoglobin A1C* AND dental; Glucose screening test* AND dental office*: OR HbA1C screening test* AND dental office*

PubMed [National Center for Biotechnology Information (NCBI) at US National Library of Congress (NLM); www.opengrey.eu; (European multidisciplinary database of grey literature sources)]

Ten studies^{39–48}, presented in ascending chronological order, were ultimately reviewed systematically (see summary: Table S1). These trials were largely classifiable as Level II.1 evidence⁴⁹. Rates of dysglycaemia among patients achieving diabetic range reported across studies ranged between 1.3% and 14%, while rates of patients achieving prediabetic range varied from 19% to 90%. Only 50% of studies provided results of diagnostic assessment following triage to further assess the validity of screening results. The relative frequencies with which co-morbid or demographic variables were tracked across these studies is summarised in Table 3, and reveals variability in glycaemic parameters selected for screening trials, instrument used to conduct screening, dental variables tracked (e.g. some studies reported on dental measures used to define periodontal health status), population differences including ages of patients screened, sample size, ethnic and racial differences, and relative representation of disparity populations in the study cohort.

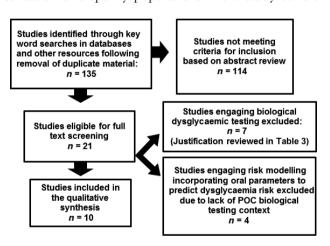


Figure 1. Literature search outcome summary.

Screening eligibility criteria applied in 60% of studies did not comply with current guidelines for screening eligibility (e.g. age). Further, variables tracked across populations ranged widely across studies (*Table S1*).

DISCUSSION

The evidence base continues to support escalating prevalence rates of DM and PD. These chronic health conditions are associated with high oral and systemic morbidity risk, poor quality of life and high cost of care, and constitute a growing global health concern. The need for early identification and intervention in stemming the tide of the diabetes epidemic has promoted population-based screening for dysglycaemia in the medical domain, especially in the primary care settings.

For patients meeting screening eligibility as defined by current guidelines, dental practices represent an additional primary care setting for dysglycaemia screening and appropriate triage to medical settings for diagnostic follow-up and management. Dental settings are especially opportune for identifying patients with no recent medical encounters and no primary care provider or medical home, who are less likely to be aware of their diabetic status.

This study undertook systematic review of outcomes of clinical trials examining glycaemic screening at POC in dental settings in order to characterise the strength and quality of the emergent evidence base targeting the evidence gap.

Qualitative systematic review findings

The main outcome variable in this study was rate of dysglycaemia defined in the dental setting applying

Table 2 Studies conducting biological glycaemic testing in dental setting excluded from systematic review and justification

Excluded study	Study objective and justification for exclusion						
1. Beikler <i>et al.</i> (2002) ³²	Study objective: compare HbA1C POC testing performed on blood obtained from gingival crevicular fluid and capillary fingerstick using glucose level self-monitoring device						
	Why excluded: study enrolled patients with known diabetic status including patients with DM dx						
2. Ojehanon and Akhiobare (2006) ³³	Study objective: screen oral health in patients with blood glucose > 126 mg/dL to determine PD status; periapical periodontitis was most frequent diagnosis						
	Why excluded: due to lack of POC blood test; study screened urine samples with dip stick and triaged to medical setting for further testing						
3. Nibali <i>et al.</i> (2007) ³⁴	Study objective: monitoring dysmetabolic status in dental patients with severe PD Why excluded: glycaemic measures were not made at POC						
	Screening was performed on urine and blood						
4. Barasch <i>et al.</i> (2013) ³⁵	Study objective: screening for dysglycaemia at POC in the dental setting Why excluded: due to inclusion of patients with DM dx and pre-DM dx						
5. Miller <i>et al.</i> (2014) ³⁶	Study objective: comparison of glycaemic level determination by a commercial laboratory to patient self-report Why excluded: glycaemic analyses were not conducted at POC in dental settings						
6. Srinivasa <i>et al.</i> (2015) ³⁷	Study objective: compare POC HbA1C levels in patients with or without PD						
7. Harase <i>et al.</i> (2015) ³⁸	Why excluded: study did not report on DM status of study patients Study objective: observe POC HbA1C levels among dental patients with PD stratified by PD severity Why excluded: only subjects with a DM dx were included						

Table 3 Reporting variability across studies included in systematic analysis in Table S1

Variable	Study citation number									
	48	47	46	45	44	43	42	41	40	39
Glycaemic measure										
HbA1C	\checkmark		\checkmark			\checkmark			\checkmark	\checkmark
FPG								\checkmark		
RPG							\checkmark			
Glucometer										
Self-monitoring glucometer		\checkmark	\checkmark				\checkmark	\checkmark		\checkmark
POC instrument	\checkmark					\checkmark			\checkmark	
Population variance in diabetes prevalence										
Racial		\checkmark	\checkmark			\checkmark			\checkmark	\checkmark
Ethnic		\checkmark	*			\checkmark			\checkmark	\checkmark
High-disparity population representation						\checkmark		\checkmark	\checkmark	\checkmark
Screened in compliance with guidelines for age										
Yes						\checkmark		\checkmark	\checkmark	
No	\checkmark		\checkmark							\checkmark
Periodontal assessment										
AAP/ADA ⁶⁶ criteria	\checkmark		\checkmark			\checkmark		\checkmark	\checkmark	
Clinical PD assessment criteria (Grades 1-4)				✓						
Partial mouth assessment				*						
Full mouth assessment	\checkmark		\checkmark	*		\checkmark		\checkmark		
Other definitions	\checkmark	\checkmark	\checkmark	\checkmark		\checkmark		\checkmark		\checkmark
Not defined or assessed			\checkmark		✓					
Variables reported										
Age		\checkmark	\checkmark	✓		\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
Sex		\checkmark	\checkmark	☑		\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
Race/ethnicity	✓		\checkmark	✓	✓	\checkmark			\checkmark	✓
BMI	☑	✓	✓	☑	_	✓	 ✓ 1	\checkmark	✓	☑
Waist circumference or % body fat	✓				✓			\checkmark		
Family history of diabetes			†	\checkmark		\checkmark	\checkmark	\checkmark	\checkmark	
Smoking	✓	☑		☑				✓		V
Hypertension	_	✓	✓	☑		✓		✓	\square	☑ ☑1
Cholesterol/hyperlipidaemia measures		✓				\checkmark		✓	\checkmark	
Other		\checkmark	\checkmark	✓			\checkmark	✓	✓	
Patient follow-up										
Patient triaged to medical setting			✓	☑					\checkmark	
Dysglycaemia validated in medical setting		⊠‡	*	☑	☑	✓			✓	
T2DM diagnosis in medical setting		☐ 1	*	☑	□ [7] ¹	☐ ☑1			☐ ☑¹	

BMI, body mass index; FPG, fasting plasma glucose; HbA1C, haemoglobin A1C; PD, periodontal disease; POC, point-of-care; RPG, random plasma glucose; T2DM, type 2 diabetes mellitus.

☑¹Based on one diagnostic evaluation or frequency of testing was not disclosed.

POC glycaemic screening. The prevalence of dysglycaemia in dental settings estimated by applying biological POC screening in undiagnosed patients across the 10 studies systematically reviewed ranged from 1.3% to 14%, and from 19% to 90% for prediabetes (Table S1). Rates reported likely reflected variability across studies surrounding factors including age, ethnicity, proportion of disparity populations across dental settings, screening devices used, and variability in definitions of dysglycaemia. Only a small subset of studies pursued clinical diagnostic laboratory testing as a follow-up to validate screening results, thus diagnosis of diabetes could not be examined as a study endpoint. Moreover, some studies equated positive screening results with 'diabetes diagnosis', without reporting whether diagnostic validation in the medical setting was performed.

Meta-analysis was precluded by substantial differences across studies, including population under study, glycaemic parameter evaluated for screening and POC methodology applied for glycaemic evaluation, process and documentation of longitudinal follow-up to screening test for purposes of validating diagnosis and extent of dysglycaemia, and definition of laboratory approaches to diagnostic determination. Collectively these studies raised important considerations in designing future studies investigating the relative clinical merits and cost-effectiveness of POC screening for dysglycaemia in a dental setting as presented below.

Considerations in screening measure selection

Notably, HbA1C and fasting plasma glucose (FPG) measurement for glycaemic screening are associated

^{*}Data collected but not reported.

[†]Data collected but only reported as a composite.

[‡]Subset tested.

with variability in performance across populations and capacity to identify true positive cases. For example, the definition of prevalence of prediabetes and undiagnosed diabetes in a nationally representative Canadian population sample (n = 3,494), applying both measures, reported higher estimates with HbA1C, especially in younger patients with lower BMI compared with FPG, which identified prediabetes and diabetes mainly in the older population subset⁵⁰. The accuracy of HbA1C for POC screening may be constrained due to clinical, demographic or racial/ethnic characteristics⁵¹, as demonstrated in the disparate outcomes obtained in studies done in a Chinese⁵² and African population⁵³. Thus, population characteristics should be weighed in selecting the glycaemic parameter and measurement approach. However, future meta-analyses may only be supportable across analogously-screened, similar populations.

Applying FPG for dysglycaemia screening holds practicable challenges in the dental setting. Importantly, statistical modelling of continuous glucose measures and HbA1C demonstrated comparable capacity of both measures for estimating glucose levels across time, validating the potential use of either measure ^{54,55} when appropriate in the population being screened. A meta-analysis concluded that while increased stringency in use of high-normal levels did not improve the capacity of HbA1C and FPG for identifying diabetic risk, both demonstrated good capacity for detecting undiagnosed diabetes ⁵⁶.

Considerations in POC screening instrument selection

Previous studies demonstrated considerable variability surrounding the accuracy of testing outcomes depending on whether POC instruments⁵⁷ or blood glucose self-monitoring (BGSM) devices were used^{58,59}. Device selection for screening trials is critical and should consider criteria issued by the US Food and Drug Administration (FDA)⁶⁰ and performance specifications⁶¹. Concerns with off-label use of BGSM devices in a clinical setting have also been raised, citing potential for patient risk in the absence of performance specifications⁶². Although planning trials with FDA-approved POC devices appears costly, cost-free placement option of POC devices is offered by some vendors⁵⁷.

Considerations for designing future clinical screening trials

Based on targets for study design improvements identified and summarised in *Table 3*, the following considerations are proposed when designing and reporting on future screening studies:

- Planning for effective patient triage and follow-up to support analysis of true false-positive and -negative rates of screening, informed by clinical determination of diagnostic status (i.e. diagnosis of diabetes based on two glycaemic measures performed by a CLIA-certified laboratory; a single positive test is sufficient for determining a pre-diabetes diagnosis)
- Applying screening in compliance with current medical guidelines
- Standardising risk factor assessment and reporting to include data on race, ethnicity and disparity status using appropriate surrogate indicators (e.g. insurance status)
- Standardising study designs surrounding inclusion/ exclusion criteria, POC instrumentation, and glycaemic measure informed by population characteristics
- Standardising reporting of oral/periodontal screening measures informed by outcomes reported by studies reviewed herein.

Notably, several studies systematically reviewed herein additionally employed risk modelling of clinical and oral health-related, environmental and demographic factors to identify variables with capacity to contribute to relative risk or dysglycaemia ^{39,40,43,46}, and/or predict relative risk for dysglycaemia compared with biological testing as the gold standard ^{40,43}. While some of these models appeared to show good sensitivity and specificity, relevance and portability to populations outside of the population in which they were developed remains to be tested. Such alternative approaches for identifying individuals at risk for dysglycaemia may merit further exploration.

Cost-effectiveness analyses overview

Cost-effectiveness of screening in the dental setting, even in the defined subset of patients currently recommended for glycaemic tracking, has been a concern. Recommendations for screening are presently preempted pending demonstration of a stronger evidence base. Recently, Neidell et al.⁶³ undertook simulation modelling to evaluate the cost-effectiveness of POC screening in a dental setting in dysglycaemic patients being managed by a weight reduction intervention. Investigators estimated the cost of one additional quality-adjusted life year (QALY) for both patients with pre-diabetes and diabetes engaging weight loss interventions over time and projected costs within or below \$50,000-60,000/QUALY, a range currently deemed cost-effective. Authors also projected that cost savings stemming from averted future healthcare cost associated with diabetes would further offset costs of screening and weight loss intervention⁶³. This model provides preliminary support that incorporation of

POC glycaemic screening into diabetes mellitus integrated care delivery models represents a viable interdisciplinary approach to early identification of high-risk patients requiring intervention. To further validate cost-effectiveness prospectively, de Graaf et al.⁶⁴ proposed an alternative approach that entails modelling cost per case detected by applying a stepwise screening approach that incorporates evaluation of three parameters: accuracy of the screening tool; cost of distribution and response rate; and incremental cost of each case detected associated with clinical follow-up to confirm diagnosis.

Summary

The removal of barriers inherent in currently-established diabetes care delivery paradigms defined across dental and medical domains 65 will require a new evidence base for demonstrating value, patient centricity and cost-effectiveness of alternative paradigms in care delivery, including integrated medical and dental care delivery models that effectively bridge these domains. Apropos to such models is the capacity to identify subpopulations at risk for dysglycaemia in the dental setting and triage them to medical care. Based on the high prevalence of dysglycaemia, especially prediabetes, among dental patients reported in studies included in this systematic review, the collective evidence supports the expansion of glycaemic screening to dental offices as an additional primary care setting for patients meeting screening criteria pending refinement of the approach. Studies demonstrated capacity to identify at-risk individuals with especially high rates of undiagnosed prediabetes identified. Future well-designed screening protocols integrated into DM-ICMs would support earlier detection and opportunity for inter-disciplinary intervention. However, the overall efficacy of screening and triage across medical-dental domains remains contingent on demonstrating referral efficacy, follow-up across medical-dental settings, and patient compliance.

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Conflict of interest

The authors have no conflict of interest to report.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Table S1. Overview of study parameters, approaches, outcomes and limitations of studies included in the systematic review (n = 10)

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