Early detection of non-diabetic hyperglycaemia and type 2 diabetes in dental practice settings.

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Synopsis

Type 2 diabetes (T2D) is a highly prevalent chronic, non-communicable disease (NCD). The high morbidity, mortality, societal and economic costs associated with T2D are well documented.

Periodontitis is also a highly prevalent NCD with a well-established independent association with T2D. Periodontitis can only be diagnosed by oral healthcare professionals and it is mandatory to screen patients for periodontitis.

This thesis, comprising three main themes, to evaluate dental settings as sites for early detection of non-diabetic hyperglycaemia (NDH) and T2D aimed to:

1) determine whether new cases of NDH/T2D could be identified in dental settings. The literature was systematically reviewed to assess whether different cohorts of the population access different healthcare settings (papers 1 and 2).
2) focus on stakeholder perception of utilising oral healthcare teams to identify NDH/T2D within dental settings. The literature was systematically reviewed and a survery conducted with key-stakeholders in the UK (papers 3 and 4).
3) explore whether current risk-assessment tools were appropriate for use in dental settings. The concordance of point of care devices was evaluated and a risk-assessment model and score was developed and validated (papers 5 and 6).

Key Findings

Undiagnosed cases of NDH/T2D can be identified in dental settings. Different population groups access different healthcare teams, providing a potential opportunity for oral care teams to assess those not tested elsewhere.

There is broad support from stakeholders for utilising oral care teams to risk-assess for NDH/T2D in dental settings.

A two-staged risk-assessment strategy utilising a questionnaire based risk-assessment for initial stratification followed by a point-of-care capilllary blood sample appears to offer the optimal approach to risk-assessment. A questionnaire utilising data routinely available to oral care teams performs at the same level as current medical questionnaires containing data dental teams would not routinely access.

Dedication

This thesis is dedicated to my brother, Timur Yonel. His pride and excitement when I told him I was joining the university to undertake a PhD was tangible. Unfortunately, he was not able to witness me achieving the NIHR / Diabetes UK, Doctoral Research Fellowship, nor the completion of this PhD. However, he was with me through this whole adventure. “Strength and Honour”.

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Critical Review

Introduction

The Burden of Chronic Non-Communicable diseases

Non-communicable diseases (NCDs) account for approximately 71% of deaths globally (1). Cardiovascular disease (CVD), cancers, respiratory diseases, and diabetes are the four most common NCDs and account for 80% of all premature NCD-related deaths (1).

NCDs are chronic in nature and can be attributed to genetic, environmental, physiological, and behavioural exposures. However, the World Health Organisation (WHO) attribute the dramatic rise in NCDs largely to modifiable (behavioural) risk factors, with the four major NCDs (CVD, cancers, respiratory diseases, and diabetes) causally linked to:

- tobacco use,
- sedentary lifestyles/ physical inactivity,
- harmful use of alcohol and
- poor diets (2).

These behavioural exposures in turn lead to metabolic risk factors including hypertension, which in 2015 had a global prevalence of 22% in adults ≥18years. Hyperglycaemia, which in 2014 had a global prevalence of 9% in adults. Obesity, which in 2016 had a global prevalence of 16%, and also hyperlipidaemia, which in 2008 had a global prevalence of 39% (1).

In the UK it was estimated that >80% of heart disease, stroke, and type 2 diabetes (T2D), and more than 33% of cancers could be prevented through eradicating modifiable risk factors (3). Furthermore in 2007, CVD alone cost the UK economy >£30 billion. Thus, the burden of NCDs is significant both in terms of health and economic costs.

Diabetes

Diabetes is a NCD which manifests in two predominant forms. Type 1 diabetes is characterised by the inability of the pancreas to produce insulin, this form of diabetes often presents in childhood and adolescence due to autoimmune destruction of the pancreatic β cells and is currently not preventable. T2D is characterised by insulin resistance, is more likely to develop in adults, and accounts for >90% of diabetes cases. There is strong evidence that T2D is preventable. This can be achieved through modification of behavioural risk factors, and control of metabolic and physiological risk factors (4-7).

The global prevalence of diabetes in 2021 in adults >20 and <80 years of age was estimated to be 10.5% (536.6 million people), which is predicted to rise to 12.2% (783.2 million) by 2045 (8).

Morbidity associated with diabetes is significant, 33% of individuals presented with microvascular disease at the time of diagnosis, with 530 myocardial infarctions and 175 amputations every week attributed to diabetes (9). More than 10,300 people in the UK had diabetic nephropathy in 2016 (10). Diabetes is also the leading cause of preventable sight loss in the UK (9, 11) and was the 9th leading cause of death, directly contributing to 1.5million deaths in 2019 (12).

Global diabetes-related health expenditures were estimated at $966 billion in 2021 and are projected to reach $1,054 billion by 2045. (8)

Diabetes is preceded by non-diabetic hyperglycaemia (NDH). According to Public Health England, in 2015 the prevalence of NDH in England was 10.7% (13). Onset of diabetes can be delayed or prevented in people with NDH through the instigation of prevention programmes.

NDH is asymptomatic, as is T2D in its early stages, which frequently results in a diagnosis being delayed until the patient experiences symptoms. The UK National Screening Committee (NSC) do not currently advocate population-based screening for NDH/T2D. However, there is significant evidence to support the importance of early detection of NDH /T2D (7, 14).

NDH is reversible, early identification and instigation of cost-effective prevention programmes can enable patients to delay or prevent the onset of T2D and the associated complications (15-17). Similarly, targeted risk-based detection of T2D can result in earlier identification and management. Unfortunately, evidence suggests that onset of disease often occurs 4-7 years prior to clinical diagnosis (16), and that at the time of T2D diagnosis up to 50% of patients may demonstrate pre-clinical or clinical manifestations of microvascular and/or macrovascular disease (18). Hence there is a drive to identify NDH / T2D earlier to reduce the risk of such complications (19).

Periodontitis

According to the NCD alliance, oral diseases are the most common globally, affecting almost half the world's population. They include dental caries, and periodontal diseases (20).

Periodontitis is a chronic non-communicable disease, characterised by inflammation of the gingival tissues and destruction of the underlying support structures. Periodontitis is initiated by a pathogenic biofilm which accumulates on the tooth surface, at or below the gingival margin (21). This results in an acute inflammatory response and results in microbial dysbiosis, which if not treated can become chronic and is characterised by a dysregulation of the immune-inflammatory response that causes collateral tissue damage and destruction of the alveolar bone supporting the teeth (22).

Periodontitis is highly prevalent with severe disease being the 6th most prevalent condiiton worldwide (23, 24). Evidence suggests that up to 50% of the world's population experience periodontitis, with approximately 11% of the global population suffering from severe disease (25).

Periodontitis is independently associated with significant morbidity and is the major causes of loss of multiple teeth within individuals. This can in turn lead to edentulism, masticatory dysfuntion, nutritional compromise and associated psycho-social impacts. The societal and economic burden of periodontitis is high, with periodontitis accounting for 3.5-million years lived with disability, US$ 54-billion per year in lost

productivity, and being a major contributor to the US$ 442-billion overall cost for oral diseases per annum (24).

Periodontitis and Diabetes Associations

A bi-directional association between periodontitis and diabetes was reported in 2001 by Taylor and colleagues (26, 27), who reported that diabetes was associated with an increased ocurrance and progression of periodontitis. Periodontitis was also associated with poorer glycaemic control in those with diabetes.

The mechanistic links between periodontitis and diabetes have been attributed to disseminating oral infection, disseminating oral inflammation and immunological memory (28, 29). Periodontal inflammation contributes to the systemic inflammatory burden, secondary to periodontal bacteraemia and triggers acute-phase and oxidative stress pathways.

Elevated levels of pro-inflammatory mediators ([interleukin 1-β, tumour necrosis factor-α, interleukin-6, receptor activator of nuclear factor-kappa-B ligand) within the gingival tissues of patients with poorly controlled diabetes may account for the increased periodontal destruction observed (30). Advanced Glycation End products (AGE)–Receptor for AGE (RAGE) interactions and oxidative-stress-mediated pathways also provide plausible mechanistic links in the diabetes to periodontitis direction (28).

Epidemiological association studies have demonstrated that in patients with and without diabetes, periodontitis is associated with worsening diabetes control and

elevated HbA1c (31) (32). Furthermore, severe periodontitis is also associated with an increase in diabetes complications (33, 34) and a positive impact on diabetes outcomes when periodontitis is treated effectively and to target. A recent study with a 12-month follow-up demonstrated a reduction in HbA1c of 0.6% in patients receiving intensive periodontal therapy (35, 36).

The role of the oral healthcare team

The “making every contact count” (MECC) behaviour change strategy is recommended by the National Health Service (NHS) and partner organisations. The principle theory behind the MECC agenda is to utilise the millions of day-to-day contacts that organisations and people have, to encourage behaviour change. The aim is to garner a positive effect on the health and wellbeing of individuals, communities and populations. In line with this approach, in the United Kingdom (UK), oral-health professionals deliver advice on a healthy diet, smoking cessation and advice regarding safe alcohol consumption, all of which are shared risk factors for several chronic NCDs (37).

In 2022, the National Institute of Health and Care Excellence (NICE) updated its guidelines to include periodontitis as a risk factor of diabetes and to acknowledge that healthcare providers should advise patients with diabetes about their increased risk of periodontitis. The NICE guidance also highlighted that patients with diabetes should have regular oral health reviews. NICE have also published guidance recommending that dental teams, in addition to other healthcare providers in the community, should use validated risk assessment tools to identify patients who may be at risk of or unknowingly have type 2 diabetes (38).

A UK Commissioning Standard was published in 2019 outlining the need for closer integrated working between primary dental and medical care teams (39). It specified that primary care physicians should inform patients with diabetes of their increased risk of periodontitis and recommend appropriate follow-up with oral-health professionals.

Gaps in Current State of Knowledge

The health and economic burden incurred by T2D and periodontitis is significant. Importantly, when identified early and with appropriate interventions, both conditions can be prevented or their onset can be delayed. This has potential to provide both health and economic benefits. Thus, there is scope for exploring pathways that emphasise early identification, prevention and collaborative working between stakeholders managing patients with both conditions. There is also a need to determine stakeholder perceptions of utilising a more integrated approach to managing NCDs and closer collaborative care-pathways in primary care.

Both periodontitis and T2D have shared risk-factors, and the epidemiological association between the conditions is strong. Evidence suggests a bi-directional relationship, where successful treatment of one condition, improves health outcomes in the other.

In the past five years, guidelines and policies advocating closer collaborative working between primary care medicine and dentistry have emerged (29, 36, 39). However, it is still unclear; what the role of the oral healthcare team would be within such a

pathway, whether stakeholder perception regarding such pathways would be postive, whether early case-detection for diabetes within the dental setting is feasible, and if so what strategy should be employed for risk-targetted early detection.

Aims of the research

- 1. Determine the potential for early case detection / risk assessment for T2D in non-medical settings (publication 1 + 2).
- 2. Analyse stakeholder views on early case detection / risk assessment for T2D / NDH in non-medical settings (publication 2 + 3).
- 3. Assess the feasibility of and models for early case detection of T2D / NDH in dental settings (publication 4).
- 4. Determine the utility, performance, and viability of point-of-care methods for HbA1C measurement (publication 5).

  5. Develop and validate a prediction model for NDH / T2D, specifically for use in dental settings (publication 6).

Research Questions

1. What is the potential for early case detection of NDH/T2D in the dental setting and what are the potential rates of identification of new cases of disease? (Publication 1 + 2)
2. What strategies have been employed to identify cases of NDH/T2D within the dental setting? (Publication 1 + 2)
3. What are stakeholders' views and perceptions relating to dental teams' risk assessing for type 2 diabetes (Publication 2 + 3)
4. Are there differences in the attendance patterns of patients to different healthcare providers? (Publication 3)
5. Can dental teams utilise risk assessment methods for type 2 diabetes in the UK, and can new cases of previously undiagnosed disease be detected? (Publication 4)
6. Do point of care testing devices demonstrate good concordance with reference standard testing? Are they appropriate for use in the dental setting to identify patients who may be at risk? (Publication 5)
7. Can a model be developed and validated using routinely available data for use in the dental setting that has a performance broadly comparable with existing tools validated for use outside the dental setting? (Publication 6)

Publications

1. Use of dental practices for the identification of adults with undiagnosed type 2 diabetes mellitus or non-diabetic hyperglycaemia: a systematic review (40)
2. The Role of the Oral Healthcare Team in Identification of Type 2 Diabetes Mellitus: A Systematic Review (41)
3. Patients' attendance patterns to different healthcare settings and perceptions of stakeholders regarding screening for chronic, non-communicable diseases in high street dental practices and community pharmacy: a cross-sectional study (42)
4. Patient acceptability of targeted risk-based detection of non-communicable diseases in a dental and pharmacy setting. (43)
5. Concordance of three point of care testing devices with clinical chemistry laboratory standard assays and patient-reported outcomes of blood sampling methods. (44)
6. The development and external validation of a diagnostic, multi-variable prediction model to identify non-diabetic hyperglycaemia and type 2 diabetes in high-risk patients attending the dental clinic: The Diabetes Risk Assessment in Dentistry Score. (45)

Critical Review of Manuscripts

Manuscript 1 of 6

Yonel Z, Cerullo E, Kröger AT, Gray LJ. Use of dental practices for the identification of adults with undiagnosed type 2 diabetes mellitus or non-diabetic hyperglycaemia: a systematic review. Diabet Med. 2020 Sep;37(9):1443-1453. doi: 10.1111/dme.14324. Epub 2020 Jun 14. PMID: 32426909.

Appendix 1: Prior published work that supports manuscript 1:

I. **Yonel Z**, Sharma P, Gray LJ. Use of Dental Practices for the Identification of Adults with Undiagnosed Type 2 Diabetes Mellitus or Nondiabetic Hyperglycaemia: Protocol for a Systematic Review. JMIR Res Protoc. 2018 Nov 19;7(11):e11843. doi: 10.2196/11843. PMID: 30455173; PMCID: PMC6277823. (46)

II. **Yonel Z**, Sharma P. The Role of the Dental Team in the Prevention of Systemic Disease: the Importance of Considering Oral Health As Part of Overall Health. Prim Dent J. 2017 Aug 31;6(3):24-27. doi: 10.1308/205016817821930980. PMID: 30188311. (47)

“Use of dental practices for the identification of adults with undiagnosed type 2 diabetes mellitus or non-diabetic hyperglycaemia: a systematic review” aimed to systematically review the literature to ascertain whether primary care dental practices could be used to identify new cases of NDH/T2D in adults. The review had a particular focus on strategies for identification of NDH/T2D within the practice and identification rates within the studies. Thus, answering research questions one and two.

A pre-specified protocol was developed, and the reporting was in accordance with “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) guidelines.

The systematic review was registered in PROSPERO (48), and the study protocol outlining the detailed methodology was published in the peer-reviewed literature for reference and critique by the scientific community (46). Details of the search strategy and methods are available within the manuscript (40).

The electronic search yielded 1,870 manuscripts with a further 16 manuscripts identified through other methods (see manuscript). De-duplication and screening of titles and abstracts resulted in 115 articles eligible for full-text review. Following this, a further 106 articles were excluded, leaving 9 eligible studies meeting criteria for inclusion in this systematic review (40). All 9 studies were observational studies, 3 were considered to have a low risk of bias, while one had a high risk of bias associated with the methodology. There was one UK based study, two based in Europe, five in the United States of America (USA) and one study was conducted in Asia. The median recruitment rate into the studies was 88% with a range of 41% to

99% recruitment. The main barriers to uptake were cost, avoidance of duplicate testing and patient wishes (40).

A major strength of this review was a clear and transparent protocol published a-priori to guide delivery of the research and ensure a robust and transparent methodology. The review highlighted several sources of heterogeneity in the methodologies of the included studies, rendering meta-analysis inappropriate.

The review answered the first research question, regarding the potential to identify new cases of NDH/T2D and potential identification rates. Dental teams can conduct targeted risk-based detection in primary care dental settings to good effect, and new cases of previously undiagnosed disease can be identified. Only 4 studies reported identification rates of NDH, and this ranged from 23-45% of their patients. All but one study reported the identification rate of T2D, and this ranged from 1.7 – 24%. The variability in the detection rate of NDH/ T2D is likely due to the variation in risk-assessment methods used.

This study also answered the second research question, which related to the strategies employed to identify new cases of NDH/T2D. The most frequently used method across the 9 studies was a two-staged process. This involved a questionnaire to determine risk, followed by a chair-side blood collection method. Four of the nine studies used point-of-care (POCT) random blood glucose testing, one study referred patients designated high-risk by questionnaire to a diabetologist for venous HbA1c and oral glucose tolerance testing, the remaining studies used point of care glycated haemoglobin (HbA1c) of capillary blood samples.

Thus, this manuscript successfully addressed research questions 1 and 2 demonstrating that dental practices can be utilised to identify people with undiagnosed NDH/T2D and provided a range of identification rates for both NDH/T2D. The heterogeneity of the data is likely due to the methodological differences in risk-assessing patients and the different risk-assessment strategies used in the included studies.

Manuscript 2 of 6

Yonel, Z., Batt, J., Jane, R., Cerullo, E., Gray, L.J., Dietrich, T., Chapple, I., 2020. The Role of the Oral Healthcare Team in Identification of Type 2 Diabetes Mellitus: A Systematic Review. Current Oral Health Reports 7, 87–97. doi:10.1007/s40496-020-00250-w

"The Role of the Oral Healthcare Team in Identification of Type 2 Diabetes Mellitus: A Systematic Review", aimed to identify stakeholder perceptions in addition to the barriers and facilitators of utilising dental teams to risk assess for NDH/T2D, thus addressing research question three.

A pre-specified protocol was developed, and the reporting was in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines.

Electronic search yielded 1,572 articles, a further 29 were identified through other sources. Following de-duplication and screening of titles and abstracts, 88 articles were deemed eligible for full text review. Fifty-two articles met our study inclusion criteria and of these; 11 were focused primarily on stakeholder opinion, 28 primarily focused on risk assessment processes, and the remaining studies had multiple elements including risk assessment and recording of stakeholder opinions.

All studies were assessed for risk of bias by calibrated assessors. Most articles were deemed to be of good quality, demonstrating a low risk of bias (n = 18). A further 17 articles showed moderate risk of bias and one article was deemed to have a high risk of bias.

Where studies sought stakeholder perceptions; 1 study sought the opinions of dental students, 1 the opinions of “authorities and organisations”, 1 physicians’ opinions, 1 dental hygienists’ opinions, 3 sought the opinions of dentists and 5 sought patient opinions. Across all stakeholders there was strong support for utilising the oral healthcare team to risk assess for NDH/T2D in the dental setting.

This review demonstrated the principal barriers to utilising the oral healthcare team to risk-assess for NDH/T2D were time, training, staff support and patient willingness to undergo the risk-assessment.

Strengths of the present study are the pre-defined study protocol and the robust methodological approach to conducting the review, including calibrating assessors prior to data-extraction and risk of bias assessment.

There were limitations to the review, due to heterogeneity of data a meta-analysis could not be performed. There was variability in the risk assessment-method employed to identify those with NDH/T2D. Whilst this makes direct comparison challenging, it does reflect the different settings and the different healthcare environments within which the risk-assessments were carried out, and despite the differences the sentiments of stakeholders were broadly similar.

A further important barrier highlighted by this review was the poor rate of onward follow-up by patients for formal diagnosis and management if they were identified as being at risk of NDH/T2D. A study by Bould and colleagues found that patients were more likely to follow-up with their general medical practitioner (GP) if they had received a finger-prick test. Their study supported a two-stage risk assessment process as patients had a 3.22 increased odds of contacting their GP if they had both a questionnaire and finger-prick test, rather than questionnaire alone (49).

Thus, this manuscript successfully addressed research question 3, demonstrating broad support across stakeholders regardless of healthcare system for utilising the oral healthcare team to risk-assess tor NDH/T2D.

Manuscript 3 of 6

Yonel Z, Sharma P, Yahyouche A, Jalal Z, Dietrich T, Chapple IL. Patients' attendance patterns to different healthcare settings and perceptions of stakeholders regarding screening for chronic, non-communicable diseases in high street dental practices and community pharmacy: a cross-sectional study. BMJ Open. 2018 Nov 3;8(11): e024503. Doi: 10.1136/bmjopen-2018-024503. PMID: 30391921; PMCID: PMC6231598.

"Patients' attendance patterns to different healthcare settings and perceptions of stakeholders regarding screening for chronic, non-communicable diseases in high street dental practices and community pharmacies: a cross-sectional study" aimed to answer research questions 3 and 4. These related to stakeholder perception and differences in attendance patterns to healthcare providers.

To gauge stakeholder perception, surveys were completed by healthcare professionals, patients attending dental and pharmacy settings, and members of the public. In total 2,919 surveys were completed by patients (n=1548) and members of the public (n=1371), with a further 222 surveys completed by primary care physicians, primary care dentists and community pharmacists.

The key finding from this manuscript was that public and patient opinions strongly supported utilising dental teams to risk assess for T2D. Seventy-four percent of the

public were in favour of screening for medical conditions in the dental setting. The conditions that had highest support were T2D followed by hypertension.

Regarding attendance patterns, approximately 70% of the public reported being registered with a dentist and of those, 75% stated that they had seen a dentist within the last 6-months for a routine check-up, this rose to over 95% seeing their dentist within 12months.

Only 29% of the public reported seeing their GP within the last 12 months for a routine check-up. Furthermore, of patients who were seen in dental practices, only 28% reported having any contact with their GP in the previous 12-months, with 7% reporting no GP contact in the last 60-months.

The study demonstrates that different members of the UK population have contact with different healthcare professionals, with a proportion of the population being more likely to see their oral healthcare team more regularly than other healthcare professionals. This may provide an opportunity for provision of preventative advice and for early targeted-risk based detection of associated co-morbidities.

The major strength of the study was the large sample size. It is the largest UK study seeking the opinions of stakeholders regarding risk-assessments for general health conditions in dental settings. A further strength is that it supports the findings of other studies, such as those reported in manuscript 2, which demonstrate broad support amongst stakeholders for utilising the dental workforce for risk-assessment in diabetes (50-55). Furthermore, this study corroborated data from the United States

that suggests there are differences in attendance patterns to different healthcare professionals (56).

However, there were also limitations to the study. The sample, whilst large, was not representative of national demographics. Members of the public were approached in a public setting (train station and market), and they were asked if they were willing to participate in the study. This limits randomisation as there are likely to be biases related to those who stopped and agreed to participate, limiting the generalisability of results. There are also limitations to face-to-face surveys whereby participants may feel under pressure to report findings they believe the researcher wishes to hear.

This manuscript successfully addressed research questions 3 & 4. The study demonstrated strong stakeholder support for targeted risk-based detection, outside of traditional medical settings. It also highlighted that, given the different attendance patterns to different healthcare settings, the potential to capture patients for targeted risk-guided detection who may not have been tested elsewhere. The study demonstrated that patients may see their GP regularly, but this is usually when they are symptomatic or for management of a particular concern rather than for preventative care or risk-assessments. Conversely, most patients routinely saw their dentists twice per year for a check-up, consistent with the preventative care model within the dental setting.

Manuscript 4 of 6

Yonel Z, Yahyouche A, Jalal Z, James A, Dietrich T, Chapple ILC. Patient acceptability of targeted risk-based detection of non-communicable diseases in a dental and pharmacy setting. BMC Public Health. 2020 Oct 20;20(1):1576. doi: 10.1186/s12889-020-09649-7. Erratum in: BMC Public Health. 2021 Feb 11;21(1):337. PMID: 33081745; PMCID: PMC7576866.

"Patient acceptability of targeted risk-based detection of non-communicable diseases in a dental and pharmacy setting" aimed to satisfy research question 5. This related to dental teams utilising risk assessment methods for NDH /T2D detection in the UK, and whether new cases of previously undiagnosed disease could be detected?

This was an exploratory study aimed at understanding the barriers to undertaking larger scale research for identification of NCDs in dental and pharmacy settings. The study also aimed to identify whether there was added benefit to using a point-of-care (POCT) device in addition to a risk-assessment questionnaire for NDH/T2D detection.

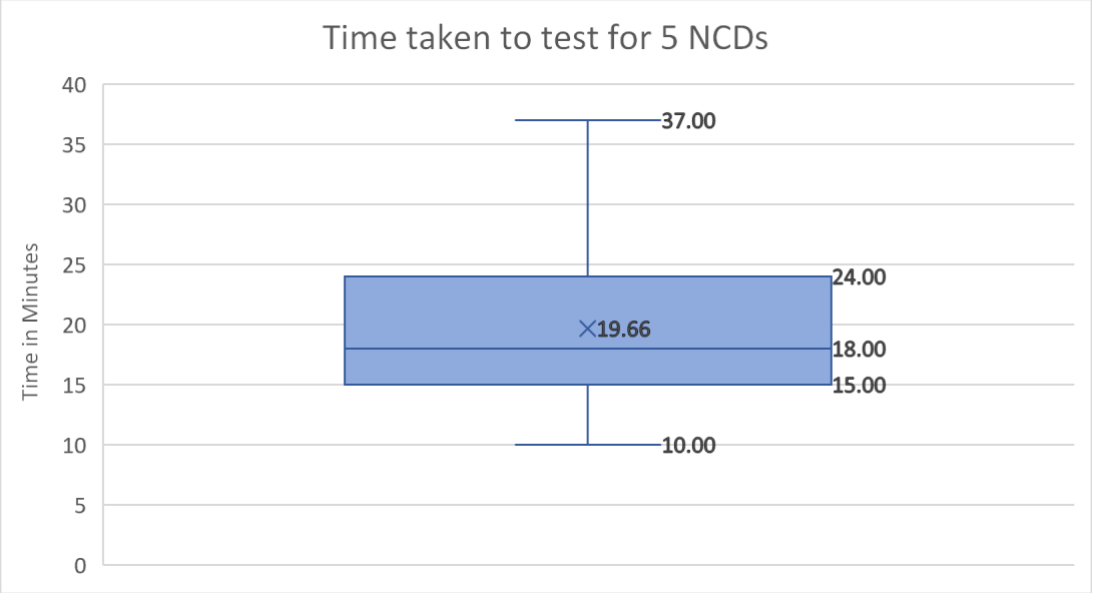
One dental practice and one community pharmacy setting in the West-Midlands were used to each recruit 50 consecutive patients. These practices were selected from known local networks. This therefore confers a degree of bias as the practices were not selected at random and were already "research ready" having participated in prior research and already undergone research training. Thus, these practices are unlikely to truly represent typical practices across the country.

The study involved research participants undertaking validated questionnaires to identify their risk of NDH/T2D and chronic obstructive pulmonary disease (COPD). Patients all had their blood pressure, pulse, and atrial fibrillation assessed. In addition to POCT for estimated glomerular filtration rate (eGFR), NDH/T2D and Vitamin D levels recorded.

A limitation of this study was that no formal sample size calculation was undertaken. Fifty participants in each site were deemed sufficient to enable identification of practical challenges which may hinder future studies. A further significant limitation is the lack of diversity of patients ethnicity across both study sites. All but one participant self-identified as “white/Caucasian”

Time was reported as the major barrier preventing recruitment. Time taken to test for all five conditions [T2D, COPD, hypertension/AF, Chronic Kidney disease (CKD), Vitamin D deficiency] was also a potential barrier (Figure 1). It is worth noting that as the researchers became more experienced the time taken to test reduced, with the longer assessment times coming earlier in the study.

Figure 1: Time in minutes to test for 5 NCDs in a general dental practice and community pharmacy setting.



A strength of this study was determining the recruitment rate, approximately 60% in each setting and a time of 8 days needed to recruit 50 participants in the dental setting. This enabled calculation of approximate time needed to recruit for future, more definitive studies.

A further strength of the study was understanding the benefits of utilising a two-phased risk-assessment process (Table 1).

Table 1: Proportion of participants deemed to be in need of referral to General Practitioner (GP) based on Leicester Risk assessment (LRA) questionnaire for T2D with their respective POCT HbA1C ranges.

	POCT (HbA1c ≥48mmol/ mol or ≥6.5%)	POCT (≥ 42mmol/ mol & <48mmol/mol or ≥6.0 & ≤6.4%)	POCT Negative (HbA1c <42mmol/mol or 6.0%)

	Diabetes range	NDH Range	Normo-glycaemia range
Questionnaire Positive dental setting (n=21)	2	7	12
Questionnaire Positive Pharmacy setting (n=13)	4	7	2

Table 1 highlights that in the dental setting almost half of those without a known diabetes diagnosis (21/45) were highlighted as needing onward referral to primary medical care by the LRA questionnaire. When the POCT was used, of the 21 that would have been referred if the LRA questionnaire had been utilised alone, 12 participants were found to be normoglycaemic. Thus, when a two-stage process of NDH/T2 detection is used the number of referrals to primary care physicians are reduced by more than half. Thus, utilising a two-staged process avoids population-based screening, which is not currently advocated by the National Screening Committee (NSC) in the UK, by targeting the more costly POCT to those most at risk. The POCT also mitigates for the reduced specificity of the screening questionnaire and thus limits the number of unwarranted referrals to a primary care medical service already working beyond capacity.

Whilst not powered to detect disease, in this small sample within the dental setting 9 out of the 45 participants recruited without a diagnosis of diabetes were considered

high-risk based upon two types of risk-assessment method, questionnaire and POCT HbA1c ≥42mol/mol (≥6.0%). Given such a small sample, those results must be interpreted with caution. However, the study does provide evidence to support further research into detection rates within primary care dental settings.

Importantly, the study also demonstrated that although questionnaires are useful to identify patients who may be at risk of T2D, the specificity of such questionnaires is limited, thus there is an argument for introducing a second step to the risk-assessment process prior to onward referral.

This manuscript successfully addressed research question 5, “Can dental teams utilise risk assessment methods for type 2 diabetes in the UK, and can new cases of previously undiagnosed disease be detected?” The study determined that risk-assessment questionnaires can be used to good effect, however, to streamline the process and mitigate for the sub-optimal specificity of risk-assessment questionnaires, a follow-up POCT within the dental setting appears beneficial.

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Yonel Z, Kuningas K, Sharma P, Dutton M, Jalal Z, Cockwell P, Webber J, Narendran P, Dietrich T, Chapple ILC. Concordance of three point of care testing devices with clinical chemistry laboratory standard assays and patient-reported outcomes of blood sampling methods. BMC Med Inform Decis Mak. 2022 Sep 22;22(1):248. doi: 10.1186/s12911-022-01999-z. PMID: 36138408; PMCID: PMC9493167.

"Concordance of three point of care testing devices with clinical chemistry laboratory standard assays and patient-reported outcomes of blood sampling methods" aimed to satisfy research question 6 relating to whether the performance of POCT devices is acceptable for risk-assessing for NDH/T2D.

As part of this study, 56 participants had a POCT, and a venous HbA1c blood sample collected within 15 minutes of each other. Participants also completed a visual analogue scale (1-100mm) at the time of each procedure and approximately 10 minutes after to understand the perceived pain associated with each test.

A strength of the study was the use of patients with HbA1c levels across the whole calibration line. This was achieved through use of healthy controls from the Birmingham Dental Hospital as well as patients attending outpatient clinics at the Queen Elizabeth Hospital, Birmingham.

The performance of the specific POCT device used was deemed acceptable for targeted risk-based detection of NDH/TDM. The Bland-Altman plot demonstrated that 53/56 (95%) results were within two standard deviations of the mean difference between the methods, indicating the two methods could be employed interchangeably and therefore good concordance of the POCT with the laboratory reference standard. Furthermore, the POCT device had a sensitivity of 87.5% (95% CI 67.6: 97.3) and specificity of 84.4% (95% CI 67.2: 94.7) suggesting acceptable performance of the device.

In the UK there is still controversy surrounding the use of POCT devices. This is largely due to the number of devices available on the market with little standardisation of performance across devices. Much of the healthcare community are still reluctant to advocate use of POCT for diagnosis despite many devices showing good levels of accuracy and concordance with reference standards.

For the purposes of this body of work, the dental team would not be using POCT to diagnose T2D. Rather, oral healthcare teams would highlight to physicians those patients who may benefit from further investigation. In that sense, given the performance of the devices in this study, they are clearly fit for purpose.

In the UK, the Diabetes Prevention Programme (DPP), initiated by Public Health England, NHS England, and Diabetes UK, represents a lifestyle change programme that patients at high-risk of diabetes (NDH) can be referred to. It is a 9-month long evidence-based programme that helps patients reduce their risk of T2D. Currently

the referral routes to the DPP "…vary according to local case finding pathways. Three primary mechanisms for referral are:

1. Those who have already been identified as having an appropriately elevated risk level (HbA1c or Fasting Plasma Glucose (FPG)) in the past and who have been included on a register of patients with high HbA1c or FPG;
2. The NHS Health Check programme, which is currently available for individuals between 40 and 74 years of age. NHS Health Checks includes a diabetes filter, those identified to be at high risk through stage 1 of the filter are offered a blood test to confirm risk; and
3. Those who are identified with non-diabetic hyperglycaemia through opportunistic assessment as part of routine clinical care…" (14)

However, discussion with the DPP revealed that at present they do not accept referrals based on POCT methods and HbA1c levels, nor from dental care teams.

Thus manuscript 5 successfully addressed research question 6. The POCT devices evaluated in this manuscript did demonstrate good concordance and performance when compared to laboratory reference standards. Whilst currently POCT results are not acceptable for referral into DPP, POCT devices require little space, are simple and quick to use, provide immediate results and overcome the technical skills and laboratory access required for venous blood HbA1C assay. Thus, making them ideal for use in dental and other community-based settings.

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Yonel Z, Kocher T, Chapple ILC, Dietrich T, Völzke H, Nauck M, Collins G, Gray LJ, Holtfreter B. Development and External Validation of a Multivariable Prediction Model to Identify Nondiabetic Hyperglycaemia and Undiagnosed Type 2 Diabetes: Diabetes Risk Assessment in Dentistry Score (DDS). J Dent Res. 2022 Oct 17:220345221129807. doi: 10.1177/00220345221129807.

"Development and External Validation of a Multivariable Prediction Model to Identify Non-diabetic Hyperglycaemia and Undiagnosed Type 2 Diabetes: Diabetes Risk Assessment in Dentistry Score (DDS)", aimed to satisfy research question 7.

One strength of this study was the robust preliminary phase to this work-package. A pre-specified statistical analysis plan was developed *a-priori*, specifying the methods to be used in the development and validation of the algorithm and point-score system. Existing literature was searched to identify potential covariates for use in the model. This allowed transparent and clear reporting and justification of method selection throughout the development and validation of the model and score. It also allowed an estimation of the sample size to be made as the predictor parameters were known at the start of the study.

Sample size calculation for diagnostic prediction models with binary outcomes has been discussed in detail. The methods proposed by Riley et al (57, 58) were used to determine whether the eligible sample was sufficient for model development. Forty-

one predictor parameters were assumed, including 13 co-variates frequently included in diabetes models (59), with the addition of dental variables based on existing literature and *a priori* knowledge of, and provision for relevant interaction terms. The prevalence of undiagnosed NDH/T2D was 11.4% in the SHIP-TREND-0 population. As an appropriate value for R^2 was not clear within the existing literature, 15% of the MaxR^2 (0.51) was used, giving an R^2 value of 0.0765. The minimum sample size requirement was a sample of 4,616 with 462 events (57). SHIP-TREND-0 (development dataset) has an eligible sample of 3,339 with 329 events.

There was less certainty around number of events and sample size required when validating multivariable prediction models (60, 61). Evidence initially suggested data with a minimum of 100 events, or ideally >250 events were required (62). The external validation data satisfied that requirement with 403 events.

Subsequent to completion of our study, Riley et al published a manuscript providing new guidance on the sample size requirements for validation studies (63). Having applied this newly described method, the required sample size (events) to validate our model is as follows for: observed by expected outcome (O/E) = 1497.86 (16.48), calibration slope = 9979.10 (109.77), C-statistic 9531 (104.84). Thus, a sample of 10,000 with approximately 110 events would be required to validate the shrinkage-adjusted model developed in SHIP-Trend-0. The validation set used for our study satisfied the number of events, but the overall sample was too small.

One of the major strengths of this study is that it was externally validated on a second independent dataset, derived from a representative population-based cohort study from the same region of Northeast Germany. A major criticism of diagnostic/prognostic research is that many development studies are undertaken, however few newly developed models are externally validated or trialled within implementation studies. A review article by Talakey et al 2021, found 10 published studies that used periodontal measures within a risk-detection model for T2D, of the 10 studies 8 were development and only 2 were validation studies. The authors concluded more robust external validation studies were required (64). Thus, external validation of the model and score is a strength of this study.

The handling of missing data was also pre-specified within the statistical analysis plan. To account for potential biases associated with missing data, multiple imputation was used. All candidate predictors plus the outcome variable were imputed (65). Twenty imputations were initially used (66, 67). The Monte Carlo error (MCE) was assessed to ensure that:

- MCE of a coefficient ≤ 10% of its standard error.
- MCE of a coefficients t-statistic ≤ 0.1.
- MCE of a coefficients p value ≤ 0.01 if the true p value is 0.05 (66).

As the above were satisfied it was concluded that the variation observed was acceptable and 20 imputations were sufficient. In addition to MCE, the fraction of missing information (FMI) was also assessed (67-69).

Multiple imputation using chained equations (MICE) was used. Linear, logistic, ordered logistic models, and multinomial logistic regression, and predictive mean

matching were specified for imputing variables identified as continuous, binary, ordered and multinomial categorical, and continuous but skewed, respectively. Conditional imputation allowed missing data related to dental variables to be handled appropriately (66-68). Where a participant had no teeth imputation of other dental variables including probing pocket depths (PPD), bleeding on bushing, mobility of teeth, number of crowns, among others, was not conducted.

Model selection was conducted separately in each of the 20 imputations (70, 71). Variable selection was carried out in each imputed dataset. The retained variables varied slightly between the imputed datasets. Where a variable was retained in at least 50% of the imputed datasets it was included into the final model (70, 71). The regression coefficients in each imputed dataset were combined using Rubin's rules to give the final model.

A slight weakness of the study was the use of heuristic shrinkage to account for optimism in the development data. Shrinkage and penalisation methods address overfitting of the data. They do this by shrinking the predictor effect estimates toward the null and reducing the mean-square predication error in new individuals. There are several methods that can be used for shrinkage (72-74).

Recently bootstrap validation methods have been established as the preferred method to account for overfitting of data (75). The method of bootstrap validation involves building a model ('bootstrap model') using the same model building/variable selection and calculating the performance of the bootstrap model in:

a) The bootstrap sample (bootstrap performance)

b) The original sample (test performance)

The optimism equates to the bootstrap performance minus test performance. The process is then typically repeated >1000 times, allowing calculation of the average optimism over the >1000 bootstrap samples. Calculation of the optimism corrected performance (apparent performance – average optimism) can then be made.

To build all the model stages, including the multiple imputation and decision making at each point in the model development process, into the bootstrap model was statistically extremely complex and beyond the scope of this study, and thus a pragmatic decision was made to use the Van Houwelingen–Le Cessie method of shrinkage. Given that the model was to be validated in an independent external dataset, it was felt this mitigated the pragmatic decision regarding the internal validation method.

A further strength of the study was the overall performance of both the model and the point-score system. They both demonstrated performances (discrimination / calibration / clinical utility) that were broadly comparable to not only models which utilise dental data but also those well-established medical models designed for use outside of the dental setting, which often include covariates such as waist circumference, diet, and biomarkers not routinely available to dental teams. A performance that is comparable but requires fewer variables for collection should improve implementation. There is evidence to support the contention that uptake of models improves with the requirement for less additional data (beyond required clinical data) collection. This further supports the use of the DDS model and point-score as a dental specific tool.

Thus, this manuscript successfully addressed research question 7, “a model and score using data routinely available to dental teams can be developed for NDH/T2D detection in the dental setting”.

Conclusions

This thesis contributes to the existing literature relating to use of dental practice settings in the early detection of NDH/T2D. It did this through establishing that:

1. Dental practices can be used to identify new cases of NDH/T2D, and the identification rate varies depending on the protocol employed.
2. A two-stage risk-assessment process utilising a questionnaire to stratify patients by risk, followed by a POCT capillary HbA1c test appears to be the optimal risk-assessment strategy.
3. There is broad support from all key stakeholders for utilising dental teams to risk-assess patients for NDH/T2D.
4. Different sections of the population appear to attend different healthcare settings. Patients report seeing their general medical practitioners when symptomatic, therefore limiting opportunity for early identification and prevention. Whereas those patients that utilise dental settings often attend at regular intervals regardless of symptoms. Therefore, dental teams have access to a cohort of patients, who have not been seen by their medical professional and who may have undiagnosed asymptomatic disease, which is ideal for targeted early-detection and instigation of prevention programmes.
5. POCT devices can demonstrate good concordance with laboratory reference standards and can be used to good effect in the dental setting to identify those with NDH/T2D.
6. The DDS model developed and validated using routinely available data for use in the dental setting has a performance broadly comparable to existing tools validated for use outside the dental setting. Thus, the DDS may provide a viable tool for oral healthcare teams to identify those with NDH/T2D.

Since embarking on this programme of work there has been an emergence of key guidance and documents calling for greater collaborative working between oral healthcare and general healthcare teams to better manage patients with NDH/T2D. These include the European Federation of Periodontology and International Diabetes Federation consensus report (29), the Commissioning Standard: Dental Care for people with diabetes (39), the updated NICE guidelines published in June 2022, and most recently the “World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians” (WONCA) position statement on diabetes and oral health.

These articles, guidance documents and standards have all called for closer integrated working between oral healthcare teams and physicians. They highlight the importance of signposting patients upon diagnosis of NDH/T2D to available dental services to ensure the most suitable oral healthcare programme can be instigated. They also acknowledge the role of the oral healthcare team in supporting patients in improving their general health.

The key next steps to build upon the work contributing to this thesis, are to validate the screening strategy on a UK population (underway). To evaluate both the clinical and cost-effectiveness of such a risk-assessment process and importantly to explore implementation strategies (underway).

Summary Sheet

Publications

1. **Use of dental practices for the identification of adults with undiagnosed type 2 diabetes mellitus or non-diabetic hyperglycaemia: a systematic review** (40)

   Yonel Z, Cerullo E, Kröger AT, Gray LJ. Use of dental practices for the identification of adults with undiagnosed type 2 diabetes mellitus or non-diabetic hyperglycaemia: a systematic review. Diabet Med. 2020 Sep;37(9):1443-1453. doi: 10.1111/dme.14324. Epub 2020 Jun 14. PMID: 32426909.

2. **The Role of the Oral Healthcare Team in Identification of Type 2 Diabetes Mellitus: A Systematic Review** (41)

   Yonel, Z., Batt, J., Jane, R., Cerullo, E., Gray, L.J., Dietrich, T., Chapple, I., 2020. The Role of the Oral Healthcare Team in Identification of Type 2 Diabetes Mellitus: A Systematic Review. Current Oral Health Reports 7, 87–97. doi:10.1007/s40496-020-00250-w

3. **Patients' attendance patterns to different healthcare settings and perceptions of stakeholders regarding screening for chronic, non-communicable diseases in high street dental practices and community pharmacy: a cross-sectional study** (42)

Yonel Z, Sharma P, Yahyouche A, Jalal Z, Dietrich T, Chapple IL. Patients' attendance patterns to different healthcare settings and perceptions of stakeholders regarding screening for chronic, non-communicable diseases in high street dental practices and community pharmacy: a cross-sectional study. BMJ Open. 2018 Nov 3;8(11): e024503. Doi: 10.1136/bmjopen-2018-024503. PMID: 30391921; PMCID: PMC6231598.

4. **Patient acceptability of targeted risk-based detection of non-communicable diseases in a dental and pharmacy setting.** (43)

   Yonel Z, Yahyouche A, Jalal Z, James A, Dietrich T, Chapple ILC. Patient acceptability of targeted risk-based detection of non-communicable diseases in a dental and pharmacy setting. BMC Public Health. 2020 Oct 20;20(1):1576. doi: 10.1186/s12889-020-09649-7. Erratum in: BMC Public Health. 2021 Feb 11;21(1):337. PMID: 33081745; PMCID: PMC7576866.

5. **Concordance of three point of care testing devices with clinical chemistry laboratory standard assays and patient-reported outcomes of blood sampling methods**. (44)

   Yonel Z, Kuningas K, Sharma P, Dutton M, Jalal Z, Cockwell P, Webber J, Narendran P, Dietrich T, Chapple ILC. Concordance of three point of care testing devices with clinical chemistry laboratory standard assays and patient-reported outcomes of blood sampling methods. BMC Med Inform Decis Mak. 2022 Sep 22;22(1):248. doi: 10.1186/s12911-022-01999-z. PMID: 36138408; PMCID: PMC9493167.

6. **The development and external validation of a diagnostic, multi-variable prediction model to identify non-diabetic hyperglycaemia and type 2 diabetes in high-risk patients attending the dental clinic: The Diabetes Risk Assessment in Dentistry Score.** (45)

   Yonel Z, Kocher T, Chapple ILC, Dietrich T, Völzke H, Nauck M, Collins G, Gray LJ, Holtfreter B. Development and External Validation of a Multivariable Prediction Model to Identify Nondiabetic Hyperglycaemia and Undiagnosed Type 2 Diabetes: Diabetes Risk Assessment in Dentistry Score (DDS). J Dent Res. 2022 Oct 17:220345221129807. doi: 10.1177/00220345221129807.

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Manuscript 1

Use of dental practices for the identification of adults with undiagnosed type 2 diabetes mellitus or non-diabetic hyperglycaemia: a systematic review. Page 35

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Systematic Review Or Meta-Analysis

Use of dental practices for the identification of adults with undiagnosed type 2 diabetes mellitus or non-diabetic hyperglycaemia: a systematic review

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Abstract

Aim Type 2 diabetes is a growing global challenge. Evidence exists demonstrating the use of primary care (non-hospital based) dental practices to identify, through risk assessments, those who may be at increased risk of type 2 diabetes or who may already unknowingly have the condition. This review aimed to synthesize evidence associated with the use of primary care dental services for the identification of undiagnosed non-diabetic hyperglycaemia or type 2 diabetes in adults, with particular focus on the pick-up rate of new cases.

Method Electronic databases were searched for studies reporting the identification of non-diabetic hyperglycaemia/type 2 diabetes in primary care dental settings. Returned articles were screened and two independent reviewers completed the data-extraction process. A descriptive synthesis of the included articles was undertaken due to the heterogeneity of the literature returned.

Results Nine studies were identified, the majority of which utilized a two-stage risk-assessment process with risk score followed by a point-of-care capillary blood test. The main barriers cited were cost, lack of adequate insurance cover and people having previously been tested elsewhere. The pick-up rate of new cases of type 2 diabetes and non-diabetic hyperglycaemia varied greatly between studies, ranging from 1.7% to 24% for type 2 diabetes and from 23% to 45% for non-diabetic hyperglycaemia, where reported.

Conclusion This review demonstrates that although it appears there may be benefit in using the dental workforce to identify undiagnosed cases of non-diabetic hyperglycaemia and type 2 diabetes, further high-quality research in the field is required assessing both the clinical and cost effectiveness of such practice. (Prospero Registration ID: PROSPERO 2018 CRD42018098750).

Diabet. Med. 37, 1443–1453 (2020)

Introduction

Type 2 diabetes is a growing public health concern; it currently accounts for 10% of the UK National Health Service (NHS) budget and this is estimated to rise to 17% by 2035 [1]. In addition to the 3.8 million people currently diagnosed with type 2 diabetes in the UK, it is predicted that almost 1 million UK residents have undiagnosed type 2 diabetes [2] and an additional 5 million people are thought to be at high risk of developing type 2 diabetes [3,4].

Impaired glucose regulation, often referred to as non-diabetic hyperglycaemia, describes the situation in which blood glucose levels are elevated, although not yet in the formal diabetic range. This is important, because individuals with non-diabetic hyperglycaemia are at increased risk of developing both type 2 diabetes and cardiovascular conditions [5]. Recent advances in diabetes care have led to the suggestion that earlier detection of type 2 diabetes may reduce the risk of complications associated with the condition, including cardiovascular complications and blindness [6,7]. There is also existing evidence suggesting that type 2 diabetes can be prevented or delayed in those considered high risk [8].

Type 2 diabetes is often symptom-free in its early stages and individuals may remain undiagnosed for many years,

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What's new?

- There is an established association between periodontitis and type 2 diabetes.
- Different populations exhibit different attendance patterns with different healthcare professionals.
- We found that primary care dental settings can be used to successfully identify previously undiagnosed cases of non-diabetic hyperglycaemia and type 2 diabetes.
- The potential early detection of non-diabetic hyperglycaemia/type 2 diabetes allows for instigation of either prevention strategies or earlier management, which may prove clinically and cost-effective.

which has implications for both secondary prevention and management of the condition [2]. Although currently opposed to population-based screening for type 2 diabetes, the UK National Screening Committee note that there are benefits to the early identification of individuals at risk of developing the condition, as well as non-diabetic hyperglycaemia and those with undiagnosed type 2 diabetes [9]. Hence, the NHS have rolled out the National Diabetes Prevention Programme (DPP). The Healthier You: NHS DPP was developed to prevent or delay onset of type 2 diabetes in adults already identified as high risk, defined as having non-diabetic hyperglycaemia [10]. This is based on evidence from randomized controlled trials (RCTs) demonstrating that the onset of type 2 diabetes can be prevented or delayed through behavioural interventions in those with non-diabetic hyperglycaemia [6]. Hence, the consideration of novel and alternative mechanisms to identify those with non-diabetic hyperglycaemia and undiagnosed type 2 diabetes earlier, which may confer benefits [11]. These benefits include potential improvements in health outcomes, quality of life outcomes, and reductions in costs to the NHS.

Severe periodontitis (gum disease) affects 11% of adults globally, with increased prevalence seen for milder forms of periodontal disease, which evidence suggests affect 50% of adults and up to 60% of those aged > 65 years [12]. The association between type 2 diabetes and severe periodontitis is considered to be significant and independent [13]. Additionally, within the UK, it is mandated that dental professionals screen people for periodontal disease, providing information on dental risk factors for type 2 diabetes that general practitioners (GPs) are unable to assess. There is also evidence that glycaemic status impacts directly upon oral health [14]. Poor glycaemic control results in undesirable consequences within the periodontal tissues, which in the absence of intervention from dental care professionals, will ultimately result in tooth loss [13,15]. Moreover, there is an established association between periodontal disease and type 2 diabetes, whereby improvements in periodontal care have been shown to result in improved diabetes control [13,16]. This was recently revealed in an RCT demonstrating a reduction in HbA_{1c} at 12 months following treatment of periodontal disease [17].

Raising awareness of non-diabetic hyperglycaemia and type 2 diabetes status via dental teams in primary care dental settings may facilitate improved and targeted strategies for both prevention and management of the conditions, ensuring better oral health outcomes. Importantly, it may also enable a pathway to improved systemic health for these individuals, by allowing earlier detection and instigation of prevention and management strategies. This would enhance the potential role of dental teams in contributing to the mounting challenges associated with type 2 diabetes.

Members of the public generally seek GP appointments when symptomatic, whereas people tend to visit their dentist on a regular (6–12 monthly) basis, often doing so even if they are dentally healthy, to prevent the onset of oral and dental diseases [18]. A study undertaken in the UK found 12% of people claiming to attend dental appointments at 6-monthly intervals also stated they had not had contact with their GP in the same 12-month period [19]. Furthermore, of the sample that identified as regular dental attenders, almost half claimed to have never had an NHS health check at their GP surgery [19]. As ~ 60% of the UK adult population are registered with a dentist [20], this places dental teams in a strong position to identify individuals for risk-based assessments, as they have access to people who would not necessarily attend their GP regularly when asymptomatic.

The National Institute for Health and Care Excellence (NICE) recommend that healthcare professionals, such as dentists, undertake a risk assessment for type 2 diabetes [21]. Data from Europe and the USA demonstrate non-diabetic hyperglycaemia and type 2 diabetes can be identified effectively in a dental setting [22–28]. Government policies exist that advocate the use of dental teams to provide preventative advice for risk factors related to systemic conditions and general health promotion [29,30]. Dental teams currently provide advice that includes reducing sugar consumption as well as broader dietary and smoking cessation advice, all of which are risk factors shared with type 2 diabetes. There may be an opportunity for collaborative working between dental teams and GPs to provide enhanced services for the prevention and earlier identification of non-diabetic hyperglycaemia, type 2 diabetes, and for developing an improved care pathway [31]. This aligns closely with the UK 'Making Every Contact Count' agenda to improve general health and well-being [32].

We recently undertook a review focusing on qualitative outcomes including assessing barriers and facilitators, as well as stakeholder opinions and perceptions of dental teams risk-assessing for type 2 diabetes [28]. The review article found strong support from stakeholders including dental teams, people with diabetes and physicians for risk-assessing for type 2 diabetes in dental settings. The studies contributing to the review, however, were undertaken in secondary care environments. In the UK, > 95% of dentistry

is delivered in dental primary care settings. These are very different from secondary care dental services in terms of person profiles, care delivery pathways and financial drivers. Therefore, given the disparity in these healthcare settings, it would have been inappropriate to pool data and as such, drawing conclusions based on both settings would not be meaningful.

This review therefore aimed to identify and synthesize all evidence relating specifically to the use of primary care dental services for the identification of non-diabetic hyperglycaemia and undiagnosed type 2 diabetes in adults.

The review had a particular focus on the identification rate of new cases of non-diabetic hyperglycaemia and type 2 diabetes, and aimed to answer the following additional questions, as per the previously published protocol [4]:

- What methodology was utilized within the dental practice for case-finding?
- What were the recruitment rates within the studies?
- What are the reported barriers to uptake of any such implemented services?

Methods

A pre-specified protocol (PROSPERO 2018 CRD42018098750) [33] was used to guide the study and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S3) for conducting and reporting systematic reviews and meta-analyses.

Search strategy

Electronic bibliographic databases including Web of Science, The Cochrane Library, MEDLINE Ovid and Clinicaltrials.gov were searched for eligible studies. Additional papers for inclusion were identified through searching the reference lists of all eligible full-text articles. The search strategy (see Table S1) included terms associated with the identification of non-diabetic hyperglycaemia and type 2 diabetes in primary care dental settings. Search terms were adapted for use with other bibliographic databases and restricted to papers in the English language. Searches were limited to articles published between 1950 and November 2019.

Because the majority of included studies were observational, the PICO method was not suitable due to the absence of a comparator arm. However, the 'Population, Intervention, Reference standard, Target condition' (PIRT) format was applied, where [P] is the stakeholder, such as adults aged > 18 years attending primary care dental services and healthcare professionals involved in the delivery of dental care; [I] is the screening method of choice; [R] is method of diagnosis for non-diabetic hyperglycaemia/type 2 diabetes; and [T] is non-diabetic hyperglycaemia or type 2 diabetes.

Risk of bias

This review was not limited solely to RCTs. The 'Study Quality Assessment Tools', validated and published by the National Institute of Health (NIH) [34], were used by two independent examiners to determine risk of bias associated with each of the included articles (Table S2). Disagreement was resolved by discussion; a third author was consulted if consensus could not be reached. If the NIH study quality assessment was deemed inappropriate or inconclusive for the included studies, the United States Preventative Task Force 'Criteria for Assessing Internal Validity of Individual Studies' was also used.

Data extraction and data management

The titles and abstracts of all returned articles were screened for eligibilityby two independent reviewers (Table S4). Reviewers undertook calibration exercises to ensure consistency in their acceptance criteria of articles for inclusion, and a third reviewer was available in case agreement could not be reached. Where screened articles were deemed to meet the inclusion criteria, a full-text review was undertaken and reasons for exclusion at this stage were recorded (Table S5). Electronic data extraction forms were developed and piloted, and then used for all data extraction [4].

Strategy for synthesis

If possible, quantitative synthesis and meta-analysis was planned, provided that studies included within the review were suitably homogenous. High levels of heterogeneity were expected. If this proved to be the case, a descriptive synthesis was planned. The synthesis was centred on the primary and secondary outcomes of the review. We expect cases of non-diabetic hyperglycaemia and undiagnosed type 2 diabetes to be well reported across the assumed small number of existing studies [4].

Results

Nine studies met the eligibility criteria [22,25–27,35–39] and were included in the systematic review (Table 1 and Fig. 1); all were observational in nature. Five studies were based in the USA [22,26,27,37,39] with one study in each of the UK [35], Germany [38], Sweden [25] and Japan [36]. Two of the included studies were based solely in one primary care dental practice [37,38]. A further two recruited participants from two dental practices [35,39]. The remaining studies involved three [25], 11 [22], 13 [26] and 28 [27] practices, with one study not reporting the number of dental practices used to recruit participants [36]. None of the studies included in this review provided information relating to the dental practices and how they were selected for inclusion, nor whether the practices were in areas of high prevalence for type 2 diabetes.

Table 1 Abbreviated summary of eligible articles included in the systematic review (for full table see Table S4).

First author	Year	Reference	Risk of bias rating [34]	Country	Percent male	Mean age (years)	Number screened	Assessment method	Recruitment rates (%)	Identification of non-diabetic hyperglycaemia (%)	Identification of type 2 diabetes (%)	Reported barriers to uptake
Barasch	2013	27	Fair	USA	45	52.2	498	Pre-screen questionnaire followed by random capillary glucose	99	No	24	Of the 7 refusing participants, 6 did so because they had just been tested at home or in their physician's office
Engstrom	2013	25	Fair	Sweden	50	48.6	1568	Finger-prick random capillary glucose	Not reported	Not reported	10	Not reported
Genco	2014	22	Low	USA	39	56.5	1022	Pre-screen questionnaire followed by HbA_{1c}	41	23	12	Not reported
Herman	2015	26	Fair	USA	44	52.8	1033	Finger-prick random capillary glucose	91	32	1.7	Further studies are needed to demonstrate the acceptability, feasibility, effectiveness and cost-effectiveness of such screening
Harase	2015	36	Low	Japan	43	61	716	Pre-screen questionnaire followed by periodontal assessment Finger-prick random capillary glucose	79	Unclear	4	Not reported
Bossart	2016	37	High	USA	54	57.8	49	Pre-screen questionnaire followed by HbA_{1c}	88	32	2	Cost or lack of dental insurance may inhibit implementation
Bould	2017	35	Fair	UK	Unclear	Unclear	1035	Pre-screen questionnaire followed by HbA_{1c}	50	45	4.1	Participant reported barriers; 'the main reasons for refusal were, a recent blood glucose test, a recent health check-up such as the Well Man's Check arranged through the GP, dental pain and fear, and lack of interest in the research'.
Mirza	2018	39	Low	USA	44	49	226	Finger-prick and gingival crevicular random capillary glucose. In the event of abnormal glucose test results, an HbA_{1c} test was performed	Unclear	Unclear	11	Introducing these practices to dental clinics will require a concerted effort to educate and introduce a procedure that will require a cultural change. It is a challenging task, albeit one that has potential
Ziebolz	2019	38	Fair	Germany	44	56	116	Pre-screen questionnaire followed by venous blood sample for HbA_{1c} and an oral glucose tolerance test	88	Unclear	Unclear	Not reported

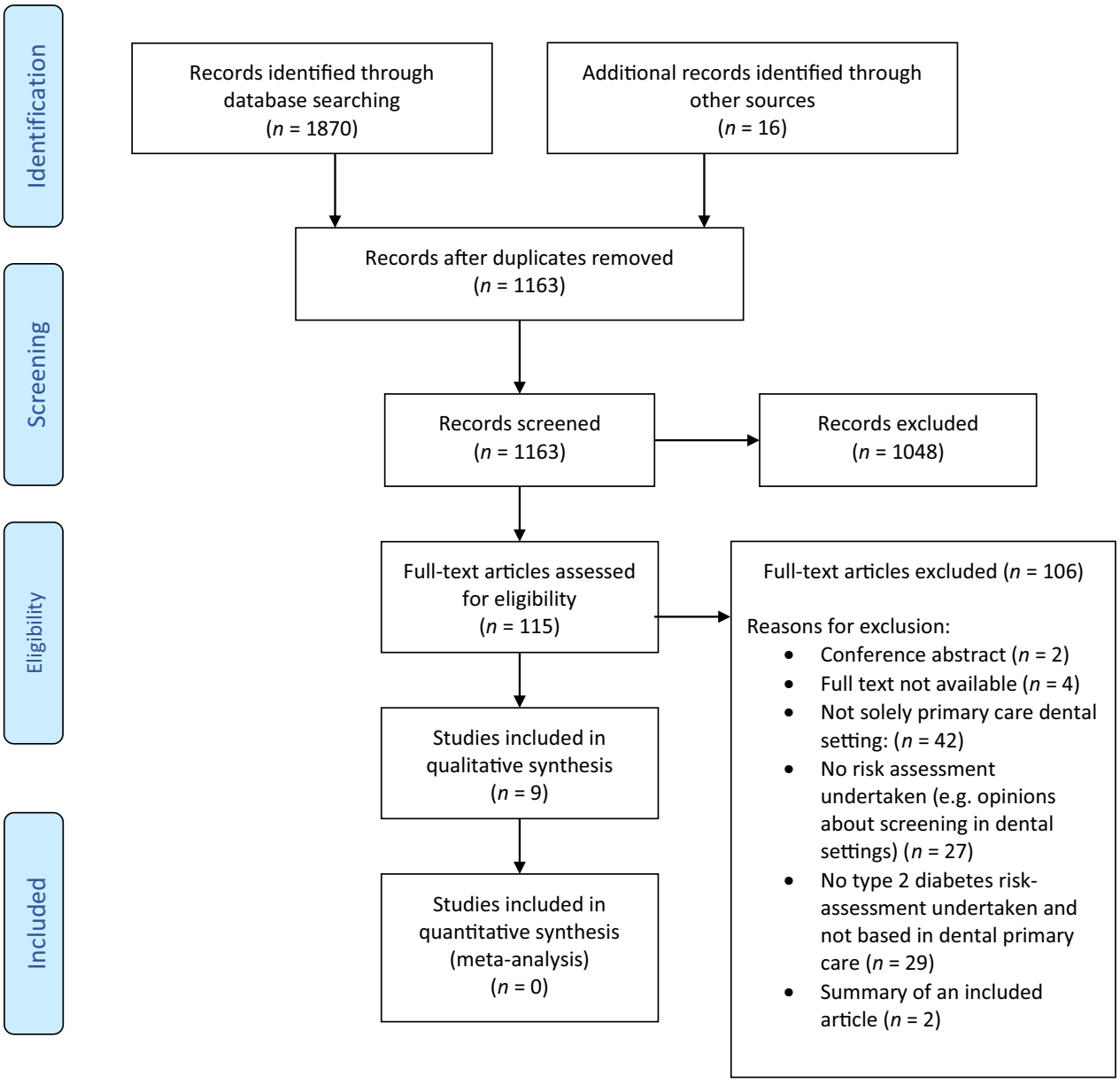

FIGURE 1 Prisma flow diagram of the search results.

In total, the combined sample screened within the included studies was 6263 participants. Studies ranged in size from 49 to 1568 participants, and the median number was 716. The reported recruitment rates within studies varied from 41% to 98%, with one study not reporting the rate of recruitment. The study-level mean age was 54.2 years and the average proportion of men was 45%. In four studies, participant ethnicity was not reported [25,35,36,38]. In the remaining studies, ethnicity was reported to be predominantly 'White', ranging from 78% to 92% of the study population. The majority of studies failed to report the socio-economic background of participants; where this was reported, one study mentioned that 96% of participants had medical insurance, 78% had dental insurance and 86% had a university degree [37]. A further study reported that > 95% of participants had health insurance. In selecting participants for inclusion, all studies used either consecutive eligible persons attending the dental practice or a convenience sample.

All studies had a 'fair' risk of bias according to the NIH study quality assessment tool [34]. Using United States Preventative Task Force criteria to assess internal validity, one study was deemed to have a high risk of bias [37], whereas three studies were deemed to have a lower risk of bias than the others [22,36,39]. The remaining studies were deemed to be 'fair' (Table S2). The main factors contributing

to increased risk of bias were related to inadequate reporting of how dental practices and participants were selected for inclusion in the study, poor follow-up to determine those who went on to receive confirmation of the risk assessment, failure to demonstrate the reliability of the risk assessment process selected, failure to clearly report follow-up procedures and limited sample size.

Eight of the nine studies reported the pick-up rate of potential new cases of type 2 diabetes or those at risk of developing the condition. Two studies reported pick-up rate based on exceeding a threshold on a validated risk questionnaire screening tool. Six studies utilized point-of-care capillary blood test (POCT) samples to determine pick-up rates, with half reporting HbA_{1c} and half reporting random blood glucose levels. There was a large range, from 1.7% to 41%, in the reported pick-up rates of potential non-diabetic hyperglycaemia and type 2 diabetes. Three of these eight studies also followed up participants to determine the proportion of those who screened positive and went on to receive a formal diagnosis from a diabetologist or primary care physician.

Two studies used the validated finnish diabetes risk score (FINDRISC) questionnaire for identifying those at risk of type 2 diabetes. One study found that 47% (247) of participants fell into the slightly elevated risk category, 19% (101) were in the low-risk category and 33% (172) were seen as having a moderate, high or very high risk of developing diabetes [35]. In this study, the participants who were deemed at increased risk then went on to have a HbA_{1c} POCT. Of those who undertook the POCT, 45% (108) had a result of between 39 and 46 mmol/mol (5.7–6.4%) (i.e. non-diabetic hyperglycaemia), a further 4.1% (10) had a HbA_{1c} > 48 mmol/mol (6.5%) (i.e. possible type 2 diabetes). All participants at elevated risk according to the questionnaire were advised to see a primary care professional for formal follow-up and testing; only 60% did so, and the results of the follow-up are not reported [35]. In the other study using a similar methodology, 31% (29) of participants screened positive with the FINDRISC questionnaire, of whom 16 attended for formal follow-up with a diabetologist for HbA_{1c} and oral glucose tolerance test (OGTT) and nine (56%) showed 'conspicuous findings' [38].

Three studies utilized HbA_{1c} POCT, one of which reported that of the tested participants: 41% (416) had HbA_{1c} > 39 mmol/mol (5.7%) and were advised to follow up with a physician; 35% (146) of whom did follow-up and of these, 23% were found to be in the non-diabetic hyperglycaemia range and a further 12% in the type 2 diabetes range [27]. A further study with a similar sample size and methodology supported these findings, also reporting 23% of participants in the non-diabetic hyperglycaemia range and a further 12% in the type 2 diabetes range [22]. An additional study undertaking HbA_{1c} POCT, found that 32% of their sample had potential non-diabetic hyperglycaemia, and a further 2% potential type 2 diabetes [37], although this study had a considerably smaller sample size.

The remaining three studies that reported potential identification rates utilized random blood glucose levels to screen people for potential non-diabetic hyperglycaemia or type 2 diabetes. One of these studies found that 31% of their sample screened within the non-diabetic hyperglycaemia range and a further 1.7% were in the type 2 diabetes range; however, formal follow-up and diagnosis rates were not reported [26]. Another study found that 3.5% of previously undiagnosed participants had hyperglycaemia [36]. In support of this, the third study reported 10% (155) of participants screened positive with a finger-prick random blood glucose sample; of these, 89% attended for follow-up in primary care within 3 years of their screening assessment and of those, 5.8% (9) were diagnosed as having type 2 diabetes according to the World Health Organization criteria. Interestingly, in this study of those who did not screen positive, 80% (1137) also attended the primary healthcare centre within the 3-year follow-up period and 0.6% (8) were found to have type 2 diabetes [25].

Two of the nine studies used a one-stage screening process; in one of the studies this involved participants having their height and weight recorded and a fingerstick random blood glucose [25]. The other study involved all participants completing questionnaires regarding diabetes status and undergoing periodontal assessment and obtaining a finger-prick capillary blood sample (see Table 2).

The remaining studies utilized a sequential screening strategy, with the first stage of the screening process being a non-invasive test in all but one of the studies. This was done using a risk score or comparison against pre-selected risk factor cut-off points, such as age, ethnicity or BMI [22,26,27,35,37,38]. In five of these studies, the second stage of the risk-assessment process was a point-of-care fingerstick blood sample, with one study choosing to refer participants for venous blood sample HbA_{1c} and an OGTT [38]. One study used a sequential screening strategy, initially using a point-of-care fingerstick and gingival crevicular blood sample, followed by a venous HbA_{1c} test in the event of an abnormal point-of-care random blood glucose level [39]. Of the studies that utilized point-of-care fingerstick blood samples, three used HbA_{1c} devices as part of their risk assessment; the remaining studies utilized random blood glucose measurements, with one opting for an additional HbA_{1c} test if the random blood glucose level was elevated [39].

Six studies recorded participant BMI as part of the risk-assessment process. In five cases, this was self-reported by participants and in one case, participant BMI was recorded in the dental setting. BMI was not included as part of inclusion or exclusion criteria. In all studies where BMI was reported, mean BMI was in the overweight category.

Use of dental data as part of the risk assessment was reported in five studies. In all cases, the periodontal health of participants was recorded and one study also the recorded decayed/missing/filled teeth score [38]. Only one study stratified the results of the diabetes screening based on dental

Table 2 Summary of identification rates.

Author	Year	Reference	Sample size	Method	Results
Barasch	2014	27	1022	Participants reported data (demographic, medical and physical). A periodontal examination and HbA_{1c} were performed by the investigators. Those with $HbA_{1c} \geq 39$ mmol/mol (5.7%) were referred to their physician for further workup and diagnosis	Of those tested, 41% ($n = 416$) had an $HbA_{1c} > 39$ mmol/mol (5.7%). Of these, 35% ($n = 146$) followed up with a physician and of those: 23% had non-diabetic hyperglycaemia and 12% had type 2 diabetes
Bossart	2016	37	50	Point-of-care diabetes screenings performed by a dental hygienist for people with periodontitis, using a diabetes risk questionnaire, periodontal findings and a HbA_{1c} analyser	32% potential non-diabetic hyperglycaemia and 2% potential type 2 diabetes
Bould	2017	35	520	Participants completed a demographics and FINDRISC questionnaire. Those with a FINDRISC score of ≥ 10 were offered an HbA_{1c} finger-prick test to explore their risk further	$n = 247$ (47%) slightly elevated risk category, $n = 101$ (19%) low-risk category, $n = 172$ (33%) moderate, high or very high risk of developing diabetes 10 participants (4.13% of those who took the HbA_{1c} test) had a result of 48 mmol/mol (≥ 6.5%). 108 participants (45% of those who took the test) had a result of between 39 and 46 mmol/mol (5.7% and ≥ 6.4%) Of the 258 participants advised to visit their GP for formal diabetes testing, 155 (60%) did so
Engstrom	2013	25	1558	Non-fasting blood glucose measured with a portable blood glucose meter. Participants with a blood glucose of 40 mmol/mol (5.8%) were referred to their primary healthcare centre for follow-up	Of the 155 (10%) participants who screened positive, 139 (90%) went to their primary healthcare centre within the 3-year follow-up period. $n = 9$ had type 2 diabetes (48 mmol/mol; ≥ 6.5%). Of the 1413 participants who screened negative, 1137 (81%) came to the primary healthcare centre and $n = 8$ (0.6%) had type 2 diabetes. Screening sensitivity was 53%, specificity 91% and positive predictive value 5.8%.
Genco	2014	22	1022	The Diabetes Risk Test questions and the A1CNow+ test	23% = potential non-diabetic hyperglycaemia; 12% = potential type 2 diabetes
Harase	2015	(36)	716	A questionnaire regarding history of diabetes mellitus was completed by all participants The periodontal condition was assessed (periodontal pocket depth and clinical attachment loss) Samples of finger capillary blood were obtained from all participants	The incidences of hyperglycaemia in the type 2 diabetes and non- type 2 diabetes groups were 32% and 3.5%, respectively ($P < 0.0001$) Proportion of participants with hyperglycaemia: 5 of 187 (2.6%) in the mild periodontitis group; 25 of 286 (8.7%) in the moderate periodontitis group, and 13 of 55 (23%) in the severe periodontitis group ($P < 0.0001$).
Herman	2015	(26)	1033	Questionnaire assessing established risk factors for dysglycaemia. Thereafter, random blood glucose using a POCT system.	32% = potential non-diabetic hyperglycaemia 1.7% = potential type 2 diabetes
Mirza	2018	39	226	After obtaining consent, POC and gingival crevicular (GC)C blood were collected, and random blood glucose levels from those samples were tested using an Accu-Chek® glucometer. In the event of abnormal glucose test results, we followed ADA guidance and performed an HbA_{1c} test simultaneously on POC and GC blood samples.	Not reported
Ziebolz	2019	38	102	FINDRISC Questionnaire was used for diabetes screening and positive results were referred to diabetologist for blood glucose and HbA_{1c}	29 previously undiagnosed participants had an elevated risk score. Only 16 of these 29 followed up with the diabetologist. Nine of the 16 were reported to have 'conspicuous' blood glucose findings

ADA, American Diabetes Association; POC, point of care; POCT, point-of-care capillary blood test.

findings. This study found that the proportion of people with hyperglycaemia increased as periodontal disease severity increased, with hyperglycaemia in 2.6% (5 of 187) of participants in the mild periodontitis group, 8.7% (25 of 286) in the moderate periodontitis group, and 23% (13 of 55) in the severe periodontitis group.

Barriers to recruitment were generally not well reported in the studies. When barriers were mentioned, they were often

in relation to recruitment and included people refusing participation due to having recently been tested by a physician, costs relating to testing and lack of dental insurance. Facilitators to recruitment were not discussed in any of the included studies. A further limitation to the studies was reported follow-up of participants post screening. Three of the included articles [22,25,37] reported follow-up, with one following up a sub-sample of their population [26]. Although the studies did not address rates of follow-up as a potential barrier to the implementation of risk assessment services, all studies that reported on follow-up showed the rates to be poor.

Discussion

This systematic review found that there is a limited number of high-quality studies assessing diabetes risk assessment in a primary dental care setting. This review highlighted that primary care dental settings could potentially be beneficial sites at which to undertake targeted risk assessment for non-diabetic hyperglycaemia and type 2 diabetes. This conclusion is based on the available studies, which demonstrated that risk assessments could identify individuals with non-diabetic hyperglycaemia, undiagnosed type 2 diabetes or risk of developing type 2 diabetes to good effect. However, more research based on large-scale robust studies with appropriate follow-up is required to determine the barriers and facilitators to such risk assessments in primary dental care settings, as these appear to be under-reported within the literature in relation to primary care. Research is also needed to determine a gold standard method of risk assessment, and to determine how many of those identified via the risk-assessment processes translate into true cases of disease, and hence the clinical and cost-effectiveness of the process.

The majority of studies utilized a two-stage risk-assessment process with risk score followed by POCT. However, there was heterogeneity in terms of both the risk score and POCT chosen, with the majority of studies using random blood glucose testing and others using HbA_{1c}. The merit of utilizing a two-stage rather than one stage risk-assessment process was not discussed in the studies in terms of time, cost effectiveness or improvements in the identification rate for non-diabetic hyperglycaemia/type 2 diabetes. However, the two studies that used questionnaire-based risk assessment alone reported pick-up rates in the region of 50%, which is far higher than studies utilizing additional POCT. The benefits of a non-invasive and low-cost questionnaire need to be weighed against the high rate of false positives, the potential for increased unnecessary referrals to primary care physicians, and the associated cost of unnecessary follow-up procedures.

There was large variation in the studies that reported detection rate of type 2 diabetes, ranging from 1.7% [26] to 24% [27] of the study sample. Despite this large variation, both studies were based in the USA and reported a mean age of 52 years, with 44% and 45% of participants identifying as male, and 81% and 80% of participants reported as 'White'; the studies were based in New York and Birmingham, Alabama [26] and Michigan [27], respectively. Thus, the studies appear to be well matched for age, sex and ethnicity. A further potential cause of the difference could be the risk-assessment method used and the accuracy of the risk-assessment process. It is recognized that different POCT devices have different levels of accuracy. Interestingly, both studies used a risk score followed by a random blood glucose measurement; furthermore, both reported using the same POCT device (FreeStyle Lite blood glucose meters and test strips; Abbott Diabetes Care Inc., Alameda, CA, USA). Hence, differences in POCT devices should not account for the large variation. A further possible explanation is that the authors used different thresholds for diagnosing an individual's risk of type 2 diabetes.

None of the studies in this review included the opinions of stakeholders relating to the risk-assessment process for type 2 diabetes in primary care dental settings. Work looking at the opinions of stakeholders, including people with diabetes, dental hygienists, dentists and physicians, regarding their attitudes to risk assessment for type 2 diabetes in dental settings has been undertaken in both the USA and UK [28,40–45]. Although these studies did not meet the eligibility criteria for this review, the overall opinion from each of the groups asked was generally positive in relation to using dental settings as potential sites for the early detection of non-diabetic hyperglycaemia and type 2 diabetes.

The studies included in the review cited cost, lack of adequate insurance cover and people having been previously tested elsewhere as the main reasons for a refusal to participate. The studies did not report widely on the barriers and facilitators of undertaking risk assessments within primary dental care. The reported barriers and facilitators to dental teams' risk-assessing for non-diabetic hyperglycaemia and type 2 diabetes have been discussed more widely in the literature, although mostly outside primary care settings [28].

A study undertaken in North America aimed to determine the perceptions of minority ethnic adults aged 50 years or more towards screening for type 2 diabetes and hypertension, as part of their routine dental assessment [43]. Several barriers to screening were identified, including a mistrust of their dental providers. Facilitators were also identified, including the acceptability of the chairside screening process and an understanding of the relationship between oral and systemic health [43].

Time and cost are often considered the most significant barriers to implementing new services. Studies in the USA and Europe have assessed time and costs relating to screening for type 2 diabetes in dental settings [46]. One study suggested the direct costs associated with undertaking a HbA_{1c} test as part of a risk-assessment process was US $9, excluding follow-up medical diagnosis. It also found the

mean time for undertaking both risk assessment and participant education to be 14 min (SD 6.2) [37]. However, this systematic review has identified a lack of consensus in the literature relating to which risk-assessment method and device to select. Given the variety of strategies reported in the literature, the time and costs associated with each process are likely to vary greatly. A further study undertaken in the USA found that three-quarters of those asked would be willing to contribute up to $20, with two-thirds willing to contribute up to $30 toward testing [42]. Whether this is viable within the UK healthcare system would need to be explored.

Following risk assessment for type 2 diabetes being undertaken within the dental setting, it is vital that there is clear communication and established care pathways with the person's GP to ensure appropriate onward management. However, a further barrier identified within the literature was poor follow-up with a physician post risk assessment [27,35,37]. Thus, although many studies stated that individuals and dental teams found risk-assessment methods feasible, acceptable and appropriate, in reality, poor follow-up by GPs mean that it is yet to be determined whether risk assessments in dental settings identified new cases of previously undiagnosed disease.

Historically, screening for type 2 diabetes has been controversial, due to limited evidence that early identification impacted sufficiently upon health outcomes and a lack of certainty regarding management of high-risk individuals. Evidence shows that population-based screening may be ineffective [9,11,47], consequently, the National Screening Committee do not currently recommend screening for type 2 diabetes in the UK. Although the evidence for population-based screening is controversial, emerging evidence supports a targeted approach to case finding [48–50].

In 2015, the US Preventative Service Taskforce recommended targeted case-finding for type 2 diabetes in overweight people aged > 40 years. This is because evidence suggests this approach is cost-effective and improves outcomes. A systematic review of clinical trials showed that screening contributes to delayed disease progression [49], and a meta-analysis has demonstrated that diabetes prevention programmes result in reductions in weight and in progression from non-diabetic hyperglycaemia to type 2 diabetes, compared with usual care [6]. In 2013, the National Screening Committee also acknowledged that advances in diabetes care may now enable benefit from early identification [9].

With ~ 60% of the UK population registered with a dentist [20], dental teams may be in an ideal position to target people for risk assessment of non-diabetic hyperglycaemia and type 2 diabetes, because they regularly interact with a population who would not necessarily attend their GP whilst asymptomatic [19,51,52].

NICE recommends a care pathway [21] that includes contributions from dental teams to identify individuals at high risk of type 2 diabetes. This pathway describes a process whereby dental teams utilized a risk-based questionnaire such as the Leicester Risk Assessment Score. However, the feasibility of undertaking targeted risk-based detection of type 2 diabetes in UK dental settings is still in its early development. This review highlights the requirement for further investigation to determine the feasibility and effectiveness of such a model in primary care dental settings. Furthermore, although much has been published relating to the use of dental settings in the identification of type 2 diabetes, most of this research is based within a secondary care environment [28]. To our knowledge, the evidence base relating to diabetes risk assessment in dental primary care is yet to be synthesized.

A recent article assessing perceptions of stakeholders in secondary care dental settings and dental university clinics demonstrated strong support for hospital-based dental professionals undertaking risk-assessment for type 2 diabetes. The results of which suggested that most hospital-based dental care professionals would be willing to undertake the required risk assessments to identify people with type 2 diabetes [28]. However, secondary and primary care dental services are very different, with different person profiles, care delivery pathways and financial drivers. In the UK, > 95% of dental care is delivered in a primary care setting and thus it was deemed important to establish whether cases of non-diabetic hyperglycaemia and undiagnosed type 2 diabetes could be identified in this environment.

The main strengths of this systematic review were a robust search, review and analysis method to provide assessment of the existing literature, which conformed to the protocol registered previously on PROSPERO [33] and published in the peer-reviewed literature for transparency and clarity of process [4]. The main weakness of this review was due in part to the heterogeneity of the available literature as a result of which, meta-analysis and summary statistics could not be calculated and presented, and we were limited to a descriptive analysis of findings.

The systematic review is based on the available literature, which is only nine studies, of limited quality and variable sample size. This limits the generalizability of results from this review. Furthermore, follow-up of participants beyond the risk-assessment process to determine whether they went on to receive formal non-diabetic hyperglycaemia or type 2 diabetes diagnosis was not widely reported. Where follow-up was reported, the numbers of people visiting their physician were poor. Additionally, different measures of an individual's risk were used, and even when the same measure was used, such as random blood glucose levels, different ranges and thresholds were utilized within the literature. This makes direct comparison between studies challenging.

This systematic review builds upon existing evidence in secondary care settings and highlights that the primary care dental setting may be a viable location to detect non-diabetic hyperglycaemia and undiagnosed type 2 diabetes. In addition, it also demonstrates that further research is required assessing the acceptability, feasibility, effectiveness and cost-

effectiveness of such methods. Future larger scale studies need to be conducted, with suitable follow-up to determine the rate of participants going on to receive a formal diagnosis of non-diabetic hyperglycaemia or type 2 diabetes and receive suitable intervention.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search strategy.
Table S2. Risk of bias assessment.
Table S3. Prisma checklist.
Table S4. Summary of eligible articles included in the systematic review.
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HOST PARASITE INTERACTIONS IN PERIODONTAL DISEASE (C GENCO AND D KINANE, SECTION EDITORS)

The Role of the Oral Healthcare Team in Identification of Type 2 Diabetes Mellitus: A Systematic Review

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Abstract

Purpose of Review Type 2 diabetes (T2DM) presents a growing global health and economic burden. Dental settings have been employed to identify individuals who may be at high risk of diabetes, who exhibit non-diabetic hyperglycaemia (NDH – also termed "prediabetes") and who already unknowingly have the condition, through the use of targeted risk-assessments. This review aims to synthesize the existing literature supporting dental teams' identification of individuals at an increased risk of or suffering from undiagnosed NDH or T2DM in dental specialist care settings.

Recent Findings Electronic databases were searched for studies reporting the identification of NDH and or T2DM, in specialist care dental settings. Screening of returned articles and data extraction were completed by two independent reviewers (RJ, ZY). A descriptive synthesis of the included articles was undertaken. Due to heterogeneity of the literature, a meta-analysis could not be performed. The search yielded 52 eligible studies, of which 12 focused primarily on stakeholder opinions. Opinions of patients, dentists, dental hygienists, dental students and physicians on case identification of T2DM by oral health professionals were generally positive. The main barriers cited were time, cost, inadequate training and low follow-up of participants by primary care physicians. The risk assessment processes varied, with most studies using a combination of methods consisting of a questionnaire followed by a chairside blood sample. Methods utilizing questionnaires, gingival crevicular blood (GCB), fingerstick blood (FSB) and urine samples have all been evaluated.

Summary This review demonstrates that there may be benefit in engaging the dental workforce to identify cases of NDH and undiagnosed T2DM and that such a care pathway has the support of multiple stakeholders. Further high-quality research is required to assess both the clinical and cost-effectiveness of such practice in order to optimize protocols and patient care pathways. Studies should include a comparison of methods, health economic analyses and protocols to ensure those identified as high-risk go on to receive appropriate follow-up care.

Keywords Type 2 diabetes · Non-diabetic hyperglycaemia · Screening · Risk assessment · Dental settings

This article is part of the Topical Collection on *Host Parasite Interactions in Periodontal Disease*

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Introduction

Type 2 diabetes mellitus (T2DM) is a growing public health concern, affecting approximately 60 million people in Europe, which equates to 10% of those aged over 25 years. More than 422 million adults are living with the condition globally according to the World Health Organization [1]. In 2017, 1 in 2 people (212 million individuals in total) were living with undiagnosed T2DM [2]. Additionally, many individuals with T2DM may remain undiagnosed for many years due to T2DM being asymptomatic in its early stages. This has implications for the secondary prevention and management of the condition [2]. Therefore, there is merit in exploring non-

traditional approaches to enhance early identification of individuals with non-diabetic hyperglycaemia (NDH) and undiagnosed T2DM.

NDH or impaired glucose regulation refers to elevated blood glucose levels that are not yet in the diabetes range. In addition to an increased risk of T2DM, individuals with NDH are also at increased risk of developing cardiovascular conditions [2]. By identifying NDH early, it can aid in the primary prevention of T2DM. The International Diabetes Federation reported that in 2017 over 325 million people were at high risk of developing T2DM. These people are classified as having NDH or prediabetes [3].

The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GBD 2017) reported that from 1990 to 2017, oral diseases (mainly periodontitis and caries) contributed the most years lost due to disability (YLD) in age-standardized prevalence rates from 354 diseases and injuries across 195 countries [4•]. Severe periodontitis affects 11.2% of adults worldwide [5]. Milder forms are even more prevalent, affecting 50% of adults and 60% of individuals over the age of 65. Importantly, severe periodontitis is significantly and independently associated with T2DM [6•, 7–9]. Furthermore, glycaemic status directly impacts oral health [10]. Poor glycaemic control brings unwelcome consequences for periodontal health which ultimately, if left untreated, may lead to tooth loss and associated psychosocial sequelae [6•, 11–18]. Due to the well-established bidirectional relationship between periodontitis and T2DM, improvements in periodontal status can lead to improvements in diabetes control [6•, 9, 18–23], as evidenced by a recent randomized control trial which demonstrated a 0.6% reduction in HbA1c at 12 months among patients who had received intensive periodontal therapy [24]. Screening for periodontitis is an established and mandatory procedure within dental settings in many countries around the world, providing information on oral risk factors for diabetes that primary care physicians are unable to assess.

In addition to the human cost of diabetes and periodontitis, and associated morbidity and mortality, there is a significant economic burden associated with both diseases. Severe periodontitis is estimated to cost $54 billion (US dollars or USD) per year globally in lost productivity [25]. Periodontitis is also a major contributor to the aggregate direct treatment costs of oral disease, estimated at $91.05 billion (USD) for western Europe and $297.67 billion (USD) worldwide in 2010. These were considerably higher when aggregated with indirect costs, amounting to $442 billion (USD) [26].

It is in the interests of dental teams to know whether their patients have NDH or undiagnosed T2DM, due to the impact of both upon periodontal stability and treatment outcomes. Given the inter-relationship between these two chronic, non-communicable diseases, raising awareness of the NDH/T2DM status of patients in the dental environment will enable dental teams to better target their prevention and management strategies to improve oral health. Moreover, earlier detection of both conditions will facilitate improved systemic health outcomes for these individuals by facilitating appropriate prevention and interventions, further demonstrating the role that dental teams can play in assisting with management of the growing health and economic burden of T2DM.

Aims and Objectives

The objective of this review is to synthesize current evidence supporting dental teams' identification of individuals at an increased risk of or suffering from undiagnosed NDH or T2DM in dental specialist care settings. Evidence evaluated includes the opinions of key stakeholders, barriers to and facilitators of subject identification and the clinical methods used.

Materials and Methods

The present study was undertaken using a pre-specified protocol and reported according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines for conducting and reporting systematic reviews and meta-analyses [27].

The Population, Intervention, Reference standard, Target condition (PIRT) format was followed for this review whereby [P] were stakeholders in the delivery of dental care, including patients aged greater than 18 years attending dental services, healthcare professionals and organizations involved in the delivery of dental care, [I] were the described screening modalities, [R] was the method by which NDH or T2DM was diagnosed and [T] was NDH or T2DM.

Inclusion Criteria

The inclusion criteria for the study included articles which met the following criteria:

- Risk assessment for NDH/ T2DM was undertaken in a hospital or specialist care dental setting.
- Opinions of stakeholders relating to diabetes risk assessment in dental settings were sought.
- Study subjects were adults (> 18 years of age).
- The article was written in the English language.

Search Strategy

Electronic bibliographic databases were searched, including MEDLINE, PubMed, the Cochrane Library, Clinicaltrials.gov and Web of Science. The reference lists of all eligible

full texts were searched for additional papers. The search strategy (Table 1) included terms relating to or describing the identification of NDH or T2DM in dental settings. The search terms were adapted for use with other bibliographic databases. Restrictions to English language were applied and searches were limited to dates between January 1950 and October 2019.

Data Extraction and Management

The titles and abstracts of all returned papers were screened for the inclusion criteria. For included papers, full texts were reviewed, and any further exclusions determined by consensus. Reasons for exclusion at the full-text stage were recorded (Fig. 1). Electronic data extraction forms were developed, piloted and employed for all data extraction.

Strategy for Synthesis

It was anticipated that included studies would be highly heterogenous, resulting in a descriptive analytical approach. The descriptive synthesis was structured around the objectives of this review.

Risk of Bias Assessment

Two independent reviewers (ZY and JB) assessed the articles describing screening undertaken in a dental setting. Quality of the papers was assessed using a published and validated risk of bias assessment tool, the "United States Preventative Task Force Criteria for Assessing Internal Validity of Individual Studies".

Table 1 Search strategy: example of search strategy used in PubMed

Search terms used
(Screening[Title/Abstract] OR "risk assessment"[Title/Abstract] OR "case detection"[Title/Abstract] OR "case finding"[Title/Abstract] OR "case identification"[Title/Abstract] OR "risk detection"[Title/Abstract] OR diagnosis[Title/Abstract])) AND (diabetes[Title/Abstract] OR TTDM[Title/Abstract] OR T2DM [Title/Abstract] OR diabetic[Title/Abstract] OR pre-diabetes[Title/Abstract] OR prediabetes[Title/Abstract] OR NDH[Title/Abstract] OR hyperglycaemia[Title/Abstract] OR hyperglycemia[Title/Abstract] OR dysglycaemia[Title/Abstract] OR dysglycemia[Title/Abstract])) AND (dental[Title/Abstract] OR dentistry[Title/Abstract] OR dentist[Title/Abstract])

Results

The search strategy yielded 52 papers to be included. Eleven studies were focused on stakeholder opinion. Twenty-eight studies were primarily focused on undertaking risk assessments. The remaining studies had multiple elements including risk assessment and recording of stakeholder opinions.

The risk of bias assessment (Supplementary Table 2) demonstrated acceptable concordance between the two independent examiners (ZY and JB) with a kappa of 0.75. Where there was disagreement in initial quality grade ($n = 9$), this was resolved through discussion and consensus in each case. The majority of articles were deemed to be of good quality, demonstrating a low risk of bias ($n = 18$). Seventeen articles showed a moderate risk of bias and one article was deemed to have a high risk of bias.

Eleven of the returned articles primarily focused on the opinions, attitudes and perceptions of stakeholders. Of these, five articles were related to patient perception, two to dental provider perceptions and the remaining four to dental hygienists, dental students, physicians and "authorities and organizations" (Table 2).

Among studies that asked patients whether they felt it was "important" that dentists identify individuals at high risk of T2DM, patient support was strong, in a range of 73%–87% [33, 35, 36, 39–41]. In addition to this acknowledgement, most patients surveyed were willing to undergo chairside screening methods that yielded immediate results and discuss the results of such tests with their dentist [35, 36, 39, 40].

In support of the positive patient opinion, one study reported that more than 60% of dentists surveyed believed that addressing T2DM was important to their role as a dentist, while 86% claimed to advise their patients with T2DM about their increased periodontal risk and 18% reported that they provided additional diabetes-related services [29]. Two-thirds of dentists in another study stated they would be interested in performing blood glucose monitoring if the costs were reimbursed [31]. A further study assessing the views of dentists reported that most felt it was important to conduct screening for diabetes (76%), and 96% of respondents were willing to refer patients to a primary care physician for consultation. When methods of risk assessment were discussed, the majority were happy to collect oral fluids for salivary diagnostics (88%) or conduct medical screening that yielded immediate results (83%). The respondents in this particular study were significantly more willing to collect saliva than record height and weight measurements or undertake FSB collection. "Insurance" was also significantly less important to the dentists compared to time, cost, liability or patients' willingness [29].

In addition to the qualified dental workforce, one study sought the opinion of dental students to determine their opinions and willingness to assess patients for NDH/ T2DM.

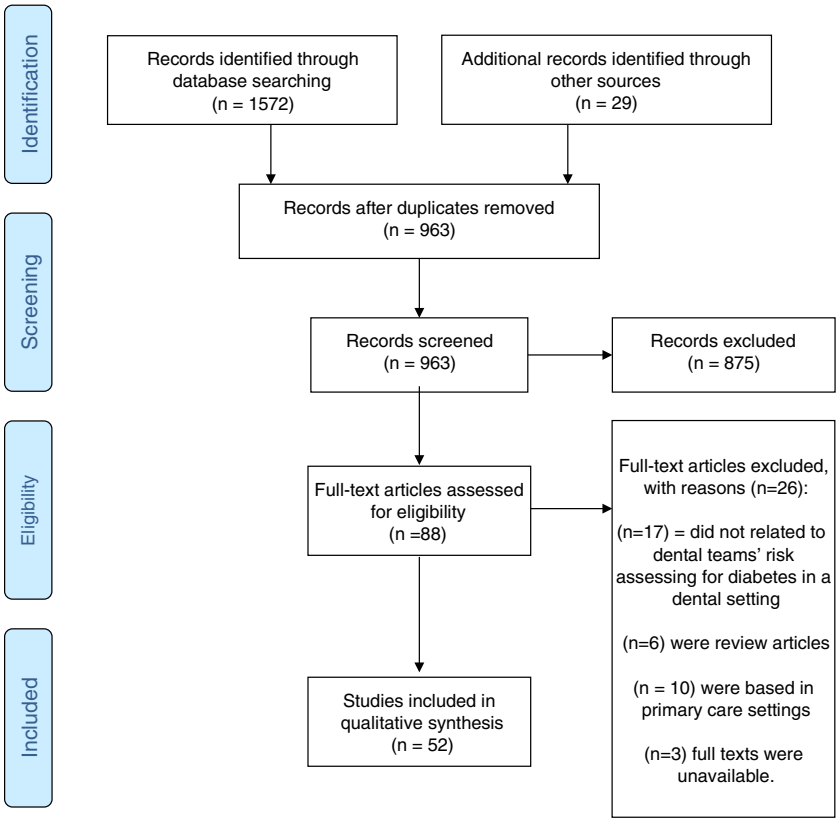

Fig. 1 PRISMA flow diagram for filtration of the search results

There was a high acceptability (84%) for FSB collection among dental students. The key factor for their acceptance was appropriate training in the required techniques [28].

In a single study reflecting opinions of dental hygienists, 85% stated they were willing to conduct screening that yielded immediate results. Ninety-four percent of dental hygienists surveyed were willing to refer patients for medical consultation if required. When asked which considerations they felt were most important, over 97% of respondents stated dentist/owner support, patient willingness and time and adequate training [42].

A study of 1508 physicians reported that 71% felt it was beneficial for dentists to conduct screening for T2DM. Respondents were willing to discuss results with the dentist (76%) and accept patient referrals (89%). The majority of respondents also felt it was unimportant that the medical referral came from a dentist rather than a physician. The factor physicians felt most important was patient willingness, and overall, primary care physicians considered chairside medical screening in a dental setting to be valuable and worthwhile [34].

One study of patients and providers identified themes that arose from the interviews, including "a good chance to check", "patient choice" and "a new way of interacting and viewing the dental visit". This study suggested that both patients and dental providers believe that dental visit is an opportune situation for diabetes screening.

The principal barriers to undertaking screening for T2DM in dental settings were time, adequate training, support of the dentist or dental practice owner and patient willingness. Interestingly, in one study that assessed the willingness of racial/ethnic minority older adults to receive hypertension and diabetes screening as part of routine dental visits, five key themes emerged. These included that they found chairside risk assessment to be acceptable, that as older adults they found screening for conditions by healthcare professionals to be routine practice, that the interrelationship between oral and general health was appreciated, and that they perceived benefit to chairside screening. In some cases, it was also felt that chairside screening for general health conditions may reduce dental anxiety [35]. This study also identified key themes relating to patient-perceived barriers, which included that for some, dental fear may limit the acceptability of dental teams conducting chairside screening. Additional themes identified included that given the routine nature of screening for this demographic that there was a perceived lack of need for dental care and chairside screening in addition to a mistrust of dental providers as primary care providers among some of the sample [35].

Another concern cited was the poor follow-up rates with primary care medical practitioners. Poor follow-up was attributed to barriers including patients' inadequate knowledge about diabetes, lack of understanding about the importance of follow-up, "general business", financial concerns, fear

Table 2 Summary of journal articles exploring stakeholder perceptions, attitudes and opinions to screening for diabetes in dental settings

Paper	Reference	Year	Country	Stakeholder	Key finding (Barriers and facilitators) key-findings
Anders et al. "Dental students' glucometer experience and attitudes toward diabetes counselling, monitoring, and screening: a comparative study."	[28]	2014	USA	Dental students	Dental students' attitudes toward T2DM counselling, monitoring and screening were generally positive and more positive for those students who had greater experience using a glucometer. A high acceptance rate (84%) for FSB among dental personnel who had hands-on experience using a glucometer was reported.
Esmeili et al. "Dentists' attitudes and practices related to diabetes in the dental setting."	[29]	2009	USA	Dentists	Sixty-one percent of respondents believed that addressing T2DM was important to their role, 86% advised patients with T2DM about periodontal risks, 18% provided T2DM-related services, 47% reported they knew how to assess for diabetes, and 42% felt well prepared to intervene with patients with diabetes. 66% of dentists reported interest in performing blood glucose monitoring if it was reimbursed.
Friman et al. "Medical screening in dental settings: a qualitative study of the views of authorities and organizations."	[30]	2015	Sweden	Authorities & organization	Approached authorities and organizations generally had a positive view of medical screening in dental settings but were uncertain about the concept. Further scientific knowledge and guidelines concerning the topic are needed before it can be commonly introduced, alongside additional research on implementation strategies and long-term follow-up.
Greenberg et al. "Dentists' attitudes toward chairside screening for medical conditions."	[31]	2010	USA	Dentists	The majority thought it was important for dentists to conduct screening for T2DM (76.6%). Respondents were willing to refer patients for consultation with physicians (96.4%), collect oral fluids for salivary diagnostics (87.7%), conduct medical screenings that yield immediate results (83.4%) and collect blood via FSB (55.9%). Respondents were significantly more willing ($P < .001$) to collect saliva than height and weight measurements or FSB. Insurance was significantly less important ($P < .001$) than time, cost, liability or patients' willingness."
Greenberg et al. "American dental hygienists' attitudes toward chairside medical screening in a dental setting."	[32]	2016	USA	Dental hygienists	Given that dental hygienists are involved in preventive and educational activities, medical screening seems like a natural extension to their roles. The majority of respondents (89%) felt it was important to perform chairside screening for T2DM. Majorities were also willing to refer a patient for medical consult (94%), conduct screening that yields immediate results (85%) and to collect data/samples needed (57%–95%). The most important considerations were dentist/owner support (98%), training (97%), patient willingness (98%) and time (98%).
Greenberg et al. "Patients' attitudes toward screening for medical conditions in a dental setting."	[33]	2012	USA	Patients	The majority of respondents were willing to have a dentist conduct screening for medical conditions with 73% specifically open to T2DM screening. The majority of clinic and private practice respondents were willing to let the dentist conduct screening that yields immediate results (90% vs 76%), discuss results during their dental visit (89% vs 79%), refer them for a medical consult (86% vs 76%) and send samples to an outside laboratory (76% vs 59%). Among potential barriers specified, both clinic and private practice respondents felt confidentiality

Table 2 (continued)

Paper	Reference	Year	Country	Stakeholder	Key finding (Barriers and facilitators) key-findings
					was important (94% vs 83%) followed by time (90% vs 80%) and insurance coverage (82% vs 80%). Seventy-six percent of clinic respondents were willing to pay $10–20, and 65% were willing to pay $21–30; the percentage who were willing to pay more than $30 dropped dramatically.
Greenberg et al. "Physicians' attitudes toward medical screening in a dental setting."	[34]	2015	USA	Physician	Of 1508 respondents, the majority felt it was valuable for dentists to conduct screening for T2DM (71%). Respondents were willing to discuss results with the dentist (76%) and accept patient referrals (89%), and a small majority felt it was unimportant that the medical referral came from a dentist rather than a physician (52%). The most important consideration was patient willingness (mean rank 2.55). Primary care physicians considered chairside medical screening in a dental setting to be valuable and worthwhile.
Greenblatt et al. "Acceptability of Chairside Screening for Racial/Ethnic Minority Older Adults: A Qualitative Study."	[35]	2017	USA	Patients	Five themes were manifest in the data regarding the willingness of racial/ethnic minority older adults to receive hypertension and T2DM screening as part of routine dental visits: (1) chairside screening is acceptable, (2) screening is routine for older adults, (3) the interrelationship between oral and general health is appreciated, (4) chairside screening has perceived benefits, and (5) chairside screening may reduce dental anxiety.Reservations centred on four major themes: (1) dental fear may limit the acceptability of chairside screening, (2) there is a perceived lack of need for dental care and chairside screening, (3) screening is available elsewhere, and (4) mistrust of dental providers as primary care providers.
Sansare et al. "Indian patients' attitudes toward chairside screening in a dental setting for medical conditions."	[36]	2015	India	Patients	A survey given to a convenience sample of adult patients visiting five university-based dental clinics (clinic group) and one private practice showed that both patient groups felt it was important for dentists to identify increased risk for medical conditions. The majority of patients were willing to have a dentist screen for specified conditions including T2DM (84.5% clinic and 77.5% private). The majority of patients were willing to participate in chairside screening that yielded immediate results and discuss results immediately.
Scambler et al. "Summary of: Patients' attitudes toward screening for diabetes and other medical conditions in the dental setting"	[37]	2014	UK	Patients	A self-administered questionnaire distributed to adult patients (≥ 18 years) attending 2 primary care dental clinics and 16 general dental practices in South West England. Overall, 87% of respondents thought that it was important or very important that dentists screened patients for medical conditions such as T2DM; 79% were very willing to let a dental team member carry out screening. Significantly higher proportions of respondents in the primary care clinics indicated willingness compared to general practices. Nearly two-thirds of primary care clinic respondents and over half of general practice patients indicated that they would be

Table 2 (continued)

Paper	Reference	Year	Country	Stakeholder	Key finding (Barriers and facilitators) key-findings
					willing to discuss test results with the dental team. Overall, 61% had never knowingly been screened or tested for T2DM; 20% reported that they had been tested within the previous 12 months.
Rosedale et al. "Diabetes screening at the periodontal visit: Patient and provider experiences with two screening approaches"	[38]	2012	USA	Patients and provider	FSB samples from 120 patients and GCB samples from 102 of these patients were collected on special blood collection cards and sent to a laboratory for HbA1c testing, with test results sent to the patients from the laboratory. Quantitative and qualitative data collection and analyses of patients and providers were conducted. Themes that arose from the interviews with providers and patients include "a good chance to check", "patient choice", "FSB versus GCB testing" and "a new way of interacting and viewing the dental visit". Periodontal patients and dental providers believe that the dental visit is an opportune site for T2DM and generally prefer GCB to FSB collection. GCB testing is well-tolerated, convenient and acceptable to patients and reduces time and liability obstacles for dental providers to conduct T2DM screening.

and denial [38]. Only 53% of participants with elevated HbA1c values contacted their primary medical healthcare provider within 2 weeks as recommended in a pilot study [43]. Though a UK-based team also found that following up with a primary medical care provider was a potential barrier, they reported that patients were three times as likely to contact their general practitioner (GP) if they had received two positive screening results when compared with a patient with only one positive result [44]. A Swedish study with a 3-year follow-up of patients found that 89% had attended their healthcare provider within that time frame and that 9% of those had been formally diagnosed with T2DM. The study also identified that of those who had screened negative, 80.5% attended the primary healthcare centre, and eight (0.6%) were found to have T2DM. Screening sensitivity was 52.9%, and specificity was 90.6% with positive predictive value of 5.8%. According to this study, when the population is limited to those 40–75-year-olds with a BMI > 25 kg /m2 and 30-to 75-year-olds with a BMI > 30 kg /m2, the number needed to screen was 96 [45].

Twenty-eight articles returned from the search involved dental teams undertaking various screening methods within a specialist dental care setting (Supplementary Table 1). The majority of these studies ($n = 10$) employed a combination of screening methods, most commonly questionnaire followed by FSB sample collection. Within the literature, a range of screening methods were explored including questionnaires alone ($n = 1$), questionnaire in addition to another test modality ($n = 6$), FSB collection alone ($n = 4$), FSB in addition to another risk assessment modality ($n = 11$) and GCB collection ($n = 6$). Where blood samples were recorded, this was HbA1c in ten cases (Supplementary Table 1).

Discussion

Principle Findings

Opinions of Key Stakeholders

Overall the opinions of stakeholders relating to dental teams' engagement in risk assessment of patients for NDH/T2DM were positive. Furthermore, among patients there was strong support for tests which were able to yield immediate results. These findings appeared to transcend specific healthcare systems and cultural barriers, as similar results were reported irrespective of their being conducted in different countries with different models of healthcare provision, including state-funded healthcare systems in Europe [39–41], insurance-based and private healthcare within the USA [33] and university-based clinics and private settings in Asia [36].

Among methodologies currently in use, there was a general preference for GCB instead of FSB collection. GCB testing was well-tolerated among volunteers and was deemed both convenient and acceptable to patients. Additionally, it was

found to reduce the obstacles of both time and liability for dental providers conducting the diabetes screening [38].

The sentiment expressed by patients, that dental teams undertaking risk-assessment for NDH/ T2DM was important, appeared to be shared by dental service providers [29, 31]. Dental hygienists also play a key role in the delivery of preventative advice and educational activities in dental practice. Thus, utilizing this skilled workforce in the delivery of NDH/ T2DM risk assessment appears to be a natural extension of their current duties, especially given their own strong support for such an intervention. Another key workforce to consider is primary care medical practitioners. Should any such additional services commence within dental settings, it is of paramount importance that any duplication of testing and generation of unnecessary referrals to primary care physicians is minimized. However, where physician opinion was sought in the literature, they were in support of the concept of utilizing dental teams to identify NDH /T2DM.

Given that patients, physicians and dental teams appear to be in favour of developing the role of the dental team to include risk-assessment for NDH/ T2DM, it was interesting to also understand the role of dental undergraduate students. These students are key to the future delivery of this additional service. One study based in the USA sought the attitudes of students toward counselling, monitoring and screening for T2DM; results were positive provided appropriate training in the required techniques was provided [28].

Barriers and Facilitators

Several patient-reported barriers and facilitators were identified within the literature including how the individuals' perception of dental teams and their own fears and anxiety may prevent uptake of additional services in such a setting. However, the patients also reported an appreciation of the interrelationship between oral and systemic disease and recognized potential benefit of routine testing by healthcare professionals [35].

A further barrier to dental teams undertaking risk assessment for NDH/ T2DM was the poor rate of follow-up with primary care medical practitioners for appropriate diagnosis and management. One study reported that while a majority of patients were interested in T2DM testing in dental offices, most dentists thought the tests were appropriate and simple to undertake and that T2DM screening in dental practice was deemed feasible; poor follow-up by patients, particularly those tested in private practices was a potential concern requiring further study [46].

In the UK based study that reported improved follow-up rates where two screening tests were undertaken, the screening was actually done by a researcher, and there was no analysis of the practices' additional workloads or their impact. Furthermore, the participants were contacted twice by telephone after their visit by the researcher and asked whether they had made an appointment with their GP. In many practices, there may be insufficient staff to undertake such additional steps, which may impact the outcome and result in an even further reduced rate of follow-up [44].

The most frequently cited barriers to uptake of new services were time and cost. Interestingly, a study in the USA found that the direct cost for each HbA1c test was $9 (USD), excluding follow-up medical diagnosis. The mean screening time including patient education was reported as 14 ± 6.2 min. However, given the heterogeneity in methods used and devices available for undertaking each risk assessment method, the costs and time taken for risk assessment are likely to vary significantly. Interestingly, one study reported that 76% of patients were willing to pay $10–20(USD) and 65% were willing to pay $21–30(USD). However, the percentage of who were willing to pay more than $30(USD) reduced dramatically [33].

Risk Assessment Methods Used

This systematic review revealed considerable variation in the methodologies adopted for risk assessing patients in dental settings for NDH/T2DM. Methods reported in the literature ranged from applying clinical guidelines and validated risk-assessment tools to undertaking chairside testing of either GCB or FSB; urinalysis was also undertaken in some cases.

There are several methodologies accepted for use at each stage of study design. Screening criteria employed by studies analysed here were predominantly derived from the recommendations of the American Diabetes Association (ADA) or the National Institute for Clinical Excellence (NICE). The American Diabetes Association (ADA) has developed criteria to classify high-risk patients as being anyone that (I) is over 45 years of age, (II) has a family history of T2DM, (III) has a BMI ≥ 26 kg/m^2, (IV) is sedentary, (V) has hypertension, (VI) has hyperlipidaemia, (VII) is of a certain racial or ethnic group (African American or Hispanic), or (VIII) has had gestational diabetes. The more risk factors an individual has, the higher their risk of developing diabetes. Many studies have applied these criteria prior to undertaking a second level of assessment such as FSB/GCB collection. Similarly, the National Institute for Clinical Excellence (NICE) guidance exists in the UK [47], which outlines similar criteria for high-risk individuals and was used as a "pre-screen" in many of the UK-based studies.

Once a method of study had been determined (Questionnaire, FSB, GCB collection, urinalysis), there are still a number of variables that differentiate the protocols of studies analysed in this review. Accepted "pre-screen" methods include NICE guidance, ADA criteria and validated risk-assessment tools such as "FINDRISC". For a chairside test following "pre-screen", either GCB or FSB collection was employed. Research teams also varied in their biomarker of choice; most chose to measure HbA1c though some opted for

random blood glucose tests. No clinical trials exist comparing the clinical effectiveness and cost-effectiveness of the various combinations of these methods. Thus, it is difficult to compare, contrast and ultimately decide which protocol offers the greatest diagnostic accuracy.

Which Risk Assessment Protocol Appears Most Robust

If risk assessment is to be undertaken in dental practices, it should be targeted to individuals at high risk in order to be time and cost-effective [2, 48, 49]. Existing evidence demonstrates that population-based screening is ineffective in terms of cost and clinical outcome [45]. Therefore, in order to determine those who may be at high risk, a targeted approach is required.

Local guidelines and geographical location have an influence on criteria adoption. For example, the ADA criteria are widely accepted and used across the USA and have been employed in many of the studies analysed in this review. NICE guidance suggests that a validated risk assessment tool such as the "Diabetes UK Risk Score" should be used to identify individuals at high risk of T2DM. It advocates that all non-pregnant adults > 40 years of age, members of high-risk minority ethnic groups (including South Asian, Chinese, African-Caribbean, black African) aged 25–39 years and any people with conditions that place them at increased risk of T2DM should be risk assessed using such validated tools. Where a score above the threshold is obtained, identifying an individual as high risk, they should then undergo a blood test such as HbA1c or fasting plasma glucose [47].

Once a "pre-screen" method has been undertaken to identify those individuals who may be appropriate for formal risk assessment, an appropriate screening method must be selected. Currently, the WHO suggests that provided the patient has symptoms such as polyuria or polydipsia, diagnosis of T2DM can be based on the following:

- A random venous plasma glucose concentration ≥ 11.1 mmol/l
- A fasting plasma glucose concentration ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l)
- A plasma glucose concentration ≥ 11.1 mmol/l, 2 h after oral administration of 75 g anhydrous glucose in an oral glucose tolerance test (OGTT).

Where the patient is asymptomatic, a diagnosis should not be based on a single glucose determination, but a further confirmatory plasma venous blood determination would be required. At least one additional glucose test result on another day with a value in the diabetes range is essential, either fasting, from a random sample or from the 2-h post glucose load. If the fasting random values are not diagnostic, the 2-h value should be used. In 2011 the WHO also determined HbA1c as a suitable method for diagnosing T2DM. They recommended an HbA1c of 48 mmol/mol (6.5%) as the cut-off point for diagnosing diabetes. A value of less than 48 mmol/mol (6.5%) does not exclude diabetes diagnosed when using glucose tolerance tests and that FSB HbA1c should not be used for diagnosis. Where FSB tests are used, they must be confirmed by laboratory-based venous HbA1c test in all patients [1].

In dental settings, the aim is not to diagnose and manage T2DM but to identify those individuals at high-risk who may benefit from formal intervention and referral to a physician for suitable follow-up. The test used must meet these objectives. Given the potential opportunistic nature of screening in this setting, OGTT and fasting plasma glucose samples are unlikely to be practical or feasible, leaving HbA1c and random plasma glucose as the remaining viable options.

In 59% of the studies contributing to this review where some form of risk assessment was undertaken in a dental setting, HbA1c was selected as the marker of choice. This was likely chosen because HbA1c provides a measure of the glucose bound to haemoglobin and is a reflection of the patient's glucose control over approximately 90 days. HbA1c has recently been advocated by the ADA as the "gold standard" test for screening and diagnosing diabetes, and it does not require the patient to fast prior to their appointment, making it practical for use in a dental setting. The decision to be made then is how to collect the blood sample. A venous sample collected and sent to a laboratory, although considered the gold standard, is time-consuming and costly and potentially requires certain members of the dental team to undergo additional training. Furthermore, as evidenced in the literature reporting on patient opinions, those tests which provided immediate results were most favoured [33]. Thus, given that chairside HbA1c testing has been shown to consistently provide results that strongly correlate with laboratory assays, and can yield results in as little as 5 min, this may be the preferred option [50].

The two methods of chairside testing covered in the literature are GCB and FSB collection. Six studies compared GCB with FSB; the concordance of the two methods was generally found to be acceptable [51–54]. Some studies reported that patients may find oral sampling less invasive and more comfortable than FSB collection [38], although it was noted that it is not always feasible to obtain blood from the gingival crevice [52–55].

Areas for Further Research

Though there is an abundance of literature relating to the use of dental practices for identifying individuals with NDH/T2DM, significant further research is required. Specifically, research into determining the most clinically and cost-effective methods of risk assessment, with a suitable follow-up period to determine the proportion of patients who go on to

receive a formal diagnosis of NDH/T2DM with a primary care medical practitioner.

Conclusions

The literature demonstrates that stakeholder opinions, including those of patients, dentists, dental hygienists, physicians and dental students, are all generally positive about the utility of dental settings to identify individuals who are at high risk of developing T2DM or who may unknowingly have the condition. This support crosses healthcare boundaries and has been explored globally. The primary barriers continue to be related to time and cost, though concern about poor follow-up of those individuals highlighted as potentially at-risk was also noted. The literature is replete with a wide range of available methodologies for identifying at-risk individuals. It would appear that a two-staged risk assessment process utilizing a prescreen or validated risk score followed by a chairside HbA1c sample may be most appropriate approach. However, this has yet to be confirmed by any large-scale clinical trial comparing different combinations of the myriad of screening methodologies available. In summary, although some research has been undertaken to determine opinions and feasibility of utilizing the dental workforce to risk assess for NDH/ T2DM, further work is needed to assess both the clinical and cost-effectiveness of such an approach and to establish clear protocols and patient care pathways.

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Compliance with Ethical Standards

Conflict of Interest Zehra Yonel, Joanna Batt, Rosemarie Jane E Cerullo, Laura J Grey, and Iain Chapple declare that they have no conflict of interests.

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Patients' attendance patterns to different healthcare settings and perceptions of stakeholders regarding screening for chronic, non-communicable diseases in high street dental practices and community pharmacy: a cross-sectional study. Page 37

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Patients' attendance patterns to different healthcare settings and perceptions of stakeholders regarding screening for chronic, non-communicable diseases in high street dental practices and community pharmacy: a cross-sectional study

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ABSTRACT

Objective Non-communicable diseases (NCDs) impose a significant health and economic burden. This study aimed to assess the differential attendance patterns of public to different healthcare professionals and gauge the opinions of key stakeholders towards screening of NCDs by allied healthcare professionals.

Design Questionnaires were designed piloted and subsequently completed by key stakeholders. The results were analysed descriptively.

Setting Public questionnaires were undertaken in a West Midlands transport station and Public Markets. High street dental and community pharmacy settings were selected via local clinical and research networks. Healthcare professionals were identified using professional networks and were emailed a web link to an online survey.

Participants 1371 members of the public, 1548 patients and 222 healthcare professionals (doctors general practitioner (GP), dentists general dental practitioner (GDP) and pharmacists) completed the questionnaires.

Outcome measures The outcome was to compare attendance patterns at GDP and GP practices to determine whether different populations were more likely to access different healthcare professionals, this included determining when patients were last screened for NCDs by their GP. Additionally, the willingness of patients to undergo the required intervention and the opinions of stakeholders regarding the concept of screening for the specified NCDs in general dental and community pharmacy settings were also explored.

Results 12% of patients who reported seeing a GDP biannually reported that they had not had contact with a GP in the last year. Over 61% of the public reported attending a GDP biannually, of this group 48% reported having never had a check-up at the GP. All stakeholders surveyed were in broad support of the concept of allied health professionals undertaking screening for specific general health conditions.

Conclusions This study has established that allied healthcare professionals may have access to different cohorts of the population to GPs. If GDPs and pharmacists have access to patients who are not using healthcare services elsewhere, they may be ideally placed to risk assess, and where appropriate offer preventative advice and test for NCDs.

Strengths and limitations of this study

- The main strength of this study was the large sample size. In total 2919 questionnaires were returned by the public and patients with a further 222 healthcare professionals completing the questionnaires.
- The results of this study align closely with the findings from studies in the UK and USA.
- In the UK, screening is controversial, National Institute for Health and Care Excellence guidelines exist on risk assessing and screening for type 2 diabetes mellitus, however, the UK National Screening Committee does not currently advocate screening for non-communicable diseases.

INTRODUCTION

The prevalence of chronic, non-communicable diseases (NCDs) is increasing worldwide and their impact on the healthcare economy is substantial[1–3] with 92% of older adults having at least one NCD and 77% having two NCDs.[4] The increasing prevalence of NCDs is partly due to an ageing population, and partly due to an increase in prevalence of shared risk factors among multiple NCDs, such as sedentary lifestyles, diets high in refined carbohydrates, smoking and

obesity. Furthermore, risk factors for NCDs contribute a significant economic burden, accounting for over 45% of total National Health Service (NHS) costs in the UK in 2006–2007, at approximately £43 billion.[5]

The National Institute for Health and Care Excellence (NICE) currently recommend that allied healthcare professionals, including community pharmacists and general dental practitioners (GDPs), should risk assess for type 2 diabetes mellitus (T2DM).[6] For example, for T2DM data from the USA suggest that screening for T2DM in a dental setting is effective in identifying both prediabetes and diabetes.[7–9] Early detection also led to the instigation of cost-effective lifestyle change measures, rendering a proportion of prediabetes patients normoglycaemic.[10] A further survey from the USA showed that 24% of people did not have contact with a general healthcare provider in 2008, yet 23% of those sampled did see a dentist in that year.[11] Furthermore, UK government policies have been set out, actively encouraging dental professionals in the provision of general health promotion[12 13] as GDPs already deliver advice on diet and smoking cessation. It has been suggested that highly skilled primary healthcare professionals, such as pharmacists and dentists (GDPs), may develop new roles and work more closely with general practitioners (GPs) to create effective multidisciplinary teams and care pathways, and provide a wider range of services such as early detection of disease.[14]

The 2011 Pharmaceutical Group of the European Union survey showed that 98% of European patients can reach their nearest community pharmacy within 30 min, while 58% indicated that their closest community pharmacy was within 5 min of their home. In addition, over the past four decades, there has been a move in pharmacy practice away from the traditional focus on dispensing towards a more patient-centred clinical role.[15] UK policy and pharmacists' professional organisations have stressed the potential of community pharmacists to extend their roles in patient care services to include services such as screening for NCDs. This role has been emphasised in policy papers calling for a wider use of community pharmacists in primary patient care.[16–18]

The development of government policies and guidelines advocating the role of allied healthcare professionals in risk assessment, prevention programmes and risk identification for NCDs suggests that a collaborative approach to tackle the growing NCD burden is required. However, the opinions of members of the public, patients and relevant healthcare professionals in this matter remain poorly explored.

Thus, the aim of this study was to collect preliminary data to provide insight into the differential attendance patterns of public and patients to different healthcare providers, and the perceptions of key stakeholders including members of the public, patients and healthcare providers (GPs, GDPs and pharmacists), regarding risk-targeted screening programmes in dental and pharmacy settings for specific NCDs (T2DM, cardiovascular disease (CVD), chronic kidney disease (CKD) and respiratory chronic obstructive pulmonary disease, COPD) known to incur a significant health and economic burden.

The choice of targeting particular diseases for screening is supported by the fact that:

1. Strong evidence suggests that the majority of patients with objective COPD are not aware of their condition, and this leads to a significant delay in diagnosis and potential treatment.[19]
2. Both T2DM and hypertension tend to be asymptomatic and are usually not diagnosed until patients develop symptoms.[20]
3. Atrial fibrillation is a major treatable risk factor for stroke, but it may be hard for patients to self-detect, because it is frequently silent and intermittent[21 22];
4. Early diagnosis of CKD and immediate referral are key steps in the management of CKD because this allows implementation of preventive measures that delay or even halt progression of CKD to end-stage renal disease.[23]

MATERIALS AND METHODS

Patient involvement

The development of the research question was informed by discussions with an advisory group comprising senior dental and medical academics working in the fields of NCDs. The research question was then taken to patient focus groups and refined following discussions with patient and public advocates at a health awareness engagement event (AGEWELL).

Patients were involved in the design of the study through feedback and discussions relating to the questionnaire design.

Results will be disseminated through publication, presentation at conferences and returning to the annual AGEWELL engagement event to present findings.

Surveys

Questionnaires were developed that explored the attitudes of the public, patients and registered healthcare professionals (GPs, GDPs and pharmacists). Data were collected on attendance with healthcare professionals, participant demographics and their opinions on having general health checks in the specified setting.

No personal identifiers were collected.

Public survey

To assess the views of members of the public, we conducted surveys in two different settings, Birmingham New Street Railway Station (n=909) and Birmingham Public Markets (n=462), between June and September 2016. There was no predefined target sample size; instead, 6 days were spent at each site with an aim to recruit as many participants as possible. Potential participants were informed about the study and offered a patient information sheet, information posters were displayed explaining the study. Participants who verbally

consented to participate were then asked to complete the electronic questionnaire on a tablet computer (figure 1).

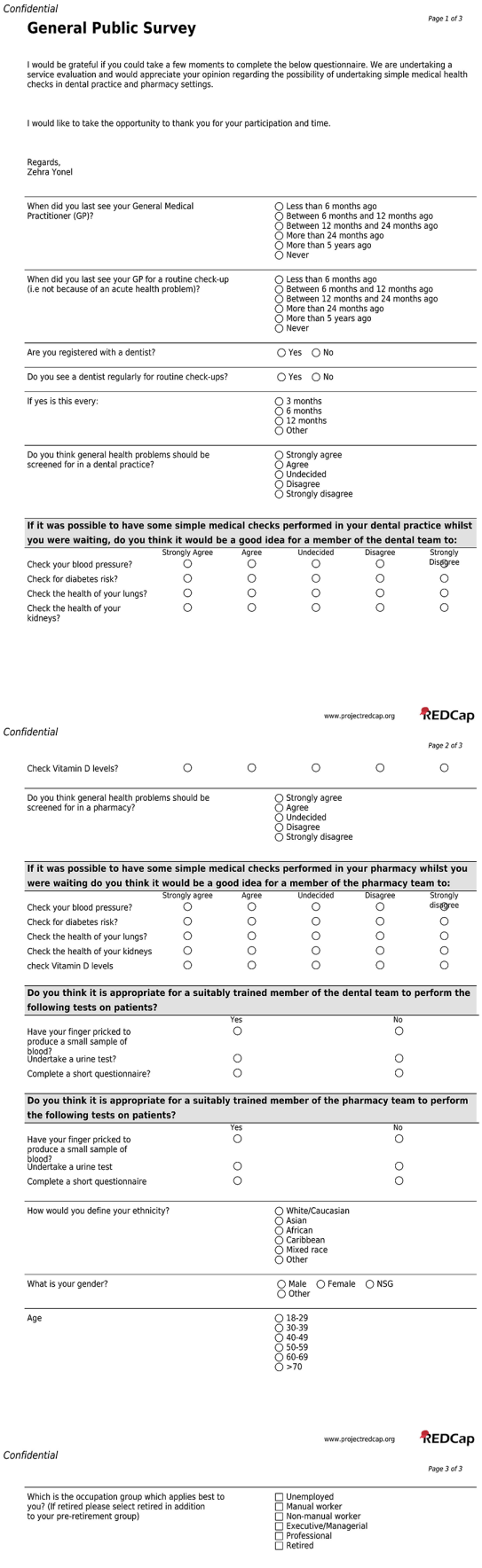
In addition to basic demographic data, including age, ethnicity, gender and occupational status, questions were asked regarding last attendance with a GP and last time a GP surgery was visited for a check-up (ie, not due to an acute health concern). Participants were also asked whether they are registered with a dentist, whether they see a dentist for a routine check-up and, if so, at what frequency. In addition, participants were also asked whether they felt general health problems should be 'screened' for in a dental or pharmacy setting. Participants were asked their opinions regarding screening for specific conditions including hypertension, diabetes, lung health and kidney health, on a 5-point Likert scale. Similarly, patients were asked to rate their willingness to undergo a finger-prick capillary blood test, urine test or complete a questionnaire for screening purposes. These questions were asked separately for screening in dental practice and for a community pharmacy setting.

Patient surveys

To assess the views of patients, surveys were conducted in dental practices and pharmacies. Patients were identified from 13 NHS dental practices in England (n=515) and a private dental practice in Scotland (n=500) and 25 community pharmacies in England (n=533). Similar to the public questionnaires, information posters were displayed explaining the study. Patients were told about the study and offered a patient information sheet. If patients verbally consented to participate, a paper questionnaire was made available for them to complete and return to the practice staff. Content and format of the patient questionnaire was similar to that of the public questionnaire.

Professional surveys

To determine the views of healthcare professionals, GPs (n=48), GDPs (n=129) and pharmacists (n=45) were contacted by email via known professional networks including the clinical research networks. The email contained a participant information sheet and electronic link to the online questionnaire. The questionnaire requested participants to disclose their occupation and whether they worked on a private, NHS or mixed (both private and NHS) basis. The respondent was also asked their opinion regarding dentists and pharmacists screening for specified NCDs (hypertension, diabetes, CKD, COPD). The survey also determined whether professionals felt it would be appropriate for a suitably trained member of the dental/pharmacy team to perform finger-prick capillary blood tests, questionnaires or urinalysis on patients to obtain the relevant biomarker information. Further to this, demographic data in terms of age, gender, location of practice were also recorded.



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General Public Survey

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I would be grateful if you could take a few moments to complete the below questionnaire. We are undertaking a service evaluation and would appreciate your opinion regarding the possibility of undertaking simple medical health checks in dental practice and pharmacy settings.

I would like to take the opportunity to thank you for your participation and time.

Regards,
Zehra Yonel

When did you last see your General Medical Practitioner (GP)?
- ○ Less than 6 months ago
- ○ Between 6 months and 12 months ago
- ○ Between 12 months and 24 months ago
- ○ More than 24 months ago
- ○ More than 5 years ago
- ○ Never

When did you last see your GP for a routine check-up (i.e not because of an acute health problem)?
- ○ Less than 6 months ago
- ○ Between 6 months and 12 months ago
- ○ Between 12 months and 24 months ago
- ○ More than 24 months ago
- ○ More than 5 years ago
- ○ Never

Are you registered with a dentist? ○ Yes ○ No

Do you see a dentist regularly for routine check-ups? ○ Yes ○ No

If yes is this every:
- ○ 3 months
- ○ 6 months
- ○ 12 months
- ○ Other

Do you think general health problems should be screened for in a dental practice?
- ○ Strongly agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly disagree

If it was possible to have some simple medical checks performed in your dental practice whilst you were waiting, do you think it would be a good idea for a member of the dental team to:

	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
Check your blood pressure?	○	○	○	○	○
Check for diabetes risk?	○	○	○	○	○
Check the health of your lungs?	○	○	○	○	○
Check the health of your kidneys?	○	○	○	○	○

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Check Vitamin D levels? ○ ○ ○ ○ ○

Do you think general health problems should be screened for in a pharmacy?
- ○ Strongly agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly disagree

If it was possible to have some simple medical checks performed in your pharmacy whilst you were waiting do you think it would be a good idea for a member of the pharmacy team to:

	Strongly agree	Agree	Undecided	Disagree	Strongly disagree
Check your blood pressure?	○	○	○	○	○
Check for diabetes risk?	○	○	○	○	○
Check the health of your lungs?	○	○	○	○	○
Check the health of your kidneys	○	○	○	○	○
check Vitamin D levels	○	○	○	○	○

Do you think it is appropriate for a suitably trained member of the dental team to perform the following tests on patients?

	Yes	No
Have your finger pricked to produce a small sample of blood?	○	○
Undertake a urine test?	○	○
Complete a short questionnaire?	○	○

Do you think it is appropriate for a suitably trained member of the pharmacy team to perform the following tests on patients?

	Yes	No
Have your finger pricked to produce a small sample of blood?	○	○
Undertake a urine test	○	○
Complete a short questionnaire	○	○

How would you define your ethnicity?
- ○ White/Caucasian
- ○ Asian
- ○ African
- ○ Caribbean
- ○ Mixed race
- ○ Other

What is your gender? ○ Male ○ Female ○ NSG ○ Other

Age
- ○ 18-29
- ○ 30-39
- ○ 40-49
- ○ 50-59
- ○ 60-69
- ○ >70

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Which is the occupation group which applies best to you? (If retired please select retired in addition to your pre-retirement group)
- ☐ Unemployed
- ☐ Manual worker
- ☐ Non-manual worker
- ☐ Executive/Managerial
- ☐ Professional
- ☐ Retired

Figure 1 Public questionnaire. REDCap, Research Electronic Data Capture.

Table 1 Demographics of public and patient respondents (figures presented as percentage unless otherwise stated)

No of questionnaires returned	Public opinion		Patient opinion		
	New Street railway station	Birmingham Public Markets	NHS dental patients	Private dental patients	Pharmacy patients
	n=909	n=462	n=515	n=500	n=533
Gender					
Male	52	40	38	38	37
Age in years					
18–29	24	22	22	8	15
30–39	15	16	25	12	17
40–49	15	16	20	20	23
50–59	17	15	17	23	19
60–69	15	17	11	25	14
>70	15	15	5	12	12
Ethnicity					
White/Caucasian	78	34	73	97	83
Asian	6	23	22	1	8
Afro-Caribbean	6	35	3	1	4
Mixed	5	4	2	0	5
Other	4	4	0	1	0
Occupation					
Unemployed	9	31	18	3	14
Manual Worker	7	16	15	10	16
Non-manual worker	16	12	13	12	12
Executive/managerial	12	3	10	17	8
Professional	31	11	30	23	24
Retired	25	27	14	34	25

NHS, National Health Service.

Analysis

Summary statistics were calculated using Stata/IC V.12.1 (StataCorp LP).

Data sharing statement

Pseudonymised individual participant data, used in preparation for this manuscript, will be available immediately following publication for a period of 36 months. This will be available to researchers providing a methodologically sound proposal and for the purposes of achieving the aims of that proposal only. Proposals should be directed to the corresponding author. To gain access, researchers will need to sign a data access agreement.

RESULTS

In total, 2919 public and patient questionnaires were returned in this study: Birmingham New Street railway station, (n=909), Birmingham Public Markets (n=462). Patient questionnaires were completed in NHS dental (n=515), private dental (n=499) and pharmacy (n=533) settings (table 1).

Public questionnaires

Attendance

Twenty-two per cent of respondents at New Street railway station and 26% at Birmingham Public Markets reported they had not had any contact with their GP within the preceding 12 months. Almost 10% of the public reported not having seen a GP in at least 5 years (table 2).

Twenty-six per cent of respondents at New Street station and 31% at Birmingham Public Markets reported attending their GP surgery for a routine check-up and not due to an acute illness within the last 12 months. Respondents in public settings were less likely to attend a GP surgery for a routine check-up compared with those patients attending dental or pharmacy settings (table 2).

Seventy-seven per cent of respondents at Birmingham New Street railway station and 61% at the Birmingham Public Markets reported being registered with a dentist. When asked about attendance pattern with a dentist, the most frequently reported appointment interval for both public settings was 6 monthly (table 3).

When comparing attendance of members of the public at their GP or their GDP, 12% of patients who reported

Table 2 Comparison of attendance patterns to general practitioner (GP) practices for the public and those attending pharmacy and dental practices (figures presented as percentage unless otherwise stated)

	Public opinion		Patient opinion		
	New Street railway station	Birmingham Public Markets	NHS dental patients	Private dental patients	Pharmacy patients
	n=909	n=462	n=515	n=500	n=533
When did you last visit your GP?					
Less than 1 year ago	78	74	71	75	83
More than 1 year ago	17	20	22	20	14
More than 5 years ago	5	4	7	5	3
Never	0	3	n/a	n/a	n/a
When did you last visit your GP for a routine health check?					
Less than 1 year ago	26	31	47	43	48
More than 1 year ago	16	24	22	22	23
More than 5 years ago	6	6	28	34	6
Never	52	39	3	2	24

NHS, National Health Service.

seeing a GDP every 6 months reported that they had not had contact with a GP in the last year. Furthermore, of the public respondents that reported being regular dental attenders 48% reported having never had a health check at their GP surgery. An additional 20% of the public who reported being regular dental attenders claimed to have not attended a GP practice for a routine check-up in the last 12 months and of the 48% that reported having never had a check-up at the GP surgery 61% reported attending a dental practice biannually.

Opinions

Public support for screening for medical conditions in both dental and pharmacy settings was strong, with 74% in favour of screening in dental settings and 70% in favour of screening in pharmacy settings. The conditions that most public respondents were in support of screening for were T2DM and hypertension in both dental and pharmacy settings. The public expressed willingness to undergo each of the proposed interventions (urinalysis, finger-prick capillary blood) in both settings with a slight preference for the dental setting.

Table 3 Comparison of the reported frequency of dental check-ups, for those members of the public who reported that they attended a dentist (general dental practitioner) regularly

	If you are a regular dental attender at what frequency do you attend the dentist for check-up appointments?			
	New Street (N)	New Street (%)	Public Market (N)	Public Market (%)
3 monthly	67	9	28	10
6 monthly	479	67	177	63
12 monthly	138	19	71	25
Other	33	5	6	2

Patient questionnaires

Attendance

Twenty-eight per cent of respondents at NHS GDP settings, 25% of respondents at private GDP settings and 17% of patients at pharmacies reported they have not had any contact with their GP within the last 12 months. Seven per cent of respondents at NHS GDP settings, 5% of respondents at private GDP settings and 3% at pharmacies reported having not seen a GP in at least 5 years.

Forty-six per cent of respondents at NHS GDP settings, 57% of respondents at private GDP settings and 51% at the pharmacies reported attending their GP surgery for a routine check-up within the last 12 months.

Patients attending dental or pharmacy settings were more likely to attend a GP surgery for a routine check-up compared with those in public settings. Those patients attending a pharmacy were not asked about dental attendance. When those attending dental practices were asked about attendance patterns the most frequently reported appointment interval was 6 monthly.

When comparing attendance of NHS dental patients at GP and GDP practices, of the 28% of NHS dental patients who reported they had not had any contact with their GP within the last 12 months, 42% were in favour of having NCD screening at their GDP. When comparing the attendance of private dental patients at GP and GDP practices, of the 25% of private dental patients who reported they had not had any contact with their GP within the last 12 months, 65% were in favour of having NCD screening at their GDP practice. When comparing attendance of pharmacy patients at GPs and pharmacies, of the 17% of pharmacy patients who reported they had not had any contact with their GP within the last 12 months 32% were

Table 4 Demographic data of healthcare professional respondents (figures expressed as percentage unless otherwise stated)

	General practitioner	General dental practitioner	Pharmacist
No of questionnaires returned	n=48	n=129	n=45
Gender			
Male	21	61	18
Female	79	39	82
Age in years			
18–29	6	23	36
30–39	21	18	38
40–49	44	26	9
50–59	25	26	11
60–69	4	6	6
70+	0	1	0
Funded			
National Health Service (NHS)	94	38	51
Private	0	13	15
Mixed (NHS and Private)	6	48	33

in favour of having NCD screening at their community pharmacy.

Opinions

Forty-eight per cent of NHS dental patients either strongly agreed or agreed with the concept of screening for NCDs in dental settings. Sixty-one per cent of private dental patients either strongly agreed or agreed with the concept of screening for NCDs in dental settings. Seventy-five per cent of pharmacy patients were in support of screening for NCDs in pharmacy settings. The conditions that most of the public and patients were in support of screening for were T2DM and hypertension in both dental and pharmacy settings.

Healthcare professionals

In total 222 completed questionnaires were returned, of those returned 48% were completed by female healthcare professionals; 58% had been completed by GDPs, 21% by GPs and the remainder by community pharmacists. More than half (51%) of those questioned were treating patients within NHS settings, 34% reported working on a mixed NHS and private basis and 15% reported working on a solely private basis (table 4).

Most GDPs were in favour of risk assessment in a pharmacy setting. A large proportion of GPs and pharmacists were supportive of risk assessment in dental settings (figure 2), but many remained undecided. There was stronger support from healthcare professionals for risk assessment for NCDs in pharmacy settings (figure 3).

DISCUSSION

Statement of principle findings

This study aimed to determine the attendance patterns of the public at different healthcare settings and to gauge public and patient opinions on using allied healthcare professionals to undertake 'screening'. Participants were more likely to attend their dental practice for a routine check-up than their GP surgery. Of those patients who reported being regular attenders to a dental surgery for routine check-ups, almost half claimed that they had 'never' had a routine health-check at their GP surgery. Furthermore, an additional 26% had not had a routine check at the GP practice in more than 12 months. This implies that dental professionals have access to a cohort of patients who are not routinely accessing their GP surgery for health checks.

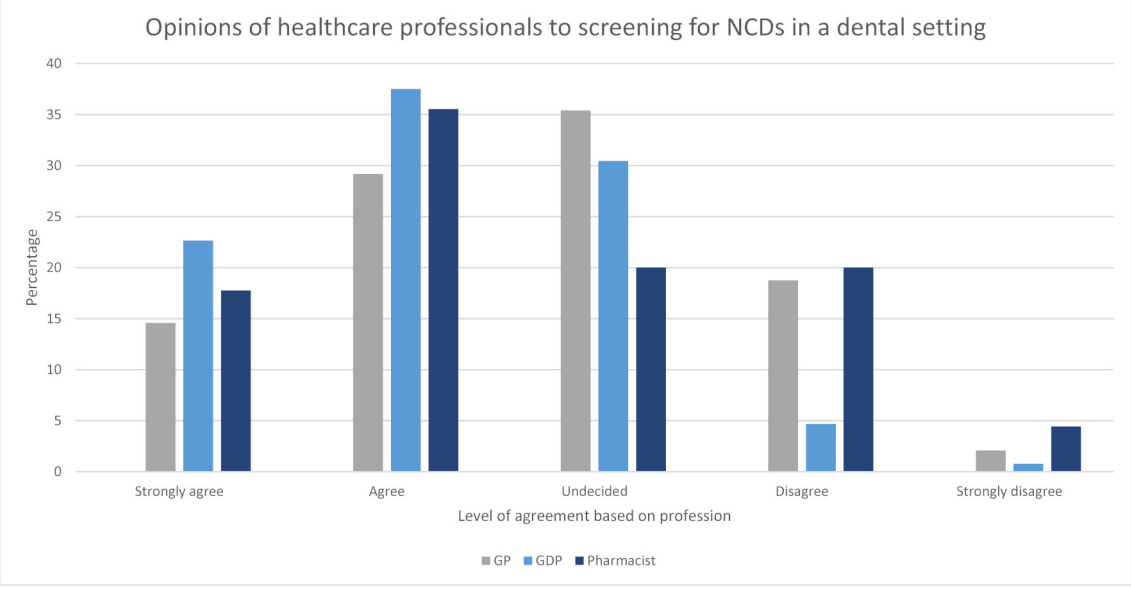

Figure 2 Showing professional opinion to screening in dental practice expressed as a percentage. GDP, general dental practitioner; GP, general practitioner; NCDs, non-communicable diseases.

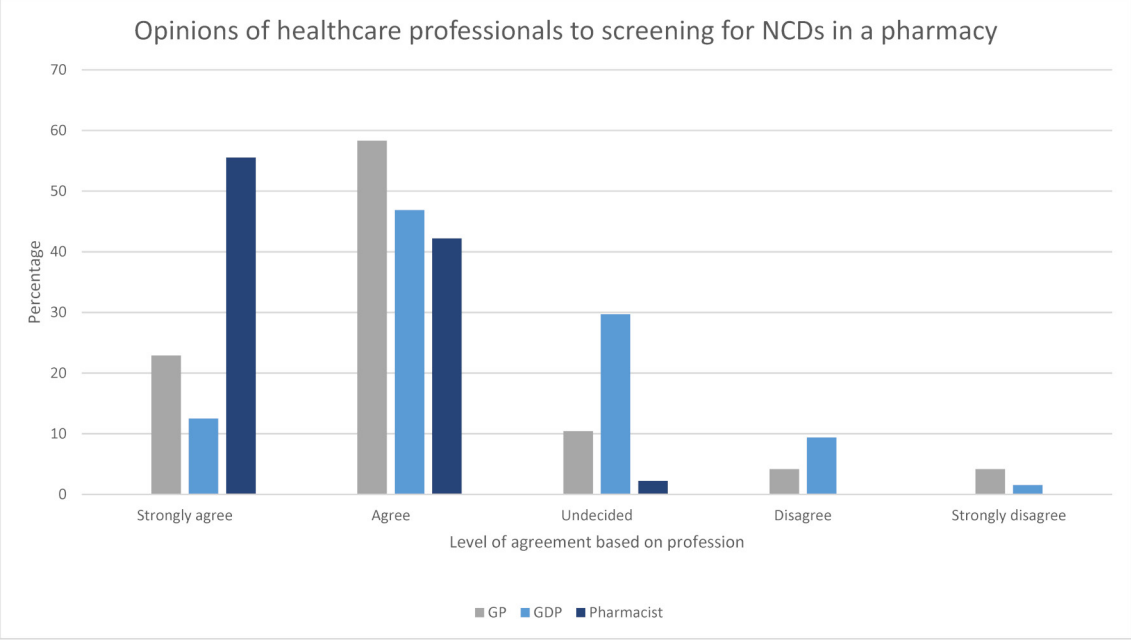

Figure 3 Showing professional opinion to screening in pharmacy expressed as a percentage. GDP, general dental practitioner; GP, general practitioner; NCDs, non-communicable diseases.

All stakeholders surveyed were in broad support of the concept of allied professionals undertaking risk assessment for general health conditions. The public were slightly more in favour for risk assessment in dental compared with pharmacy settings, whereas healthcare professionals expressed slightly greater support for risk assessment in pharmacy compared with dental settings. The conditions receiving the greatest support for risk assessment were T2DM and CVD. The methods for risk assessing that were mostly accepted were validated questionnaires and finger-prick capillary blood testing.

Strengths and weaknesses of the study

The main strength of this study was the large sample size. In total 2919 questionnaires were returned by public and patients with a further 222 healthcare professionals completing the questionnaires. However, the population captured was not representative of the UK population as a whole and caution should be applied in relating findings to the general population. The sampling method used did not allow for calculation of a response rate. Thus, potential bias cannot be ruled out. The NHS dental and pharmacy respondents were the most likely to have attended their GP practice for a routine check-up, with respondents in both public settings being the least likely to attend a GP surgery for a routine check-up. This may suggest that those patients already engaged with healthcare are more likely to take up any proposed risk assessment, should a new service become available. This finding may limit the value of any such service as those in most need of early identification, who are not in contact with a GP are also the group least likely to contact other healthcare professionals.

Strengths and weaknesses in relation to other studies

Health screening in the UK is controversial, although NICE guidelines exist on risk assessing and screening for T2DM, the UK National Screening Committee (UK NSC) currently does not advocate screening for T2DM or the other mentioned NCDs. Despite the current UK NSC position on screening, when asked whether they felt screening for NCD in dental and pharmacy settings was worthwhile most healthcare professionals were supportive of this in both settings.

The results of this study align closely with the findings of Greenberg's study in the USA, which reported that dentists were in support of chairside screening for medical conditions and were willing to undertake the screening procedures.[24] Creanor *et al* undertook a similar study in the UK whereby patients attending dental clinics in the Southwest of England were asked about diabetes screening. They found that 61% of respondents had never knowingly been screened for diabetes, 87% were in support of screening for medical conditions such as diabetes at the dental clinic.[25] This was further supported by a study in Warwickshire where adult patients with diabetes attending medical clinics were asked about screening for diabetes in dental settings. Bowyer *et al* reported that over half of respondents supported the idea of dentists' involvement in diabetes screening.[26]

Furthermore, a study by Bould *et al* found that the uptake of risk assessment methods for diabetes in dental settings was positive, patients were amenable to finger-prick testing and when a two-stage screening process was employed (validated questionnaire prior to finger-prick test) patients were three times as likely to follow-up with

their GP compared with those receiving only one positive result.[27]

In a recent review of community pharmacy clinical services Murray 2016 (PSNC, 2016) concluded that community pharmacists should develop interventions to further prevent disease progression. Previous evidence from systematic reviews and meta-analyses has shown that community pharmacies could be feasible sites for screening for isolated risk factors.[28 29] Screening for individual risk factors in pharmacies has been shown to be effective, in studies in the UK[30] and in countries outside the UK.[31 32] Furthermore, UK public health initiatives have been previously tested in pharmacies and claimed some success, such as healthy living pharmacies (public health-related services) and health checks (cardiovascular risk assessment). However, further research is needed to determine the uptake of pharmacy recommendations and referrals following the screening and the cost-effectiveness of screening in pharmacies compared with screening from other providers.

Meaning of the study

The choice to seek public, patient and professional opinions for using allied health professionals to undertake proactive targeted risk assessment to the specific NCDs was based on the significant health and economic burden that NCDs have on individuals and society as a whole.[33]

Utilisation of allied healthcare professionals would be particularly interesting if different healthcare providers could reach/access different population groups. Our surveys demonstrated that, of those patients who reported being regular attenders to a dental surgery for routine check-ups, almost half of patients claimed that they had 'never' had a routine health check at their GP surgery. Furthermore, an additional quarter of those surveyed had not had a routine check at their GP practice in more than 12 months. This may indicate that dental professionals have access to a cohort of patients who are not routinely accessing their GP surgery for health checks. However, there is a possibility that many GPs use appointments that were not necessarily booked with health checks in mind to offer opportunistic risk assessment to patients they deem high risk. Thus, patients were also asked about general attendance at GP surgeries, and of those respondents who reported attendance at a dental practice within 12 months, 21% claimed to have not attended their GP practice within the same period. Therefore, this still suggests a potential missed opportunity for risk assessment and preventative advice as one in five patients attending dentists have not had contact with a GP practice within that year.

Our findings support the concept that many people only attend their GP when they are unwell, whereas by contrast, they may visit allied health professionals on a regular basis, even when asymptomatic. With longer opening hours for pharmacies and easy accessibility to dental practices, this potentially places dental teams and community pharmacists in an ideal position to target patients for risk assessment and health screening, especially for those who may not visit their GP regularly.

Many pharmacies already successfully offer screening programmes for a variety of conditions. This may be an opportunity to broaden the scope of this service further and given that opinions of stakeholders are comparable across the settings assessed and screening can be performed to good effect in pharmacy settings, it may be of benefit to explore this concept further in dental settings.

Unanswered questions and future research

The reported study has shown that key stakeholders are in broad support of greater utilisation of allied professionals in the early risk assessment and detection of NCDs. Further work is needed to determine feasibility of implementation of these principles and to establish whether the opinions translate into uptake of the service by patients and the public. It is also important to determine whether long-term intervention by allied professionals' results in improved outcomes in patient care and whether that also conveys any health economic benefits. Furthermore, consideration must be given to how such a service would be funded as it is unlikely that healthcare professionals will undertake this risk assessment under existing funding arrangements. Therefore, health economic analysis will need to be undertaken to determine the cost savings to the NHS, or wider society and whether these savings can be used to fund the risk assessment. Another option may be exploring patients' willingness to pay for such risk assessment. Future exploratory work to determine whether allied healthcare professionals would be willing or able to conduct such methods of targeted early detection of NCDs within existing funding arrangements must be considered. Likewise, whether patients would be willing to pay an additional fee or contribution for such a service would need to be determined.

CONCLUSION

The four key players in the NCD global challenge are CVD, respiratory disease, diabetes and cancer. It has been established that allied healthcare professionals may have access to different cohorts of the population and those members of society less likely to visit a GP may be more likely to visit a community pharmacy or general dentist. It is therefore possible that if dentists and pharmacists have access to patients who are not using healthcare services elsewhere, they may be ideally placed to risk assess, and where appropriate offer preventative advice and test for NCDs. In the dental clinic, this may be especially pertinent where those NCDs share common risk factors and associations with primary dental diseases, such as periodontal disease, for which prevention strategies are already established.

Increased collaboration between general medical practitioners and allied healthcare professionals to stem the rise in NCDs, by assisting with early identification,

provision of preventative advice and where appropriate, targeted risk-based identification of disease, may prove beneficial to patients' general health and oral health alike. The results from this survey suggest that all stakeholders appear to be largely supportive of potential risk identification services for NCDs, especially diabetes and CVD in both dental and pharmacy settings.

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Contributor Substantial contributions to the conception or design of the work or the acquisition, analysis or interpretation of data for the work: ZY, PS, AY, ZJ, ILC and TD. Drafting the work or revising it critically for important intellectual content: ZY, PS, ZJ, TD and ILC. Final approval of the version to be published: ILC. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ZY.

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Competing interests ILC acts as a consultant to Oral Health Innovations who provide PreViser and DEPPA risk and disease assessment technologies for dental practices. The other authors of this article have no conflicts of interest to declare.

Patient consent Obtained.

Ethics approval All surveys were approved by the National Research Ethics Service (NRES 16/YH/0293) or the Ethics Committee of the University of Birmingham (RG_15–195).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Pseudonymised individual participant data, used in preparation for this manuscript, will be available immediately following publication for a period of 36 months. This will be available to researchers providing a methodologically sound proposal and for the purposes of achieving the aims of that proposal only. Proposals should be directed to the corresponding author. To gain access, researchers will need to sign a data access agreement.

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RESEARCH ARTICLE Open Access

Patient acceptability of targeted risk-based detection of non-communicable diseases in a dental and pharmacy setting

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Abstract

Background: Non-communicable diseases [NCDs] are the major cause of mortality globally and are increasing in prevalence. Different healthcare professionals' access different population groups; and engaging allied healthcare professionals in risk-driven early case detection of certain NCDs may be beneficial, especially those who have not been tested for NCDs within the previous 12 months.
The objectives of this study were to determine: whether NCD case finding in dental/community pharmacy settings is feasible in terms of patient acceptability, barriers to recruitment, impact on the existing service. Determine time taken to test for: type 2 diabetes risk [T2DM], chronic obstructive pulmonary disease [COPD], hypertension, vitamin D deficiency and chronic kidney disease [CKD]. Determine whether there is added benefit of point of care testing [POCT] to identify diabetes risk compared to a validated screening questionnaire alone.

Methods: An exploratory study was undertaken to explore issues associated with NCD assessment in one dental practice and one community pharmacy within the West-Midlands, UK. Fifty patients > 40 years-of-age were recruited per site. Participants undertook: a questionnaire providing demographic data, any previous NCD diagnosis or positive family history. Validated questionnaires for determining NCD risk [T2DM/COPD]. Chair-side capillary blood [finger-prick] samples for HbA1C, creatinine/eGFR, Vitamin-D.
Prior work had been undertaken to measure the agreement between point of care testing [POCT] devices and a central laboratory method, and to gauge the opinions of participants regarding discomfort experienced using venous (antecubital fossa) and capillary (finger-prick) blood collection, via a 10 cm Visual-Analogue-Scale. The POCT devices demonstrated good concordance with laboratory testing and were acceptable methods of blood collection for participants.

Results: Recruitment rates demonstrated that 8 days were needed to recruit 50 participants and 60% of those approached opted to participate. The principal barrier to participation was time, with average time taken to test being 19mins. Utilising dental and pharmacy settings identified potential cases of previously undiagnosed disease.

Conclusions: Risk-targeted testing for NCDs in high street dental and community pharmacies is both attractive and acceptable to patients.

Keywords: Non-communicable diseases, Screening, Prevention, Dental, Pharmacy

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Background

The prevalence of chronic non-communicable diseases [NCDs] is increasing and their impact on the global disease burden and healthcare economy is substantial. Evidence in 2015 suggested that 92% of older adults have at least one NCD and 77% have two NCDs [1]. The reason for the increasing prevalence of NCDs is, in part, the result of an ageing population, and also due to an increase in the prevalence of risk-factors common amongst most NCDs such as sedentary lifestyles, refined diets and overweight/obesity. In addition to the substantial health burden, risk-factors for NCDs also contribute a significant economic burden, accounting for over 45% of total NHS costs in the UK in 2006–2007, at approximately £43-billion [2].

Allied healthcare professionals in the UK access large proportions of the population who frequently do not access general medical practice [GP] services [3]. Given the growing NCD burden, this study aimed to determine patient acceptability and potential barriers to utilising allied healthcare professionals such as dentists and pharmacists in order to assist GPs with the NCD epidemic, through targeted risk-based assessment and early detection.

Rationale for risk directed early NCD detection in dental practice and community pharmacy settings

Dental

Members of the public usually only attend their GP when they are unwell, whereas, many people routinely visit their dentists on a regular (6–12 monthly) basis, thus facilitating prevention and lifestyle interventions [4]. Evidence from the USA suggests that, in 2008, 24% of people did not have contact with a general healthcare provider, yet 23% of those accessed a dentist during that time [5]. This was also reported for a UK population, where 12% of patients who reported seeing a dentist bi-annually reported they had not had contact with a GP in the same 12-month period [3]. Furthermore, 48% of those who reported being regular dental attenders advised having never had a health check at their GP surgery [3]. With approximately 60% of the UK population registered with a dentist [6], this places dental teams, with access to patients who would not necessarily attend their GP regularly, in an ideal position to target patients for risk assessments.

Pharmacy

The 2011 Pharmaceutical Group of the European Union survey reported that 98% of European patients can reach their nearest community pharmacy within 30 min, while 58% indicated that their closest community pharmacy was within 5 min of their home. This may render pharmacy settings ideal for early identification of NCDs and provision of preventative advice for large population groups, who may not routinely have access to other healthcare professionals. In addition, over the past four decades there has been a move in pharmacy practice away from the traditional focus on dispensing towards a more patient-centred clinical role [7]. United Kingdom [UK] policy and pharmacists' professional organisations have stressed the potential of community pharmacists to extend their roles in patient care services to include screening for NCDs. This has been emphasised in policy papers calling for a wider use of community pharmacists in primary patient care [8–10].

Inter-professional collaboration

The development of government policies and guidelines advocating the role of allied healthcare professionals in risk-assessment, prevention programs and risk identification for NCDs, suggests that a collaborative approach to tackle the growing NCD burden is required [11]. It is currently common for dentists to liaise with GPs in relation to medications a patient may be taking, especially where these may have an impact on oral health, such as calcium channel blockers which may result in gingival overgrowth. Dentists also work closely with a patient's medical team when the dentist suspects underlying conditions based on the oral manifestations of systemic diseases. One such example is poorly controlled type 2 diabetes [T2DM]. T2DM may present with oral signs and symptoms including multiple lateral periodontal abscesses. Recently the International Diabetes Federation and European Federation of Periodontology produced joint guidelines for medical and dental professionals for the effective management of patients with periodontitis and, or T2DM in recognition of the strong associations between oral and systemic health [12].

Community pharmacists play an important role in delivering public health services for example vaccinations, health checks, smoking cessation and weight management to complement GP roles. In addition to pharmacist role in optimising the use of medicines in liaison with GPs, providing advice about safe and effective use of medicines when dispensing to patients with prescriptions for the treatment of diabetes, heart disease and hypertension and thus relieving the pressure on the GP practices and A&E. Furthermore, pharmacists work directly in general practice as part of the multi-disciplinary team, in patient facing roles when managing conditions such as diabetes and hypertension [13]. A recent systematic review and meta-analysis which included 21 RCTs (8933 patients) showed that pharmacists-led interventions, as part of a team in general practice, can significantly reduce medical risk factors of CVD events when managing patients with hypertension, diabetes and dyslipidaemia [14].

Risk-assessments

Risk-assessment strategies need to ideally provide high sensitivity and specificity so we can discriminate between those who truly do and do not have the condition, be acceptable to patients undergoing assessment, acceptable to the professional delivering the assessment and also demonstrate cost-effectiveness. Venous blood samples are often considered the "gold-standard" testing method for diagnosing many NCDs. The feasibility of primary care dental teams and community pharmacies undertaking venous blood sampling to assess for NCDs is low – as this is not within their routine scope of practice, in addition to the time and resources required to test in this way. Alternative methods for undertaking risk-assessments were considered in this study including the use of validated risk-assessment questionnaires and point-of-care testing [POCT] devices.

Validated questionnaires may be effective ways of stratifying the population into risk groups to allow more invasive and costly tests to be targeted to those in the population most in need. Though, the identification of "at risk" individuals with risk-assessment questionnaires are often satisfactory they often have lower sensitivity and specificity than conventional testing methods. But this has to be weighed up against the advantages of ease of testing, patient acceptability and relatively low associated costs. Given that the aims of risk-assessment in primary care dental and pharmacy settings are not to formally diagnose but to indicate those who may be at elevated risk, the reduction in accuracy may be acceptable given the aforementioned advantages.

POCT remains controversial due to the historical challenges associated with a wide range of devices available, each with their own advantages, disadvantages and varying levels of accuracy [15, 16]. However, the improved quality of POCT devices for capillary blood sampling has resulted more recently in NICE and other national bodies recommending their use for diagnosis of certain NCDs [15, 17–20]. Given that we are not proposing primary care dental teams and community pharmacists formally diagnose, but instead identify those who may be at risk and require further management, they may be ideal for the purpose of risk-assessment in primary care and community settings. The relative ease of use, the near immediate results and the reported patient satisfaction related to POCT are also advantageous. However, it is important that practitioners are aware of the limitations associated with their specific device and the cost associated with these devices may be higher than conventional testing methods.

Patient acceptability of undertaking targeted risk-based detection for NCDs in UK dental and pharmacy settings is currently unknown and requires further investigation. Therefore, an exploratory study was undertaken within one dental practice and one community pharmacy within the West-Midlands, UK, to determine patient acceptability of risk-assessment for NCDs in these settings.

Aims and objectives

The overarching aim of this study was to assess patient acceptability of screening for NCDs in a primary dental care and a community pharmacy setting. Further objectives of the study included:

1. To identify whether testing for NCDs in a high street dental practice and a community pharmacy setting was feasible in terms of logistics, environment and process. Including feasibility of participant recruitment and barriers to recruitment.
2. To determine whether there is benefit to the finger prick HbA1C test to identify diabetes risk compared to a validated screening questionnaire alone.
3. To ascertain changes needed in the study protocol and barriers to a larger scale study.
4. To determine whether any patients potentially at high-risk of NCDs could be identified where disease status was previously unknown.

Methods

One dental practice serving both National Health Service (NHS) patients and private patients was selected for participation in the study. Only those patients attending the practice for provision of NHS dental services were approached for participation in the study. The dental practice was situated in the West Midlands, as was the Community Pharmacy. Screening was undertaken for 50 consecutive patients recruited at each site.

Patients over 40 years of age were given a patient information leaflet (PIL) and consented to participate in the study, and a member of the research team conducted the screening as per the standard operating protocol (SOP) (Additional file 1: Appendix 1). A recruitment log was completed, as was any reason cited for non-participation. Time taken to complete the process from consent to completion was also recorded. Participants completed a questionnaire outlining demographic data and previous diagnosis and family history of NCDs. Upon completion of the risk-assessment process participants were also asked to provide feedback or additional comments related to the risk-assessment process (Additional file 1: Appendix 2).

Validated risk-assessment questionnaires were undertaken for determining participants' risk of T2DM [21] and chronic obstructive pulmonary disease [COPD] [22]. The "Diabetes Risk Score" developed by Leicester University and Diabetes UK is a validated tool recommended by NICE. The risk-assessment consists of seven

questions giving a score between 0 and 47. Depending on the patients total score they are categorised into one of four groups: low risk, increased risk, moderate risk or high risk. The risk assessment gives both the current risk of having undiagnosed T2DM, but also a 10 year risk of developing the condition [21]. The COPD risk score "Drive4COPD" is also a validated tool. This risk-assessment consists of five questions resulting in a score from 0 to 10. Depending on the total score awarded patients are then categorised into one of two groups those with a total score that is greater than or equal to 5 or those with a score less than 5 [22].

POCTs to ascertain the presence or absence of risk-factors for the following NCDs: T2DM (HbA1c capillary blood sample), hypertension, atrial fibrillation [AF], height and weight (BMI calculation) - as surrogate markers for cardiovascular disease [CVD], chronic kidney disease [CKD] (creatinine and eGFR capillary blood sample) and Vitamin-D deficiency (capillary blood sample).

Inclusion and exclusion criteria

Inclusion criteria

1. Be able to provide informed consent to participate in the trial
2. Patients aged ≥40 years
3. treatment via NHS services

Exclusion criteria

1. Not meeting the inclusion criteria or
2. Not amenable to proposed testing method i.e. finger-prick testing.
3. Solely private patients

As part of screening the participant undertook:

1. A questionnaire to provide basic demographic data and to ascertain any previous diagnosis of any of the NCDs, or a positive family history of any of the NCDs. (Additional file 1: Appendix 2)
2. A validated questionnaire to determine risk of COPD [Drive4COPD] [22].
3. A validated questionnaire for risk of diabetes [Leicester Risk Assessment Tool, Diabetes Know your risk] [21].
4. Blood pressure, pulse and AF monitoring using the National Institute for health and Care Excellence [NICE] approved WatchBP device.
5. A chair-side finger-prick sample to assess HbA1C concentration/levels [Siemens/Bayer DCA Vantage]
6. A chair-side finger-prick sample to assess eGFR [Nova StatSensor]
7. A chair-side finger-prick sample to assess vitamin-D levels [Cityassays.org.uk]

Two methods were utilised to risk assess for non-diabetic hyperglycaemia (NDH) and T2DM. The "Leicester Risk-Assessment" questionnaire [LRA] tool, which is validated and recommended by NICE and Diabetes UK; and a point-of care HbA1c test (DCA-Vantage, Siemens).

All analyses were performed by trained members of the research team and the logistics and time involved recorded alongside patient feedback.

Initial data was analysed to establish answers to the research questions. Accepted reference values were used based on current UK guidelines for each of the specific conditions assessed.

Recruitment process

In each setting a consecutive sampling approach was adopted with potential participants identified by a member of the study team who applied the inclusion/exclusion criteria and if eligible, written informed consent for their participation in the trial was obtained. Recruitment continued until the recruitment target of 50 participants was met, refusal rate was recorded and if participant was willing to disclose reason for refusal this too was documented.

Those participants for whom an abnormal finding or presumptive diagnosis was identified were advised to visit their GP and a follow-up letter was forwarded to their GP, with participant consent. Only if the participant did not provide consent for their GP to be contacted was a general letter with their results of interest provided to the participant such that they could present it to their GP at a later date should they so desire.

Statistical analysis plan

Descriptive statistics were used to analyse the study findings. Data on the recruitment to the study was also analysed descriptively, including the number of patients approached, the number that agreed to participate and number eligible to participate. Reasons for non-entry into the study were assessed. Reasons for non-completion were also analysed descriptively.

No formal sample size calculation was undertaken for this study. The sample size ($n = 50$, in each site) was deemed sufficient to enable identification of practical challenges involved with running such a study in a dental and pharmacy setting and allowed identification of areas where change is required prior to implementing such a model on a larger scale. The intention of this phase of the study was to identify barriers to conducting a similar style study using a larger sample within multiple primary care dental practices and pharmacies,

across a broader geographical area. This study was not powered to detect new cases of disease.

Results

Table 1 demonstrates that the study was balanced for males and females in both settings. There was a spread across each of the age categories with the average age of participants in dental settings being younger than those recruited in pharmacy settings, with a mean age of 58 years and 65 years respectively. In the dental setting all participants identified themselves as white/Caucasian and in the pharmacy setting all but 1 participant identified themselves as white/Caucasian. Most participants reported themselves to be retired with the second highest category being professionals in both settings. There were approximately three times as many professionals in the dental setting compared to the pharmacy setting (32: 11) and more participants in the pharmacy setting considered themselves to be in manual or non-manual work. In both dental and pharmacy settings about half of participants considered themselves non-smokers who had never smoked (52% & 51% respectively) (Additional file 1: Appendix 3), with approximately a third of participants reporting being previous smokers (38% & 32% respectively) in both settings (Table 1).

Recruitment and impact on existing service

There was a 60% conversion rate in the dental setting and the recruitment target of 50 participants achieved in 8 days. Recruitment in the pharmacy setting showed a 59% conversion rate and the recruitment target of 50 participants achieved in 14 days. The main reason cited for declined participation in both settings was time. In addition to being the major barrier to recruitment, time was also the major consideration when determining impact on existing services. The average time taken for case-detection in both settings was 19mins.

Table 1 Summarising demographic data of participants recruited from dental and pharmacy settings

	Dental	Pharmacy
Number recruited (N)	50	51
Time taken to recruit (days)	8	14
% Female	47	53
% Age category:		
40–49	18	10
50–59	37	20
60–69	29	30
70+	16	40
% Occupation:		
Unemployed	0	4
Manual	14	10
Non-Manual	2	10
Executive/Managerial	8	4
Professional	32	11
Retired	44	61

Demographic data

The most common age category sampled within the dental setting were participants between the ages of 50–59 years followed by the 60–69 years category. The mean age was 58 years with the oldest participant being aged 89 years and the youngest aged 41 years. The most common age category sampled within the pharmacy setting were participants aged 70+ years followed by the 60–69 years category. The mean age was 65 years with the oldest participant being aged 83 years and the youngest participant aged 40 years.

Female participants made up 47% of the dental sample and all participants in the dental setting identified their ethnicity as white/Caucasian. 44% of volunteers were retired, 32% considered themselves to be a professional, 14% were manual workers, 2% were non-manual workers and 8% considered themselves to be executive/managerial workers (Table 1). Female participants made up 53% of the pharmacy sample and all participants except 1 in the pharmacy setting identified themselves to be White/Caucasian ethnicity. 61% of patients were retired, 11% considered themselves to be a professional, 10% were manual workers, 10% were non-manual workers and 4% considered themselves to be executive/managerial workers (Table 1).

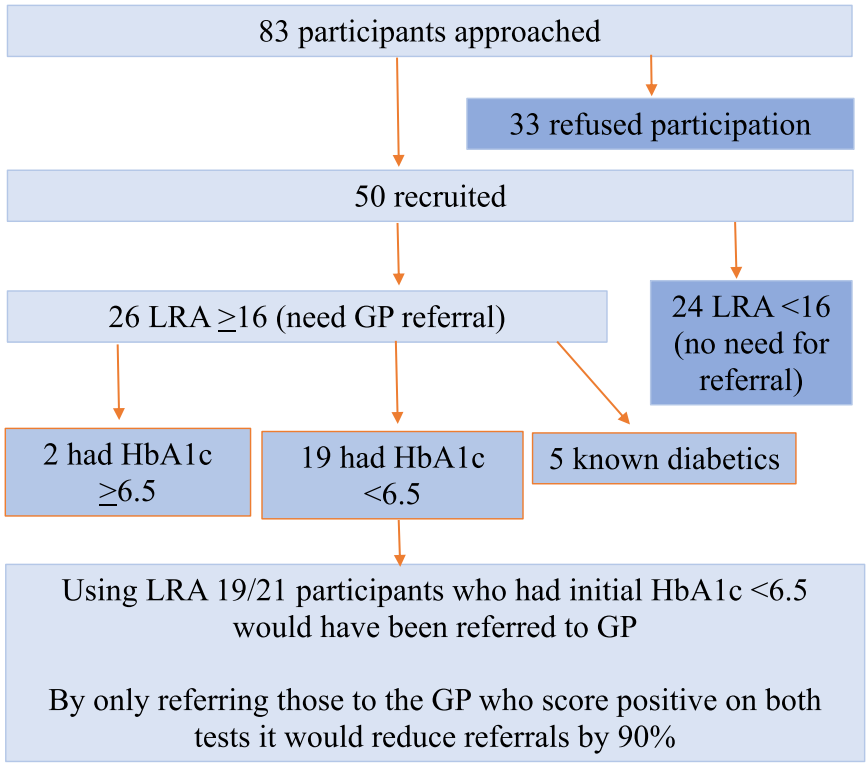
Diabetes

In the dental setting of 45 patients without an existing diagnosis of diabetes, 21 (47%) rated high-risk on the LRA, the recommendation for which is GP referral. Of these 2 (4.4%) had an HbA1c in the diabetes range (> 48 mmol/mol). A further 7 (16%) had scores 42-48 mmol/mol (NDH). However, 12/21 who were highlighted as in need of referral to a GP according to the LRA, actually had a HbA1C within the healthy reference range (< 42 mmol/mol) (Fig. 1a and b).

In the pharmacy setting of 44 patients without an existing diagnosis of diabetes, 13 (30%) rated high-risk on the LRA, with a further 13 (30%) rated moderate risk, the recommendation for which is GP referral. Of these, 4 had an HbA1c in the diabetes range (> 48 mmol/mol) A further 7 had scores between 42 and 48 mmol/mol (NDH). In the pharmacy setting a total of 26 participants were highlighted as needing referral to GP according to the LRA, with only 11 having a HbA1C greater than 42 mmol/mol according to the POCT. One participant who had a finger prick HbA1c in the NDH range was flagged in the increased risk category (which according to the

a

Flow diagram showing risk-assessment process for undiagnosed T2DM and benefit of 2-stage process in dental setting.



b

2x2 diagram showing risk-assessment process for undiagnosed T2DM and benefit of 2-stage process in dental setting.

		Risk assessment questionnaire	
		Positive (≥ 16)	Negative (< 16)
Finger prick HbA1c	>6.5%	2	0
	<6.5%	19	24

Fig. 1 a Flow diagram showing risk-assessment process for undiagnosed T2DM and benefit of 2-stage process in dental setting. **b** 2 × 2 diagram showing risk-assessment process for undiagnosed T2DM and benefit of 2-stage process in dental setting

LRA does not require referral to GP but advises lifestyle changes to be made).

CVD

In the dental setting 34% of participants were deemed to be overweight based on their BMI with a further 28% having a BMI greater than 30 classifying them as obese. Of those who stated they did not believe themselves to have CVD or hypertension, 17 (44%) had an elevated systolic reading (> 140 mmHg) and 13% had a diastolic reading > 100 mmHg.

In the pharmacy setting 47% of participants were deemed to be overweight based on their BMI with a further 25% having a BMI greater than 30 classifying them as obese. Of the 26 participants who stated they did not believe themselves to have CVD or hypertension, 9 (41%) had an elevated systolic reading (> 140 mmHg) and 35% had a diastolic reading > 100 mmHg.

CKD

Only one participant in the dental setting stated they had known chronic kidney disease when asked. Although most participants had an estimated glomerular filtration rate (eGFR) > 90, 11 participants had an eGFR of 89–60 (stage 2 kidney disease) and a further 4 had an eGFR of between 55 and 49 (stage 3a kidney disease).

Only one participant in the pharmacy setting stated they had known chronic kidney disease when asked. Yet, although 16 participants had an eGFR > 90, 19 participants had an eGFR of 89–60 and a further 6 had an eGFR of between 55 and 49.

COPD

Two participants in the dental setting reported knowing they had COPD. In addition to correctly identifying those 2 participants the COPD risk assessment tool also highlighted a further 2 participants in the dental setting who may be at increased risk of COPD.

The COPD risk assessment tool identified 7 people who may be at increased risk of COPD in the pharmacy setting. Three participants in the pharmacy setting reported knowing they had COPD, of which 1 participant was picked up by the risk assessment tool as being high risk while the other 2 were missed. A further 6 participants who thought themselves not to have COPD were identified by the risk assessment tool as being high risk and in need of referral to a GP.

Vitamin D

In the dental setting 8 participants were highlighted as having insufficient vitamin D levels, none of whom were aware of having vitamin D insufficiency. Of the three participants who reported thinking they were deficient in vitamin D, all had results within the healthy reference value.

In the pharmacy setting 7 participants were highlighted as having insufficient vitamin D (30.1-50 nmol/L) and a further 2 were deficient (15-30 nmol/L), none of whom were aware of having vitamin D insufficiency/deficiency. Of the 2 participants who reported thinking they were deficient in vitamin D, all had results within the healthy reference range.

Patient acceptability

Of those subjects who participated acceptability and satisfaction was very positive with only 3 participants providing neutral or negative feedback (Additional file 1: Appendix 4). Of those patients who declined participation no additional feedback was received except for reason for refusal, the most common being a lack of time.

Discussion

This overarching aim of this study was to assess patient acceptability of screening for NCDs in primary care dental practices and community pharmacy settings, with a view to determine practical challenges and barriers relating to logistics, environment and process, whether there was benefit to POCT testing HbA1c in addition to risk-assessment tool alone and to ascertain barriers to a larger scale study. A further objective was to determine whether potentially high-risk of NCDs could be identified within these settings where individual risk or disease status was previously unknown.

Recruitment rates were better in a dental setting with half the amount of time required to reach the recruitment target of 50 participants. However, the time take to recruit participants in both settings was satisfactory with no obvious recruitment challenges experienced by the study team. However, it must be noted that although the participants enrolled in the study were of a range of ages and a satisfactory gender balance. The study participants were not representative of the general population of the West Midlands in terms of ethnic identity. Thus it remains to be determined whether recruitment of individual's from ethnic backgrounds known to be associated with increased risk of these specific NCDs is achievable based on the results of this study.

The demographic data for patients in both the dental and pharmacy settings were comparable although more people identified themselves as professionals within the dental than the pharmacy setting. In both the dental and pharmacy setting the patient satisfaction and acceptability was high. Participants found the method of testing acceptable and participant feedback relating to testing for NCDs in both dental and pharmacy settings was positive (Table 2).

The main reason cited for non-participation in both settings was lack of time. The average time taken to test in both settings was 19mins. Where an additional member of staff was not available to undertake risk-assessment the potential impact on routine activities in both settings would be significant with increased delays. In the dental setting patients arriving for appointments often attended the practice in advance of the scheduled appointment time, thus could be offered a risk assessment prior to seeing the dental team or could be offered a risk-assessment immediately upon completion of their dental appointment. In this particular practice there was a spare surgery available for the risk-assessment to take place. However, where an additional room was not available increased waiting time and potential delays to risk-assessments or scheduled dental activity may pose an additional barrier. The key finding relating to impact on current service was therefore for risk-assessment to be undertaken effectively an additional member of dedicated staff would be required to undertake testing and an additional room dedicated to the risk-assessment process.

The benefit of undertaking a two-step risk-assessment process for identifying potential T2DM was shown to be beneficial in improving the specificity of the T2DM risk-assessment (Fig. 1a). When questionnaire based risk-assessment alone was used it resulted in potentially 90%

more referrals to GP than when a two-step risk assessment process was utilised. Clearly given how busy GP colleagues are and the time burden they are already under caring for patients, it is important that their time is protected and not taken up by inappropriate, unnecessary referrals. Thus a two-stage risk-assessment would appear preferable, however a full economic evaluation comparing these methods has not been undertaken.

The risk-assessment methods used appeared to identify people at high risk of NCDs who were previously undiagnosed and unaware of their risk status. Potential cases of previously undiagnosed disease were identified in both dental and pharmacy settings. This is despite the fact that the demographic of the study population predominantly identified as "White/Caucasian" and of higher socio-economic status; not being the groups conventionally considered as being highest risk for developing NCDs. Further research to determine whether the findings are also applicable in groups commonly considered of higher-risk and also research to follow-up patients to determine how many go on to receive formal diagnosis and onward management is needed to understand the true potential impact of risk-assessment for NCDs in these settings.

The main challenges associated with the study include the sample size employed, this was small as the purpose of the study was to demonstrate patient acceptability and potential barriers prior to undertaking a formal feasibility study for a definitive trial. The study was not-representative of the population with almost 100% of participants identifying themselves as white/Caucasian. Whilst we demonstrated that testing in these locations can be undertaken to good effect when a dedicated member of staff is undertaking the risk-assessment process, this may not be possible in everyday practice where an additional staff member may not always be available. In the pharmacy and dental settings, the additional service was logistically challenging alongside traditional duties when no additional staff were available to undertake the risk-assessments associated with the study. Additionally, securing funding at the individual pharmacy and dental practice to provide such services could act as a barrier. Further work is needed to demonstrate that this can be done by the existing team within each setting and to demonstrate the cost-effectiveness of the risk-assessment process should an additional dedicated member of staff be required.

To our knowledge this method of risk-assessing for multiple NCDs in a dental setting has not previously been undertaken. Utilising dental settings to test for T2DM has been demonstrated to good effect outside of the UK and this study further supports those findings [23–27]. We also demonstrated the advantage of a 2-step risk-assessment process for T2DM which is supported by the study of Bould et al. [28]. Similarly, in a pharmacy setting isolated small-scale pilot initiatives have shown promising results, but nationally POCT and risk assessment for multiple NCDs is not standard practice. Although small initiatives for screening for NCDs have been undertaken in UK pharmacies, besides the NHS Health Check (which is a health check-up designed to spot early signs of kidney disease, heart disease and type 2 diabetes) and The Healthy Living Pharmacies (HLPs) initiative very few services in UK pharmacies have been consistent. This is despite these being part of the NHS Long Term Plan, therefore, this study could add to the existing evidence and support prevention roles for pharmacists [29, 30].

NICE currently recommends that allied healthcare professionals, including community pharmacists and general dental practitioners [GDPs], should risk-assess for T2DM [31]. To the authors knowledge this is not currently undertaken in general dental practice nor is it routine practice in community pharmacies at a national level. Furthermore, the feasibility of such risk-assessments has yet to been determined. Our study provides the groundwork for investigating this further, having determined a positive response from patients accessing these services and that the potential devices required to undertake the risk-assessments perform well. This study demonstrated strong support from participants for the use of allied healthcare professionals to provide targeted risk-assessments for NCDs. It also demonstrated that the methods required to undertake such assessments were acceptable to participants.

However, the concept of dentists and pharmacists testing for NCDs is not without controversy. Firstly, the UK National Screening Committee clearly states that it does not support population-based screening for NCDs [32]. Though evidence suggests a population-based screening programme lacks benefit, the potential benefits of an opportunistic risk-directed assessment of patients who have risk-factors for NCDs, and who may not have had contact with another healthcare professional in the proceeding 12 months is yet to be determined. Opticians currently identify potential signs of CVD and T2DM and advise patients to seek GP follow-up and refer patients to their GP for formal assessment. The present study provides insights into the potential for a similar approach in high street dental surgeries and community pharmacies. Further work is needed to determine feasibility of such a model within the UK healthcare system to assess both the effectiveness and cost-effectiveness of such a strategy and to ensure suitable care pathways for those patients identified with new cases of disease are accessible.

Before further larger scale studies can be undertaken to determine cost-effectiveness and clinical effectiveness

of undertaking such targeted risk assessment's in dental and pharmacy settings, careful consideration must be given to the patient's care pathway following identification of a previously unknown elevated risk status. Moreover, care must be taken to avoid duplicated testing as many patients may have already undergone a NHS Health-check with their GP in the previous 12 months. In addition, care and consideration is required to prevent adding to the ever-growing burden on GPs by increased referral loads without consideration of how these patients should be managed and how the additional referrals will be funded. Further work is needed to determine what the additional burden to Primary Care services could be and to mitigate for this, whilst also assessing the health economic impact of such an approach.

Conclusion

Although there is controversy surrounding the precision and accuracy of POCT, the devices tested in this study demonstrated good levels of concordance with standard laboratory methods and may present a viable alternative to laboratory-based methods when risk-assessing patients for NCDs in community settings. Participant acceptability to finger-prick testing was positive. Further work is required to determine whether testing for NCDs in a dental practice and pharmacy setting is feasible in terms of logistics, environment and process. Based on this work it appears that to minimise the negative impact on day-to-day running of current services additional dedicated staff may be required to undertake the risk-assessment in dental and pharmacy settings. Further work also needs to be undertaken with suitable follow up to determine whether there are health and economic benefits to such a model.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12889-020-09649-7.

Additional file 1: Table 1. Sample of positive feedback and all neutral and negative feedback from participants in dental and pharmacy settings. **Table 2.** Summarising demographic data of participants recruited from dental and pharmacy settings.

Abbreviations

NCDs: Non-communicable disease; POCT: point of care testing; eGFR: estimated Glomerular-Filtration-Rate; CVD : Cardiovascular disease; T2DM : Type-2 diabetes mellitus; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; NICE: National Institute for health and Care Excellence; GDPs: General dental practitioners; NDH: Non-diabetic Hyperglycaemia (Prediabetes); PIL: Patient Information Leaflet; VAS: Visual analogue score; SOP: Standard operating procedure; BDH: Birmingham's Dental Hospital; AF: Atrial fibrillation; LRA: Leicester Risk Assessment

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Authors' contributions

All authors have contributed to the completion of the study and/or production of this manuscript. Conception / design of the work: Zehra Yonel, Thomas Dietrich and Iain Chapple. The acquisition, analysis, or interpretation of data: Zehra Yonel, Alistair James and Asma Yahyouche. Have drafted the work or substantively revised it: Zehra Yonel, Zahraa Jalal, Thomas Dietrich and Iain Chapple. The author(s) read and approved the final manuscript.

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The role of the funder funded the acquisition of equipment and consumables required to undertake the finger-prick capillary blood-spot testing, but remained independent of the study design, data collection, data analysis, data interpretation and subsequent reporting of results.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethics committee approval was sought and granted from the Coventry and Warwickshire ethics committee and the University of Birmingham was the study sponsor (RG_16–102). Written consent for participation was obtained from all participants.
West Midlands – Coventry and Warwickshire Research Ethics Committee
REC reference: 17/WM//0022
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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH

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Concordance of three point of care testing devices with clinical chemistry laboratory standard assays and patient-reported outcomes of blood sampling methods

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Abstract

Background: Point of care testing (POCT) devices have been developed to facilitate immediate results with the potential to aid screening for new disease and enable patients to self-monitor their disease. Non-communicable diseases (NCDs) are the major cause of mortality globally and are increasing in prevalence as the population ages. Allied health care professionals (AHPs) are skilled in undertaking risk assessment and delivering preventative advice, providing opportunities to access large proportions of the population who may not visit their doctor, within non-traditional community settings. There is evidence of high levels of support from public, patients and health professionals for engaging AHPs in risk-targeted early case detection of certain NCDs. Thus, POCT devices offer a potential alternative to traditional venous blood collection, as novel care pathways for increasing early case detection and access to preventative care. The objectives of this study were to: (i) determine the concordance of the specific POCT devices with laboratory-based standard assays employed within clinical biochemistry laboratories. (ii) compare the sampling experience of both methods via patient-reported experiences.

Methods: A prospective, two-centre study was undertaken involving 158 participants who provided informed consent. Venous blood was collected for traditional assays of HbA1c, creatinine/ estimated Glomerular-Filtration-Rate (eGFR) and vitamin-D. Capillary blood was collected by finger prick test and also assayed for the same biochemical indices (Nova StatSensor (creatinine/eGFR); Siemens DCA-Vantage (HbA1C); CityAssays (vitamin-D)). All users were provided with device training. Participants reported any discomfort experienced by each simultaneously applied method (randomised in order) via a 100 mm Visual-Analogue-Scale.

Results: Results for each POCT device and the laboratory standard were analysed by Bland-Altman plots to determine assay concordance. POCT devices demonstrated good concordance with laboratory testing, with at least 95% of all samples being within two standard deviations, for each of the devices tested. The majority of participants reported less discomfort with POCT than venepuncture, with the average reported discomfort being 17/100 mm less for POCT compared to venous blood sample collection on the visual analogue scale.

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Conclusions: The POCT devices demonstrated acceptable concordance with laboratory-based assays, and patients reported lower levels of discomfort compared to traditional means of blood collection. This study demonstrates the potential of using these devices as acceptable methods for opportunistic testing of "at-risk" individuals within non-traditional community care settings.

Keywords: Point of care testing, Screening, Prevention

Background

The prevalence of non-communicable diseases (NCDs) is increasing worldwide. This has a significant impact on the global disease burden and healthcare economy. The impact of the major NCDs (diabetes, cardiovascular diseases, cancer, chronic respiratory diseases and mental disorders) account for an estimated 86% of the deaths and 77% of the disease burden in Europe [1]. The increasing prevalence of NCDs is, in part, attributed to an increasingly ageing population, but also due to an increase in the prevalence of risk-factors common amongst most NCDs such as physical inactivity, refined diets and overweight/obesity. In 2011 the United Nations General Assembly received the commitment from world leaders to take measures to tackle NCDs. Subsequently there have been several policy interventions to support this agenda. Notably the inclusion of NCDs, with measurable targets and indicators, under the third of the "Sustainable Development Goals" [2].

The incidence of NCDs is a key example of the health inequalities that pervade modern society, as lower socioeconomic groups struggle to access preventative services due to cost and geographic location. In addition to the substantial health burden, NCDs also contribute a significant economic burden. A report published by the World Economic Forum and the Harvard School of Public Health in 2011, predicted that over the next 20 years, NCDs will cost more than 30 trillion US$, which is the equivalent of 48% of global GDP in 2010. The report goes on to state that lost output from the five most prevalent NCDs over the period 2011–2030 is estimated at nearly 47 trillion US$ [3]. Furthermore, in Europe in 2015, public expenditure on health was 7.8% of GDP in the EU as a whole and in 2013, premature deaths due to major NCDs cost EU economies around 0.8% of GDP. Moreover, non-health costs of NCD in the EU such as productivity losses due to mortality and morbidity associated with CVD cost €54 billion in 2015 alone [4].

Given the growing NCD burden and the fact that allied health professionals (AHPs) have access to large proportions of the population who may not engage with other healthcare services [5], AHPs are ideally placed to assist with the early identification of NCDs in non-traditional community settings. Dental care professionals (DCPs) and pharmacists are trained and skilled in risk-assessment and routinely deliver preventative advice, such as smoking cessation, exercise and advice on healthy nutrition. Risk assessment for specific NCDs, followed by early case detection is a natural extension of their current roles. Importantly, stakeholder opinion for AHPs undertaking risk assessments for certain NCDs is extremely positive [5, 6]. Public support for screening for medical conditions in both dental and pharmacy settings is strong, with particular support for risk-targeted early case detection in type 2 diabetes (T2DM) and hypertension [5]. Patients as well as pharmacists, physicians and dentists also support public opinion for such novel care pathways [7].

Point of care testing (POCT), is a testing method that does not require samples to be sent to an accredited laboratory, and instead is undertaken near the patient, often chairside or bedside and provides results in a short timeframe [8]. POCT can be of benefit when an immediate result is required or when access to a laboratory is not feasible, practical or readily available. This may be the case in community-based healthcare settings such as primary care dental practices and community pharmacy settings.

The National Institute for Health and Care Excellence (NICE) in England currently recommends that AHPs risk-assess for T2DM [9]. Data from the US and Europe suggest that screening for T2DM in a dental setting is effective for identifying those at high risk and those who already unknowingly have the condition [6, 10–15]. Whilst NICE guidance currently suggests using a validated risk assessment questionnaire, the literature suggests POCT devices are often used in conjunction or instead of these validated questionnaires [6, 10, 14–17].

UK government policies actively encourage dental care professionals (DCPs) to deliver general health promotion [18, 19]. It has been suggested that highly skilled primary healthcare professionals, such as DCPs, may develop new roles and integrate care provision more seamlessly with GPs to create effective multi-disciplinary teams and care-pathways to benefit patients. The provision of a wider range of services by AHPs in collaboration with GPs, such as early detection of systemic NCDs, provides greater access to care for vulnerable groups and helps to address the highly prevalent healthcare inequalities that have been highlighted by the SARS-COV-2 pandemic

[20, 21]. This aligns closely with the UK "Making Every Contact Count" agenda to improve general health and wellbeing [22]. Similarly, UK policy and pharmacists' professional organisations have stressed the potential of community pharmacists to extend their roles in patient care services to include screening for NCDs. This has been emphasised in policy papers calling for a wider use of community pharmacists in primary patient care [20, 23, 24]. In the UK, POCT is considered an important development area for the future of pharmacy, it is supported by the Royal Pharmaceutical Society and the National Pharmaceutical Association. Several pilot initiatives in pharmacies across the UK have taken place, including testing for T2DM, coronary heart disease and cholesterol [25].

This study forms part of a broader body of work to determine: the acceptability to stakeholders (patients, the public, and healthcare professionals) of utilising AHPs to undertake risk-targeted early case detection of potentially high-risk individuals for specific non-communicable diseases (NCDs) [5], patient acceptability of undertaking risk-targeted early case detection for NCDs within a general dental practice and community pharmacy setting [6, 26], and the concordance of point of care testing (POCT) devices against laboratory methods.

Controversies surrounding the reliability and accuracy of POCT devices has traditionally provided a barrier to their uptake [27, 28], as has the variability in precision of the large number of available devices [29]. Venous blood analysis using laboratory-based methods remains the reference standard. However, the improved quality and precision of POCT devices for capillary blood sampling has led to NICE and other national bodies recommending their use for diagnosis in some cases [27, 30–33]. Despite this recommendation, the preference for conventional diagnostic methods by a physician for formal diagnosis and appropriate provision of treatment plans remain. Given that venous sample collection in many community settings is challenging it is important that POCT devices if utilised demonstrate high concordance with current standard reference-assays.

Here we report a two-staged exploratory study. Stage one aimed to measure the agreement between POCT devices with a central laboratory method for: HbA1C (diabetes), creatinine/e-GFR (chronic kidney disease) and total vitamin D. The devices calibrated were the Nova StatSensor (creatinine/estimated Glomerular-Filtration-Rate [eGFR]), Siemens DCA Vantage (HbA1c), and CityAssays (vitamin D capillary blood-spot tests). This stage also aimed to gauge the opinions of the participants regarding acceptability of the method of blood collection. Stage two comprised a study within one dental and one community pharmacy in the West-Midlands, UK, to determine patient acceptability of risk-assessment for NCDs in these settings, utilising validated risk-questionnaires followed by the POCT devices [26].

Methods

This was a prospective study of 158 volunteers, recruited from the Queen Elizabeth Hospital (QEH) and Birmingham Dental Hospital (BDH). Ethical approval was obtained from South East Scotland Research Ethics Committee (REC reference: 16/SS/0197) and informed written consent obtained from each participant. All methods were carried out in accordance with relevant guidelines and regulations.

Inclusion & exclusion criteria

Inclusion criteria

a.Aged > 18 years.

b.Willing and able to provide valid informed consent.

c.Attend outpatients' departments at Queen Elizabeth Hospital, Birmingham (QEH) or Birmingham Dental Hospital (BDH).

Exclusion criteria

a.Aged < 18 years.

b.Unable or unwilling to provide valid informed consent.

Recruitment

Consecutive patients meeting the study eligibility criteria and attending outpatient appointments at the QEH and BDH were approached by a member of study team and offered the opportunity to participate. If the patient was interested, further information relating to the study including the patient information leaflet was provided by a study team member trained in consent.

Blood collection

Venous blood samples were collected alongside the patient's routine care requirements and sent to the Clinical Chemistry laboratory at University Hospital Birmingham Foundation Trust's QEH for assay. The time of blood collection and testing by both capillary and venepuncture methods was recorded to ensure they were within 15 min of each other. In this study all patients received their venous blood sample collection first, followed by POCT.

The laboratory methods employed at the QEH Clinical Chemistry Laboratory were: the TOSOH G8 High Performance Liquid Chromatography (HPLC) for HbA1c measurement. Serum creatinine was measured by Alinity c enzymatic method. All blood collection methods being subject to external accreditation by UKAS against ISO15189 for quality assurance.

Finger-prick (capillary) testing was performed according to standardised operating procedures (SOP), in

accordance with manufacturer's guidelines and study protocols. The same brand and gauge lancet was used for each participant in order to draw blood.

Nova StatSensor

An analytical method correlation was performed using discarded whole blood lithium heparin samples. Quality control (QC) tests were performed daily for each POCT device as per device protocols. Fifty-three patients attending for outpatient appointments at the QEH with different stages of chronic kidney disease (CKD) were asked to contribute a StatSensor finger-prick sample for serum creatinine at a routine visit at the renal clinic, where formal kidney function testing was also undertaken. Twelve patients with eGFR ≤ 20 were recruited, 13 patients with eGFR 20–29, 15 patients with eGFR 30–44 and 13 patients with eGFR 45–59. Each sample was processed in accordance with manufacturers guidelines.

DCA vantage and city assays

No prior calibration of equipment was required for either the CityAssays or DCA Vantage POCT. Fifty participants were recruited at Birmingham Dental Hospital and consented for a finger-prick blood spot CityAssay vitamin D test and a venous (control) blood sample. The capillary vitamin D test required the capillary test strip to be mailed to the laboratory for assay with results returned to both the patient volunteer (via an online reporting platform) and study team directly and within 3 working days. One participant's sample was deemed insufficient to provide a result; the remaining forty-nine results were analysed.

Fifty-six T2DM patients with different levels of glycaemic control were asked to contribute a finger-prick sample at a routine outpatient visit at the QEH, where routine HbA1c testing on a venous blood sample was also undertaken. Systemically healthy controls ($n=10$) were also recruited at BDH for the lower end of the calibration line. Each sample was processed in accordance with manufacturers' guidelines.

Visual analogue score (VAS)

Each participant who consented to undergo finger-prick testing was also asked to complete a Visual Analogue Scale to assess the perceived discomfort related to that experience [34]. Discomfort was recorded at the time as well as the residual level of discomfort they felt "some time" later (5 min -15 min post-sample collection).

Primary outcome

The primary outcome of interest was the concordance of results from the capillary POCT with the laboratory tested venous sample for identifying creatinine, HbA1C and vitamin D levels.

Data analysis

The percentage bias of each POCT result compared to the laboratory reference result was calculated and analysed using a Bland Altman plot in order to assess accuracy [35]. Descriptive statistics were also used to analyse data and for the VAS. Wilcoxon Signed-rank Test was used to compare VAS results for finger-prick and venous blood sample. A subgroup analysis was undertaken, as some of the cohorts were familiar with either venous blood samples, due to regular visits to outpatient services, or finger-prick testing amongst the T2DM cohort due to regular home testing. The sensitivities and specificities for each POCT device were also calculated comparing the finger-prick sample to the venous reference standard.

Results

Overall, the data demonstrated that the POCT devices used for HbA1c, Creatinine and Vitamin D testing were comparable to the current reference-standard venous blood sample assays, with strong levels of concordance. Patients reported that POCT was an acceptable method of blood collection, generally being less uncomfortable than traditional venous blood tests at the time of sample of collection.

Nova StatSensor [POCT creatinine]

A Bland–Altman (BA) plot was used to compare the creatinine concentration measured within the standard venous sample and that obtained with the POCT device [Fig. 1]. The BA plot demonstrates that 50/52 results were within two standard deviations of the mean difference

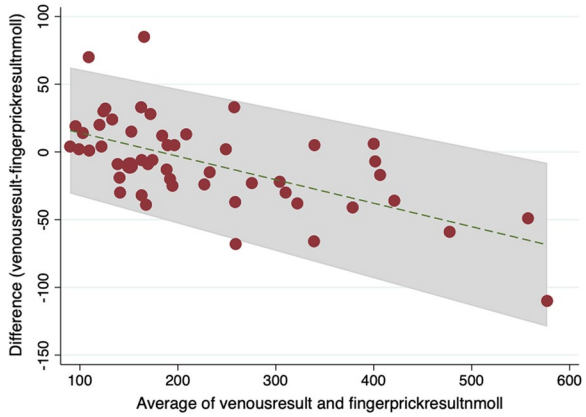

Fig. 1 BA plot comparing venous sample with POCT creatinine results in nmol/L

between assays, indicating that the two methods could be used interchangeably [35, 36]. Despite the results showing good concordance, the BA plot for creatinine does indicate a possible proportional bias, whereby for those patients who have a low creatinine, the POCT finger prick sample gives a lower result than the venous sample (reference standard) and for higher creatinine, the POCT finger prick samples are higher than the venous sample. POCT had 98.8% sensitivity (95% CI 95.6: 99.9) and 100% specificity (95% CI 29.2: 100) for a reference standard test outside the reference range.

Siemens/Bayer DCA vantage

The BA plot demonstrates that 53/56 results are within two standard deviations of the mean difference between the methods, indicating acceptable levels of comparability [Fig. 2]. The POCT device showed a sensitivity of 87.5% (95% CI 67.6: 97.3) and specificity of 84.4% (95% CI 67.2: 94.7).

CityAssays

The BA plot shows that 48/49 results were within two standard deviations of the mean difference between the methods, suggestive that the two tests are comparable [Fig. 3]. POCT device showed a sensitivity of 91.3% (95% CI 72: 98.9) and specificity of 61.5% (95% CI 40.6: 79.8).

Visual analogue scores (VAS)

Discomfort as a result of the procedure was recorded at two timepoints; at the time of procedure and residual discomfort after the procedure (5–15 min) for both the POCT and venous blood samples. Wilcoxon Signed-rank Test comparing of VAS results for finger-prick and venous blood sample revealed the two testing methods to be comparable in relation to patient comfort.

Overall, the median pain scores with venous blood sampling 17/100 were significantly higher than the median pain scores with a finger-prick test 7/100. When asked at time of testing, people experienced more discomfort with the venous blood test compared with a finger-prick test, with the venous blood test scoring 9/100 higher than finger prick testing. Whereas on average people found the venous blood sample and finger-prick testing to be comparable, for residual pain after the sampling procedure, with an average difference in score of 0 points out of a hundred [Fig. 4].

Sub-groups

Patients accustomed to venous blood tests, such as patients with CKD (n = 52), on average experienced more discomfort at the time of testing with the venous blood

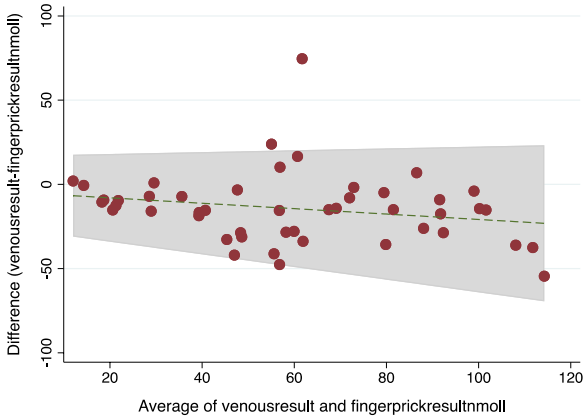

Fig. 3 BA plot comparing venous sample with POCT Vitamin D results in nmol/L

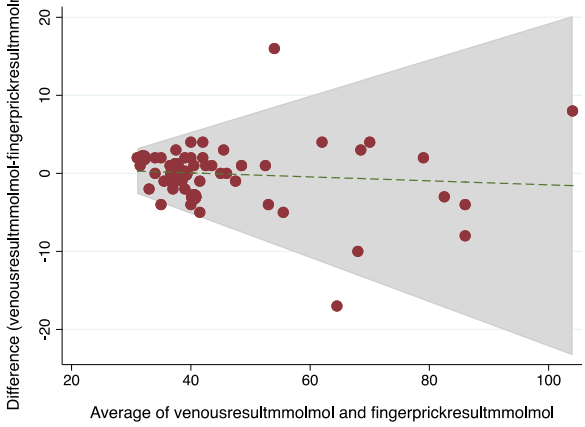

Fig. 2 BA plot comparing venous sample with POCT HbA1C results in mmol/mol

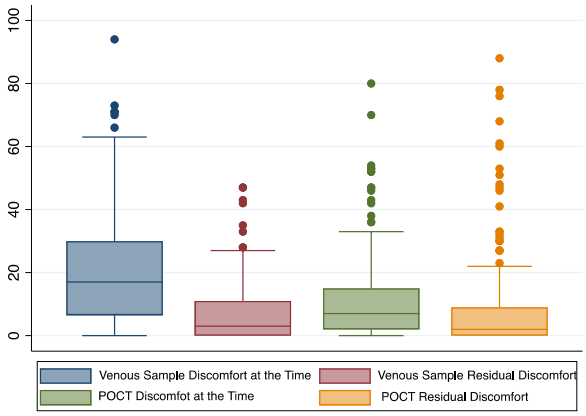

Fig. 4 Box and Whisker plot demonstrating discomfort at time and after sampling method

sample scoring on average 11/100 more than finger-prick testing. Whereas they found venous blood testing comparable (0/100 difference) to finger-prick testing in terms of residual pain post-procedure.

Patients accustomed to finger-prick testing, such as patients with diabetes (n = 56), on average also experienced more discomfort at time of testing with the venous blood sample scoring on average 10/100 more than finger-prick testing. This patient group also found venous blood testing to be broadly comparable to finger-prick testing in terms of residual pain after the procedure, with venous blood sample being on average only 1/100 greater than finger prick testing.

Patients accustomed to neither finger-prick nor venous sampling (n = 49), such as patients likely to access dental and pharmacy settings, on average experienced more discomfort with the venous blood score at the time of procedure of 4/100 more than with a finger-prick test at the time of the testing. This group also found venous blood testing comparable to finger prick testing in terms of residual pain after the procedure.

Discussion

This study has demonstrated that the POCT devices evaluated for HbA1C, creatinine and vitamin D testing were comparable to current laboratory-based assays used in day-to-day hospital practice. Level of discomfort reported by patients was comparable overall for both methods of blood sample collection, finger-prick and venous. Finger-prick testing was identified as an acceptable method of testing for the majority of participants and deemed less uncomfortable than venous sampling by the majority of participants at time of sample collection [Table 1].

Historically, controversies surrounding the reliability and accuracy of POCT devices have been a barrier to their use in detection and diagnosis of NCDs [27]. Likewise, the variability in precision of the large number of devices available has also impacted on the uptake of POCT [28, 29]. However, this study has demonstrated that despite the controversies surrounding POCT, in particularly in relation to a perceived lack of accuracy, reliability and concerns relating to interpretation of results, the devices used in this study demonstrated high levels of concordance with conventional laboratory-based assays of venous blood. All three devices showed good concordance with results being within two standard deviations of the mean difference between the methods, indicating acceptable levels of comparability. Furthermore, all three tests showed specificities > 80%, thus were reasonable at identifying those who do not have the target condition. The sensitivity for both creatinine and HbA1c were also greater than 80%. As AHPs should not use POCTs for diagnosis but more risk-targeted early case detection, this level of accuracy would be sufficient to identify those who may benefit from follow up with their healthcare provider. Furthermore, the POCT would supersede the accuracy of conventional risk-prediction models available for these target conditions, thus potentially streamlining the onward management process and limiting unnecessary referrals to primary care colleagues.

The results for the DCA vantage POCT for testing HbA1c levels showed both a sensitivity and specificity > 80% and concordance with the reference standard. A recent study comparing 7 POCT devices for HbA1c found only 4 instruments met the generally accepted performance criteria for HbA1c, of which the DCA vantage was one [37]. However, a systematic review and meta-analysis released recently has urged caution in use of POCT devices when used for diagnosis [38]. Nine of the devices considered, including the DCA Vantage showed potential for a negative bias which may lead to under diagnosis. However, a meta-regression was used to explore temporal effects and demonstrated the precision of the DCA vantage improved over time. In the meta-regression studies were dichotomised into those prior to 2006 and those from 2006 to 2016. The results suggested a significant reduction in bias within

Table 1 Table showing descriptive statistics relating to reported discomfort according to a 100 mm visual analogue scale

	Number of observations	Mean	Median	Standard deviation	Minimum value	Maximum value
Conventional venous sample at the time of procedure	164	30.0	17	18.8	0	94
Conventional venous sample—residual symptoms	164	7.0	7	9.7	0	47
POCT Finger-prick at time	164	12.0	7	15.0	0	80
POCT Finger-Prick—residual symptoms	164	9.2	2	16.7	0	88
Difference between venous sample at the time of procedure & POCT Finger-prick at time	164	9.0	6	18.2	-53	83
Difference between conventional residual symptoms & POCT Finger-Prick Residual symptoms	164	2.2	0	17.1	83	39

those studies undertaken post 2006 compared to those studies prior to 2006 [38]. The DCA vantage was one of two devices to show no difference in bias between clinical or laboratory operators, thus suggesting reduced technique sensitivity and ease of use in the clinical setting [38]. This is an important consideration if the device is to be considered for used by AHPs in community settings.

A recent study comparing two POCT devices for assessment of renal function, one of which was the Nova StatSensor, reported that the POCT devices were only moderately accurate at detecting renal impairment in patients undergoing radiological investigations, but seemed to be a good screening tool. The study recommended, any low eGFR (≤ 30) values should be further examined due to the under-reporting of eGFR values in some cases, although the POCT devices did not actually miss any high-risk patients [39].

In our study we found the Nova StatSensor to have the highest sensitivity and specificity of the three POCT devices assessed, and it showed good concordance with the reference standard as demonstrated via the Bland–Altman plot. A further study evaluating the Nova StatSensor reported that it showed results that were "acceptable-to-good" in terms of repeatability, inter-device reproducibility and between-run reproducibility over time using quality control reagents. The analyser was also found to be sufficiently accurate for detecting pathological values in patients (age > 10 years) [40].

Though not strictly POCT, CityAssays requires a dried blood spot from a finger prick blood sample and is designed for use by the patient directly for home testing, with a reported turnaround time of 3 days for results. Dried blood spots obtained through unsupervised sampling of participants at home have been reported in the literature as a viable methodology for obtaining vitamin D status information [41]. Thus, as with the other devices tested, although there are limitations when compared with the reference standards, there may be benefit in community settings to identify high risk individuals in need of formal testing, diagnosis, and onward management.

The growing burden of NCDs is widely documented in the medical literature [1–3] and there is growing support for community based AHPs, such as dental professionals and pharmacists working collaboratively with medical colleagues to facilitate improved early identification of NCDs. The impact of incorporating POCTs into routine care is yet to be fully established. However, POCT may assist in the early identification of patients at risk of NCDS and facilitate prevention strategies. However, further research would be needed to ascertain this and to evaluate the cost-effectiveness of such methods.

AHPs undertaking risk-targeted early case detection for individuals at high risk of NCDs may be a viable option to detect these conditions early, allowing upstream intervention. In the UK, government policy and NICE guidance [9] already exist supporting AHPs contributing to the early detection of certain NCDs. Furthermore, many dentists and pharmacists already use POCT devices thus, studies such as this, highlighting devices that demonstrate good levels of concordance are important to assist allied healthcare professionals who may be considering undertaking such testing. However, it is important to bear in mind the controversies related to such a model including the potential for increasing the number of referrals to a GP service already working at and beyond capacity. It is important that prior to undertaking any targeted risk-based detection AHPs establish whether patients are already being monitored or have been tested elsewhere to avoid duplication of testing. Likewise, it is important to remember that AHPs should not formally diagnose NCDs, nor would they be the healthcare professional best placed to manage these patients once they are formally diagnosed. AHPs would undertake the test as a means of identifying those patients who would benefit from more formal investigation and management from their primary care practitioner. Thus, it is imperative that clear care pathways are developed in conjunction with the appropriate healthcare professionals to ensure that patients identified as high-risk can be directed to the appropriate service for formal diagnosis and management.

Limitations of this present study include the relatively small sample size of approximately fifty patients per device. However, care was taken to ensure an adequate proportion of participants demonstrating a full range of biochemical values across the distribution curve were recruited. A further limitation of the study was that the results are only applicable to the specific devices tested and cannot be generalised to other devices available in the market. Although the vitamin D testing strips utilise a collection method for capillary blood samples, akin to that for other POCT devices, as the sample needs to be posted to the laboratory, the analytical pathway is not strictly a POCT pathway. However, for the purposes of determining feasibility of use by AHPs in community settings, it fulfils the requirements of being practical and feasible and providing results directly to patients within a reasonable timeframe, hence its inclusion in the present study. A further limitation is the subjective nature of VAS scores. It is recognised that patients assess pain subjectively and that there is likely to be considerable variation of pain thresholds amongst patients tested.

Conclusion

This study provides evidence to support the use of POCT devices in addition to validated risk assessment questionnaires to identify those at increased risk of, or who unknowingly have NCDs. The study contributes to a broader body of work demonstrating support from stakeholders for allied healthcare professionals undertaking risk assessments for NCDs [5, 6, 17]. The POCT methods employed demonstrated high levels of concordance with standard laboratory methods. Thus there is potential for POCT devices to be used as screening tools leading to further confirmatory tests for formal diagnosis. Further, larger scale studies are however required to determine the effectiveness and cost-effectiveness of POCT devices being used in risk-targeted early detection for NCDs by allied healthcare professionals.

Abbreviations

AHPs: Allied Health Professionals; NCDs: Non-communicable disease; POCT: Point of care testing; T2DM: Type-2 diabetes; CKD: Chronic kidney disease; NICE: National Institute for health and Care Excellence; NDH: Non-diabetic hyperglycaemia (Prediabetes); PIL: Patient information leaflet; VAS: Visual analogue score; SOP: Standard operating procedure; BDH: Birmingham's Dental Hospital; QEH: Queen Elizabeth Hospital; QC: Quality control; BA: Bland–Altman.

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Author contributions

All authors have contributed to the completion of the study and/or production of this manuscript. Conception **/** design of the work: ZY, TD, IC. The acquisition, analysis, or interpretation of data: ZY, PS, KK, MD, PC, JWJ, PN. Have drafted the work or substantively revised it: ZY, PS, KK, MD, JWJ, TD, IC, ZJ.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics committee approval was sought. Written consent for participation was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations. South East Scotland Research Ethics Committee 1. REC reference: 16/SS/0197. Protocol number: RG_16-128. IRAS project ID: 212214.

Consent for publication

Not applicable.

Informed consent

Patients over 18 years of age with capacity were provided with a patient information leaflet (PIL), had the opportunity to read it prior to discussion with their healthcare professional, and prior to volunteering written informed consent.

Competing interests

The authors declare that they have no competing interests.

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Manuscript 6

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Development and External Validation of a Multivariable Prediction Model to Identify Nondiabetic Hyperglycemia and Undiagnosed Type 2 Diabetes: Diabetes Risk Assessment in Dentistry Score (DDS)

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Abstract

The aim of this study was to develop and externally validate a score for use in dental settings to identify those at risk of undiagnosed nondiabetic hyperglycemia (NDH) or type 2 diabetes (T2D). The Studies of Health in Pomerania (SHIP) project comprises 2 representative population-based cohort studies conducted in northeast Germany. SHIP-TREND-0, 2008 to 2012 (the development data set) had 3,339 eligible participants, with 329 having undiagnosed NDH or T2D. Missing data were replaced using multiple imputation. Potential covariates were selected for inclusion in the model using backward elimination. Heuristic shrinkage was used to reduce overfitting, and the final model was adjusted for optimism. We report the full model and a simplified paper-based point-score system. External validation of the model and score employed an independent data set comprising 2,359 participants with 357 events. Predictive performance, discrimination, calibration, and clinical utility were assessed. The final model included age, sex, body mass index, smoking status, first-degree relative with diabetes, presence of a dental prosthesis, presence of mobile teeth, history of periodontal treatment, and probing pocket depths ≥5 mm as well as prespecified interaction terms. In SHIP-TREND-0, the model area under the curve (AUC) was 0.72 (95% confidence interval [CI] 0.69, 0.75), calibration in the large was −0.025. The point score AUC was 0.69 (95% CI 0.65, 0.72), with sensitivity of 77.0 (95% CI 76.8, 77.2), specificity of 51.5 (95% CI 51.4, 51.7), negative predictive value of 94.5 (95% CI 94.5, 94.6), and positive predictive value of 17.0 (95% CI 17.0, 17.1). External validation of the point score gave an AUC of 0.69 (95% CI 0.66, 0.71), sensitivity of 79.2 (95% CI 79.0, 79.4), specificity of 49.9 (95% CI 49.8, 50.00), negative predictive value 91.5 (95% CI 91.5, 91.6), and positive predictive value of 25.9 (95% CI 25.8, 26.0). A validated prediction model involving dental variables can identify NDH or undiagnosed T2DM. Further studies are required to validate the model for different European populations.

Keywords: dysglycemia, periodontitis, prediction modeling, external validation, dental, prediabetes

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A supplemental appendix to this article is available online.

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Introduction

Type 2 diabetes (T2D) affects 60 million Europeans; 10% of those older than 25 y. Worldwide, 422 million adults are living with the condition (World Health Organization [WHO] 2016), with an estimated 325 million at high risk of developing T2D (WHO 2016). Diabetes-associated morbidity is significant, as is the associated economic burden, estimated as 1.32 trillion US dollars (2015), and expected to rise to 2.1 trillion US dollars by 2030 (Bommer et al. 2018). Prevention of T2D is an international health priority (WHO 2017). People with nondiabetic hyperglycemia (NDH) can delay the onset of, or even prevent, T2D via lifestyle measures or metformin (Barry et al. 2017).

Dental care professionals (DCPs) are aware of the association between tooth loss and T2D and the established bidirectional relationship between periodontitis and T2D (Sanz et al. 2018). Importantly, many people attend dental services regularly, irrespective of their general health. The reported proportion of dental patients identified as high risk for hyperglycemia approximates 32% to 40%, with the proportion with undiagnosed diabetes 11% to 47% (Chinnasamy and Moodie 2020).

DCPs are trained in risk assessment and delivering preventative advice, such as smoking cessation and dietary advice, both shared risk factors for periodontitis and T2D. There is growing support from multiple stakeholders for engaging DCPs in this manner (Greenberg et al. 2015; Yonel, Batt, et al. 2020; Yonel, Yahyouche, et al. 2020). Furthermore, studies in Europe, Africa, America, Asia, and the Middle East demonstrate support, feasibility, and cost-effectiveness of using DCPs to undertake targeted risk assessments of patients at high risk of T2D (AlGhamdi et al. 2013; Neidell et al. 2017; Yonel, Cerullo, et al. 2020).

Several risk-assessment models for T2D exist. However, many of these models have been developed for use outside dental settings and involve collecting data that would not routinely be available to dental teams, such as waist circumference, cholesterol, and blood pressure (Gray et al. 2010; Collins et al. 2011; Talakey et al. 2022). FINDRISC is a widely used model across Europe to identify people at risk of developing T2D and has been validated for use in several European populations (Jølle et al. 2019; Kraege et al. 2020). Only 2 models containing dental variables have been validated specifically for use in dental settings (Talakey et al.2022). Given the association between T2D and periodontitis, the addition of dental parameters within prediction models may aid the detection of NDH/T2D; however, further validation studies are required to demonstrate this.

Here we assessed whether measures routinely available to DCPs, such as periodontal parameters and the number of missing teeth, could be incorporated into a prediction model to allow DCPs to identify individuals who have undiagnosed NDH or T2D. Importantly, external validation was undertaken using an independent data set from the same geographic region.

Current literature supports a 2-staged targeted risk-detection process in dental settings, with a score identifying potentially at-risk patients, with anyone above the threshold being offered a point-of-care HbA1c test to confirm risk status (Yonel, Batt, et al. 2020; Yonel, Cerullo, et al. 2020). This validated risk assessment tool may assist in identifying those patients who would most benefit from blood sample collection and onward referral to an appropriate health care professional for formal diagnosis and management.

Methods

Study Design, Setting, and Source of Data

This was a 2-phased study using data sets derived from the Studies of Health in Pomerania (SHIP) project. The SHIP project comprised representative population-based cohort studies conducted in northeast Germany. SHIP-TREND-0 recruited 4,420 participants aged 20 to 84 y (50.2% response), of whom 4,322 received an oral examination (Schutzhold et al. 2015; Table 1). Phase 1 of our study involved the development of a model and point score for dental settings using SHIP-TREND-0.

Phase 2 involved external validation of the model and point score, using an independent data set, SHIP-START-0. This cohort included 4,308 individuals aged 20 to 81 at the time of baseline examination (Hensel et al. 2003). The cohort recruited 4,308 individuals, of whom 4,288 underwent oral examination (Schutzhold et al. 2015). Both SHIP-TREND-0 and SHIP-START-0 contained relevant medical and dental clinical data for model development and validation (Völzke et al. 2011).

Eligibility Criteria

Participants aged ≥40 y were eligible for inclusion. Those with existing physician-diagnosed diabetes or taking medications for diabetes were excluded.

Outcome and Candidate Predictors

The outcome variable was either NDH or undiagnosed T2D. A participant was deemed to have NDH if their HbA1c was ≥6.0% (≥42 mmol/mol) and <6.5% (<48 mmol/mol). A participant was considered to have undiagnosed T2D if they recorded an HbA1c of ≥6.5% (≥48 mmol/mol; National Institute for Health and Care Excellence 2017).

Thirteen candidate predictors were identified a priori using existing literature (Gray et al. 2010). Candidate predictors consisted of those recognized risk factors used in the previously developed T2D prediction models (Gray et al. 2010; Acharya et al. 2018), which are routinely available in a dental setting, for example, age, sex, and smoking status (Talakey et al.2022). The oral and dental risk factors were selected based on mechanistic plausibility and literature review (Gray et al. 2010; Strauss et al. 2010; AlGhamdi et al. 2013; Engstrom et al. 2013; Lalla et al. 2013; Neidell et al. 2017; Jølle et al. 2019; Kraege et al. 2020). Prespecified interaction terms were identified a priori, including age × body mass index (BMI), age × smoking status, BMI × smoking status, and first-degree relative (parent or sibling) with T2D × smoking status (Appendix 1).

Table 1. Baseline Characteristics of Eligible Participants in Both Development and Validation Data Sets for Complete Case Data.

	SHIP-Trend-0	SHIP-START-0
	Development Data	Validation Data
Variable	*n* = 3,339	*n* = 2,381
Age, y	58.6 ± 11.3	56.3 ± 9.9
Male sex	1,646 (49.3)	1,182 (49.6)
BMI, kg/m^2 (derived from self-reported height and weight)	28.9 ± 5.2	28.0 ± 4.5
Waist circumference, cm	94 ± 14.2	91.9 (SD 12.8)
Smoking status		
Never smoker	1,266 (37.9)	896 (37.6)
Former smoker	1,342 (40.2)	872 (36.6)
Current smoker	731 (21.9)	613 (25.7)
First-degree relative (parent or sibling) with T2DM, yes	1,014 (30.4)	714 (30.0)
Known hypertension or prescribed antihypertensive medication, yes (self-reported)	1,797 (53.8)	1,729 (72.6)
Glycated hemoglobin, %	5.5 ± 0.87	5.4 ± 0.68
Edentulism, yes (complete)	269 (8.1)	301 (12.6)
Self-reported bleeding on brushing, yes	1,194 (35.8)	772 (32.4)
Self-reported mobility of teeth, yes	368 (11.0)	329 (13.8)
Dental prosthesis—removable (partial or complete), yes	1,155 (34.6)	555 (23.3)
Number of missing teeth	10.1 ± 8.9	12.3 ± 9.2
Visited the dentist in the last 12 mo, yes (self-reported)	2,634 (78.9)	2,047 (86.0)
CDC/AAP classification of periodontitis		
No/mild periodontitis	1,341 (40.2)	923 (38.8)
Moderate periodontitis	1,229 (36.8)	879 (36.9)
Severe periodontitis	769 (23.0)	579 (24.3)
Undiagnosed NDH/T2DM, yes	329 (9.9)	403 (16.9)
Undiagnosed T2DM, yes	74 (2.2)	99 (4.2)

Data are presented as mean ± standard deviation or number (percentage). AAP, American Association of Periodontology; BMI, body mass index; CCA, complete case analysis; CDC, Centers for Disease Control and Prevention; NDH, nondiabetic hyperglycemia; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Sample Size Determination Phase 1 (Model Development)

We assessed whether the available data were of sufficient size for model development using criteria proposed by Riley et al (Riley et al. 2018; Riley et al. 2020). The minimum sample size required was 4,616 individuals with 462 events (Riley et al. 2020). SHIP-TREND-0 (development data set) has an eligible sample of 3,339 with 329 events (an outcome fraction of 9.9%).

Sample Size Determination Phase 2 (Model Validation)

The sample size of the validation cohort (SHIP-START-0) was 2,381 with 403 events (an outcome fraction of 16.9%).

Missing Data

Data were imputed for participants who did not receive an oral exam (Appendix 2). To account for potential biases associated with missing data, multiple imputation using chained equations was used (Appendix 3). All candidate predictors plus the outcome variable were imputed (Moons et al. 2006). Twenty imputations were used (Von Hippel 2020).

Phase 1: Model Development

Initially, descriptive analyses of the original data were undertaken for candidate predictors to determine potential complexity and degree of nonlinearity within the model. Departures from linearity were tested and continuous predictors modeled with restricted cubic splines using 3 knots and assessed graphically. The Wald's test statistic was used to assess if nonlinear terms offered improvement in fit over a linear model (Vittinghoff et al. 2012). Loess smoother plots, Bayesian information criterion, and likelihood ratio tests were assessed at each stage.

Variables included in the model were selected using backward selection with a threshold of 0.2 for inclusion (Moons et al. 2012; Harrell 2015). The 0.2 threshold is the *P* value at which variables are retained in the model. A higher significance level for variable selection was used so that important variables relevant to the outcome were not missed and to avoid deleting less significant variables that may satisfy practical and clinical reasoning. Model selection was conducted separately in each of 20 imputations (Wood et al. 2008; Harrell 2015). Where a variable was retained in at least 50% of imputed data sets, it was included into the final model (Wood et al. 2008; Harrell 2015). Regression coefficients in each imputed data set were combined using Rubin's rules to provide the final model. Having fitted the main effects model, additivity assumptions

were checked through testing the prespecified interaction terms. Where the global test for additivity was significant or equivocal, prespecified interactions were retained in the model (Harrell 2015).

Heuristic shrinkage (Van Houwelingen–Le Cessie method) was applied to account for potential overfitting. The shrinkage factor was calculated and applied to the model and the intercept reestimated. The shrinkage-adjusted model is reported as the final model (Moons et al. 2012; Harrell 2015; Steyerberg 2019).

Discrimination was assessed via the area under the receiver operator characteristic curve. Calibration was assessed visually using calibration plots (Appendix 4–7) and quantified by the calibration in the large (CITL; an ideal calibration slope is 1, whereas CITL should be 0, representing the number of observed outcome events matching the number of predicted outcome events).

Score Development

The Diabetes risk assessment in Dentistry Score (DDS) was developed for simple and efficient use in dental settings. It is designed as a paper-based point-score system limiting the need for computers and additional chairside software, allowing greater accessibility. The same model development process reported in phase 1 was repeated with the omission of the prespecified interaction terms, allowing regression coefficients and intercepts to be reestimated for development of the simplified score. The method outlined by Bonnet et al. (2019) was used to create the point score system (Appendix 8a).

Engstrom et al. (2013) proposed a basic model for diabetes detection for use in dental settings that involved using only age and BMI. This model was used as a comparator for the DDS.

Phase 2: External Validation

The external performance of both our model and DDS was assessed using data from SHIP-START-0. This was assessed in each of the imputed data sets, and the intercept was reestimated to ensure the mean predicted risk equaled the observed risk. Calibration, discrimination (c-statistic), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Decision curve analysis (DCA) was undertaken as a measure of clinical utility. DCA allows the net benefit of the DDS point score to be compared with alternative strategies (i.e., current practice, which involves no testing in dental settings or alternatively a population-based screening approach of testing everyone). The net benefit is assessed over a range of threshold probabilities.

All analyses and modeling were completed in Stata/SE 16.0 (StataCorp, College Station, TX, USA).

Results

SHIP-TREND-0 included 3,339 eligible participants and 329 (10%) outcome events, of whom 74 (2%) had undiagnosed T2D and 255 (8%) had NDH. SHIP-START-0 included 2,381 eligible participants including 403 (17%) outcome events, of whom 99 (4%) had undiagnosed T2D and 304 (13%) had NDH.

Model Development

Most missing data involved the dental variables, as immobile study participants were examined at home and did not undergo oral examinations. The percentage missing data related to the outcome variable was 0.5% and <1% for all nondental predictors. Missing data for dental predictors ranged from 0.0 to 18.1% (Appendix 3).

Predictors included in the final model are presented in Table 2 with their respective β coefficients, the model intercept, and shrinkage factor used to adjust the model. Nonlinear terms were not required. The shrinkage factor was 0.90 and applied to account for model optimism. The c-statistic for the shrinkage-adjusted model was 0.72 (95% confidence interval [CI] 0.69–0.75), and the CITL was acceptable at −0.025. The calibration plots of the unadjusted and adjusted models for each imputation set are in Appendix Tables 4 and 5, respectively, and showed unadjusted model slopes of 0.98 to 1.01. The expected/observed (E/O) ranged from 0.98 to 1.02. Shrinkage-adjusted models in each imputation showed slopes of 1.07 to 1.10, and E/O ranged between 1.00 and 1.04.

The DDS (Table 3A and B, Appendix Table 8a) had an area under the curve (AUC) of 0.68 (95% CI 0.65, 0.72), and calibration plots are shown in Appendix Figure 9. The mean score was 7.81 (95% CI 7.66, 7.95), with a range of 0 to 20. At the optimal threshold, the sensitivity and specificity were 77.0 (95% CI 76.8, 77.2) and 51.5 (95% CI 51.4, 51.7) respectively. The PPV was 17.0 (95% CI 17.0, 17.1), and the NPV was 94.6 (95% CI, 94.5, 94.6).

External Validation

The AUC for the final model was 0.69 (95% CI 0.67, 0.72). Calibration plots for each imputation are presented in Appendices 6 and 7 and show unadjusted model slopes of 0.90 to 0.94 and E/O of 0.68 to 0.69. The shrinkage-adjusted models show slopes of 0.92 to 0.96. DCA was used to assess clinical utility over a range of thresholds; the graphs for each imputation are given in the supplemental material (Appendix 9a). These demonstrate the net benefit of the final model in the validation data at thresholds of 0.1 to 0.35.

The DDS had an AUC of 0.69 (95% CI 0.66, 0 71; Table 3), and calibration plots can be seen in Appendix 10. The mean score was 8.1 (95% CI 8.0, 8.3). At the optimal threshold defined in SHIP-TREND-0, the sensitivity and specificity were 79.2 (95% CI 79.0, 79.4) and 49.9 (95% CI 49.8, 50.0), respectively, with a PPV of 25.9 (95% CI. 25.8, 26.0) and NPV of 91.5 (95% CI 91.5, 91.6).

The model proposed by Engstrom et al. (2013) for use in the dental setting had an AUC in SHIP-START-0 of 0.65 (95% CI 0.63, 0.68).

Table 2. Model Parameters for the Final Model Based on SHIP-TREND-0 (Development Data).

Variable	β (95% CI)	OR (95% CI)
Male sex	0.226 (−0.030, 0.483)	1.25 (0.97, 1.62)
Age, y	0.150 (0.080, 0.220)	1.16 (1.08, 1.25)
BMI, kg/m^2	0.236 (0.083, 0.390)	1.27 (1.09, 1.48)
Smoking status (ref. never smoker)		
Former smoker	−1.667 (−3.340, 0.008)	0.19 (0.04, 1.01)
Current smoker	−1.495 (−3.399, 0.409)	0.22 (0.03, 1.51)
First-degree relative (parent or sibling) with type 2 diabetes, yes	0.167 (−0.251, 0.585)	1.18 (0.78, 1.80)
Self-reported mobility of teeth, yes	0.305 (−0.049, 0.659)	1.36 (0.95, 1.93)
Edentulism, yes	0.455 (0.035, 0.875)	1.58 (1.04, 2.40)
Have you been treated for gum disease in the last 5 y (periodontitis treatment)?, yes	−0.261 (−0.619, 0.097)	0.77 (0.54, 1.10)
Number of sites with ≥5 mm pockets (ref. 0 sites)		
Up to 2 sites	−0.183 (−0.536, 0.171)	0.83 (0.59, 1.19)
3 or more sites	0.100 (−0.266, 0.466)	1.11 (0.77, 1.59)
Interaction term for Age × BMI	−0.003 (−0.006, −0.001)	1.00 (0.99, 1.00)
Interaction term for BMI × Smoking status		
BMI × Former smoker	0.043 (−0.012, 0.098)	1.04 (0.99, 1.10)
BMI × Current smoker	0.069 (0.005, 0.134)	1.07 (1.01, 1.14)
Interaction term for first-degree relative (parent or sibling) with type 2 diabetes × Smoking status		
First-degree relative (parent or sibling) with type 2 diabetes × Former smoker	0.662 (0.081, 1.242)	
First-degree relative (parent or sibling) with type 2 diabetes × Current smoker	−0.376 (−1.092, 0.340)	
Intercept	−12.257 (16.835, −7.678)	

The shrinkage factor applied was 0.912. β, linear regression coefficient; BMI, body mass index; CI, confidence interval.

Discussion

This model, which used data routinely available to DCPs, exhibited acceptable performance for the detection of NDH/undiagnosed T2D. Many diabetes prediction models exist for use in medical settings, but most include data unavailable to DCPs (cholesterol/waist circumference). Our model demonstrates that the omission of data inaccessible to DCPs offered a broadly comparable performance with those validated for use in medical settings.

A recent series of papers by Riley et al. (2018, 2020) highlights the importance of adequate sample sizes when developing models and outlines a novel method to calculate the required sample size and number of events per sample. Of the models developed for use in the dental setting (Appendix 12), most did not undertake external validation (Talakey et al. 2022) nor report their full model, limiting the ability of external validation by others.

Our study used representative population-based cohort studies for development and external validation. Although potentially marginally underpowered, it has been validated on an independent external data set, unlike most published studies in this field. A further strength is publication of the full model enabling independent validation. Our study includes parameters routinely available to DCPs to facilitate uptake within dental settings. (supplemental table, Appendix 12).

Guidance on sample size (and number of events) required to validate multivariable prediction models is less clear (Collins et al. 2016; Riley et al. 2016). Consensus was that >250 events were required to validate multivariable prediction models (Steyerberg 2019). After completion of our study, new guidance on sample size requirements for validation studies were published (Riley et al. 2021). To account for optimism within the data, a shrinkage factor was derived and applied to the model. Importantly, the model was also externally validated using a second independent data set from the same region.

The model described was designed for use in high-street dental settings. The threshold was therefore designed to optimize sensitivity, accepting a reduction in specificity; accepting a higher proportion of false positives to minimize the false negatives. Limiting false positives is important at a population level, as it may result in unwarranted referrals for diagnostic tests with associated cost. This has been addressed in the literature previously, whereby a 2-stage risk-assessment process was advocated (Yonel, Batt, et al. 2020; Yonel, Cerullo, et al. 2020). The ease of use and improved practical application of a risk model that identifies true cases can be used as a first-stage assessment. Subsequent point-of-care tests within dental settings then improve the precision of the overall risk assessment by filtering the false positives (Yonel, Yahyouche, et al. 2020).

The proportion of missing data associated with a subsection of the population sample is a study limitation. Where data were collected within the clinical setting, there was a low level of missing data (Appendix 3). A subset of the population (SHIP-Mobile) was unable to access the research site. Those participants were visited at home; thus, this negatively affected data capture and disproportionately affected the dental variables. The low levels of missing data in the clinical setting, however, reflect the proposed real-world application for our model.

Models developed in 1 population are applicable only to that population, and models rarely transfer geographically or temporally; thus, validation studies for other populations are required (Steyerberg and Harrell 2016). Although this model

Table 3. (A) DDS A Points-Score System for Probability of NDH/T2DM for Use in Dental Settings.

Variable Definition	Score
Sex	
Female	0
Male	1
Age, y	
40–49	0
50–59	2
60–69	4
70+	7
Body mass index, kg/m^2	
<25	0
25 and <30	2
30 and <35	3
≥35	6
Smoking status	
Never smoker	0
Former smoker	1
Current smoker	2
First-degree relative (parent/sibling) with type 2 diabetes?	
No	0
Yes	1
Do you have mobile teeth?	
No	0
Yes	1
Are you edentulous?	
No	0
Yes	2
Have you been treated for gum disease in the last 5 y (periodontitis treatment)?	
No	0
Yes	1
Number of sites with ≥5-mm probing pocket depths	
0–2	0
≥3	1

(B) Probabilities of the Outcome That Corresponds to the Points Total.

Points Total	Estimation of Risk
0	0.016
1	0.0205
2	0.0261
3	0.0333
4	0.0423
5	0.0536
6	0.0677
7	0.0852
8*	0.1067
9	0.1329
10	0.1643
11	0.2014
12	0.2444
13	0.2932
14	0.3473
15	0.4057
16	0.4668
17	0.529
18	0.5902
19	0.6488
20	0.7033
21	0.7525
22	0.7959
23	0.8334

Accompanying table of probabilities (absolute risk predictions) to allow the point score to be translated to predicted risk.
*In our data, the optimal point at which to refer patients is a score ≥8; at this cut point, the performance of the score is an area under the curve of 0.69 (95% confidence interval [CI] 0.66, 0.71), sensitivity of 79.2 (95% CI 79.0, 79.4), specificity of 49.9 (95% CI 49.8, 50.00), positive predictive value of 91.5 (95% CI 91.5, 91.6), and negative predictive value of 25.9 (95% CI 25.8, 26.0)

performs well in a German population, further validation studies by independent research groups are needed to determine its performance in other diverse populations. Further work is also needed to determine how well the model performs within different health care systems across Europe.

To date, 14 studies have been published in the peer-reviewed literature describing the development of models that use dental data to identify those at risk of NDH/T2D. Of those 14 studies, half were developed in a US population, only 2 were externally validated, and only 3 reported their full model allowing others to externally validate their work (supplemental table, Appendix 12).

Strauss et al. (2010) used data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and found that 63% of those without periodontitis and 93% of those with periodontitis met American Diabetes Association guidelines for diabetes screening. Of those at risk with periodontitis, 34% had seen a dentist in the past 6 mo, 50% in the past 12 mo, and 60% in the past 24 mo. The study highlights that patients with periodontitis are both at higher risk for developing T2D and likely to be seen by a DCP, placing dental teams in an ideal position to undertake targeted risk-based detection for NDH/T2D.

There is broad stakeholder support for DCPs identifying cases of NDH/T2D (Yonel, Batt, et al. 2020). The literature supports a 2-stage process with initial targeted risk-based detection via screening questionnaire followed by point-of-care testing for those above the threshold (Yonel, Cerullo, et al. 2020). A 2-stage process is likely to reduce the number of unnecessary onward referrals to medical professionals for formal diagnosis and management.

Our model is reported in full and thus provides a foundation for further research to validate both the model and the DDS in different populations and to test the clinical and cost-effectiveness of DCPs undertaking such a process. If future research proves the model performs well with different populations, there may be scope for inclusion of such a model in digital health records, opening the door to the development of new integrated care pathways that bridge medical and dental primary care.

Care pathways need to be developed with caution and in conjunction with all stakeholders. It should be ensured that DCPs can refer appropriately to primary care physicians for formal diagnosis, management, and appropriate prevention services. Clear referral protocols must be developed and will likely differ between countries and health systems. Importantly, all relevant stakeholders must remain informed about the patients' journey after risk assessment.

Although our results are promising, further work is required to externally validate the model in different populations, especially given that a limitation of the SHIP data set is a lack of racial/ethnic diversity and the local population characteristics are unique to the region in East Germany. Unlike many other reported studies, we have been transparent in our reporting, publishing our full model as we recognize this limitation and wish to facilitate and support robust external validation of the model in further populations to account for regional differences in population composition.

In addition, further work of interest could include the comparison of our model with other models reported in the literature. A recent study comparing 4 validated and frequently used T2D risk tools in medical settings found considerable variation between the tools in the proportion of patients identified as high risk (Gray et al. 2015). This highlights the importance of ensuring that model performance is assessed in the specific population on which it will be used. Additional research on viability, feasibility, implementation, and cost-effectiveness within different health care systems is also required.

To conclude, we report a validated prediction model for NDH/T2D in dental settings. Validation in additional populations is required.

Author Contributions

Z. Yonel, contributed to conception and design, data analysis and interpretation, drafted and critically revised the manuscript; T. Kocher, contributed to data acquisition, critically revised the manuscript; I.L.C. Chapple, contributed to conception, critically revised the manuscript; T. Dietrich, contributed to conception, data interpretation, critically revised the manuscript; H. Völzke, M. Nauck, contributed to data acquisition and analysis, critically revised the manuscript; G. Collins, contributed to data analysis, critically revised the manuscript; L.J. Gray, contributed to data analysis, conception and design, critically revised the manuscript; B. Holtfreter, contributed to conception and design, data acquisition, analysis, and interpretation, critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

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Disclaimers

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Resources

Data from SHIP are available after data application and signature of a data transfer agreement. The data dictionary and the online application form are available at fvcm.med.uni-greifswald.de/dd_service/data_use_intro.php. Involving a local collaborative partner to facilitate the application process is recommended.

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Statement of Candidates Contribution

1. **Use of dental practices for the identification of adults with undiagnosed type 2 diabetes mellitus or non-diabetic hyperglycaemia: a systematic review** (40)

ZY was responsible for the search strategy, screening of titles, abstracts, and full texts. Generating data extraction forms and piloting data extraction. Data extraction, data synthesis and drafting the manuscript.

2. **The Role of the Oral Healthcare Team in Identification of Type 2 Diabetes Mellitus: A Systematic Review** (41)

ZY was responsible for the search strategy, screening of titles, abstracts, and full texts. Generating data extraction forms and piloting data extraction. Data extraction, data synthesis and drafting the manuscript.

3. **Patients' attendance patterns to different healthcare settings and perceptions of stakeholders regarding screening for chronic, non-communicable diseases in high street dental practices and community pharmacy: a cross-sectional study** (42)

ZY was responsible for planning and delivery of the study, data collection, management and analysis and drafting the manuscript.

4. **Patient acceptability of targeted risk-based detection of non-communicable diseases in a dental and pharmacy setting.** (43)

ZY was responsible for planning and delivery of the study, data collection, management and analysis and drafting the manuscript.

5. **Concordance of three point of care testing devices with clinical chemistry laboratory standard assays and patient-reported outcomes of blood sampling methods.** (44)

ZY was responsible for planning and delivery of the study, data collection, management and analysis and drafting the manuscript.

6. **The development and external validation of a diagnostic, multi-variable prediction model to identify non-diabetic hyperglycaemia and type 2 diabetes in high-risk patients attending the dental clinic: The Diabetes Risk Assessment in Dentistry Score.** (45)

ZY was responsible for planning and delivery of the study, statistical analysis plan, data management and analysis and drafting the manuscript.

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SCHOOL OF DENTISTRY

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Director of Research, Institute of Clinical Sciences,
College of Medical & Dental Sciences

P.A. [redacted]

Monday, 31 October 2022

To Whom it may concern

Re: Zehra Yonel – PhD thesis by publication - *Early detection of Non-diabetic Hyperglycaemia / type 2 diabetes in dental practice settings*

Zehra Yonel was successful in securing an NIHR Doctoral Research Fellowship for a period of 3-years for the above proposal. At the same time, she became the Diabetes UK Fellow due to a collaboration between the NIHR and Diabetes UK.

Zehra has worked tirelessly on her research and achieved substantial success with several prizes won and excellent collaborations secured with Leicester, Oxford and Greifswald (Germany). She has also set up a primary care practice-based network to validate the predictive model she has developed for detecting cases of diabetes or pre-diabetes in high street dental practice settings.

I confirm that the 6 papers she has presented as part of her thesis are her work, and her statements of contribution are accurate. The sixth paper "*The development and external validation of a diagnostic, multi-variable prediction model to identify non-diabetic hyperglycaemia and type 2 diabetes in high-risk patients attending the dental clinic: The Diabetes Risk Assessment in Dentistry Score*" is published in the prestigious Journal of Dental Research, the top dental research journal in the world.

Yours sincerely

[redacted]

Professor Iain Chapple
Head of the School of Dentistry

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Appendix 1: Prior published work that supports manuscript 1:

I. **Yonel Z**, Sharma P, Gray LJ. Use of Dental Practices for the Identification of Adults with Undiagnosed Type 2 Diabetes Mellitus or Nondiabetic Hyperglycaemia: Protocol for a Systematic Review. JMIR Res Protoc. 2018 Nov 19;7(11):e11843. doi: 10.2196/11843. PMID: 30455173; PMCID: PMC6277823. (46)

II. **Yonel Z**, Sharma P. The Role of the Dental Team in the Prevention of Systemic Disease: The Importance of Considering Oral Health As Part of Overall Health. Prim Dent J. 2017 Aug 31;6(3):24-27. doi: 10.1308/205016817821930980. PMID: 30188311. (47)

Appendix Manuscript I

Use of Dental Practices for the Identification of Adults with Undiagnosed Type 2 Diabetes Mellitus or Nondiabetic Hyperglycaemia: Protocol for a Systematic Review.

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Protocol

Use of Dental Practices for the Identification of Adults With Undiagnosed Type 2 Diabetes Mellitus or Nondiabetic Hyperglycemia: Protocol for a Systematic Review

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a growing global health burden and is expected to affect more than 590 million people by the year 2035. Evidence exists to demonstrate that dental settings have been used for risk assessment and identification of individuals who may be at high risk for T2DM or who may already unknowingly have the condition.

Objective: This protocol aims to outline the methodology that will be undertaken to synthesize the literature relating to the use of primary care (nonhospital-based) dental services for the identification of undiagnosed T2DM or prediabetes—often termed nondiabetic hyperglycemia—in adult patients.

Methods: This paper outlines the protocol that will be followed to conduct a systematic review and meta-analysis of the available literature. The protocol outlines the aims, objectives, search strategy, data extraction and data management methods, as well as the statistical analysis plan. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines were followed in developing the protocol as were elements of the Cochrane handbook.

Results: We expect the systematic review to be completed within 18 months of publication of this protocol and expect to see a high degree of heterogeneity in the existing literature.

Conclusions: This review is of importance as it will synthesize the existing evidence base and inform future studies in the field. Following the publication of the protocol, the review will be registered on Prospective Register of Systematic Reviews. Following the completion of the review, results will be published in a suitable peer-reviewed journal.

International Registered Report Identifier (IRRID): PRR1-10.2196/11843

(JMIR Res Protoc 2018;7(11):e11843) doi:10.2196/11843

KEYWORDS

adults; case-finding; dental; diabetes; nondiabetic hyperglycemia; risk assessment

Introduction

Type 2 diabetes mellitus (T2DM) is a growing public health concern, accounting for 10% of the UK National Health Service (NHS) budget, a proportion predicted to rise to 17% by 2035 [1]. In addition to the 3.8 million people currently diagnosed with T2DM in the United Kingdom, it is estimated that almost 1 million UK residents have undiagnosed T2DM [2] and a further 12 million are at high risk for developing the condition [3]. Globally, the incidence of T2DM is expected to exceed 592 million by the year 2035 [4]. Individuals may remain undiagnosed for many years due to the condition being symptom-free in its early stages [5]. This has implications for the secondary prevention and management of the condition.

The UK National Screening Committee states that there are benefits to early identification of individuals at risk for

developing diabetes and those with nondiabetic hyperglycemia (NDH), also known as prediabetes, as well as those with undiagnosed diabetes [3]. Advances in diabetes care mean that earlier detection may reduce the risk of complications, such as heart attacks, stroke, and blindness [6,7]. Evidence exists that diabetes is preventable in those at high risk [8]. Hence, the NHS has developed the Diabetes Prevention Programme. Novel approaches to identify cases of previously undiagnosed diabetes and high-risk individuals may result in improved health outcomes, improved quality of life for patients, and reductions in cost to the NHS.

In the United Kingdom, 60% of the adult population routinely attends high-street dentists for regular check-ups, even when they have no concerns [9]. Furthermore, patients' diabetes status influences their dental management; therefore, it is useful for dentists to be aware of this condition. Using dental visits for early diabetes detection represents a unique opportunity to access large proportions of the population for diabetes screening.

The National Institute for Care and Health Excellence pathways exist for allied health care professionals, including dentists, relating to risk assessment for diabetes [10] in community and primary care settings. Some UK community pharmacists perform risk assessment of patients for diabetes. However, using primary dental practices has not been widely explored as an option for identifying high-risk individuals and, therefore, represents a potential missed opportunity.

Studies conducted in the United States have indicated that dental practices can be effective in identifying those at high risk for diabetes [11-13]. There have also been studies in Europe that support these findings [14-16]. Dental practices in the United Kingdom may also offer the opportunity for proactive, early case detection of high-risk individuals and those who already unknowingly have T2DM.

Despite the existing literature published in the field to date, no published systematic reviews have synthesized the current evidence base for the use of primary care dental settings for the detection of T2DM and NDH. The aim of this protocol is to outline the design of a systematic review investigating the available literature for utilizing dental settings to case-find previously undiagnosed T2DM and NDH. The primary aim of the review will be to establish the identification rate of previously undiagnosed diabetes and NDH and the opinions, benefits, and barriers related to case-finding T2DM and NDH in dental settings.

Methods

Protocol Guidelines Followed

The intention to conduct a systematic review is evidenced through registration with the prospective register of systematic reviews (PROSPERO), the Web-based international prospective register of systematic reviews, at the time of protocol conception. This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement [17] alongside elements from the Cochrane handbook for systematic reviews [18].

Review Question and Objective

This review aims to identify the literature relating to the use of primary care (nonhospital-based) dental services for the identification of undiagnosed T2DM and NDH—often termed prediabetes—in adult patients. The review will have a particular focus on the pick-up rate of new cases of NDH and T2DM with the following additional questions, which this review will aim to answer:

- What methodology was utilized within the dental practice for case-finding?
- What were the recruitment rates within the studies?
- What are the opinions of patients and health care professionals relating to such services?
- What are the reported barriers to uptake of any such implemented services?
- What are the reported benefits of utilizing such services?

The Population Intervention Control Outcome format was followed; this format involves clearly identifying participants, intervention, comparator, and outcome within the research question. For this review, these were patients (P) aged >18 years attending primary care (nonspecialist practice) dental services. The specific intervention (I) for this review is focused on the risk assessment methods used for identification of T2DM or NDH (prediabetes). It is recognized that a number of methods for risk assessment of patients have been discussed in the literature. This includes using questionnaires, finger-prick point-of-care testing, gingival crevicular fluid samples, and both one- and two-stage procedures utilizing a combination of these methods; these differing methods will act as the comparators (C). This review will attempt to capture and compare the full range of assessments used.

Outcome Measure

The primary outcome measure for this systematic review is the identification of patients with NDH or T2DM using risk assessment methods in dental care settings. The secondary outcomes include identification of methodologies utilized in the dental practice for case-finding, establishing recruitment rates in the studies, and gaining insight into the opinions of patients and health care professionals relating to case-finding. In addition, the review will aim to enhance the understanding of reported barriers to uptake of any such implemented services and any reported identified benefits to utilizing dental settings to case-find NDH and T2DM.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria have been presented in Textboxes 1 and 2, respectively.

Textbox 1. Inclusion criteria.

- Adults aged >18 years
- English language literature
- Diabetes risk assessment conducted
- Risk assessment based in primary care dental settings

Textbox 2. Exclusion criteria.

- Non-English language
- Animal studies
- Nonprimary care dental settings

Table 1. Draft of search strategy to be used.

Query	Items found
Search (((((((((screening) OR "risk assessment") OR "case detection") OR "case finding") OR "identification") OR "risk detection") OR "diagnosis")) AND ((((((((("diabetes mellitus") OR "diabetes") OR "type 2 diabetes") OR "type two diabetes") OR TTDM) OR T2DM) OR prediabetes) OR Pre-diabetes) OR "non diabetic hyperglycaemia") OR NDH)) AND (((((dental) OR dentistry) OR "primary dental care") OR "general dental practice") OR dentist)	1466
Search ((((dental) OR dentistry) OR "primary dental care") OR "general dental practice") OR dentist	73,7631
Search (((((((("diabetes mellitus") OR "diabetes") OR "type 2 diabetes") OR "type two diabetes") OR TTDM) OR T2DM) OR prediabetes) OR Pre-diabetes) OR "non diabetic hyperglycaemia") OR NDH	600,088
Search ((((((screening) OR "risk assessment") OR "case detection") OR "case finding") OR "identification") OR "risk detection") OR "diagnosis"	3,232,401

Search Strategy

To identify the eligible literature, the following electronic bibliographic databases will be searched: Medical Literature Analysis and Retrieval System Online, PubMed, The Cochrane Library, and Web of Science. The reference lists of all eligible full texts will be searched for additional papers for inclusion. In addition to electronic databases, trial registries such as Clinicaltrials.gov will be searched.

The search strategy will include terms relating to or describing the identification of NDH and T2DM in dental settings. The search terms will be adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials, where these are available (Table 1). There will be restrictions to English language only. Searches will be limited to 1950—search date to allow for replication. Furthermore, the searches will be rerun just before the final analyses and further studies retrieved for inclusion.

Risk of Bias

This review will not be restricted to only randomized controlled trials. A published and validated risk of bias assessment tool appropriate to the study type will be utilized [19] independently by two reviewers to determine the bias associated with included papers. The tool will be specific to the study design, and all papers included in the review will be appraised by the authors. Disagreement will be resolved by discussion, and where required, a third author will be consulted.

Data Extraction and Data Management

The search will be undertaken; all returned papers will have title and abstract screened independently by two researchers to establish studies that potentially meet the inclusion criteria. Calibration exercises will be undertaken until authors are consistent in their acceptance of suitable papers. Where there is disagreement regarding a paper's exclusion, consensus will be reached by a third reviewer. For the papers included, full text will be reviewed by the two authors, and any further exclusions will be determined by consensus and agreement among authors with reason for exclusions reported. Reason for exclusion at full-text stage will be recorded.

Electronic data extraction forms will be developed and piloted. The standardized prepiloted form will be used to extract data from included studies to assess the study quality and evidence synthesis. Extracted information will include the following: study setting, population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment, completion, and pick-up rates; outcomes and times of measurement; indicators of acceptability to users; suggested mechanisms of intervention action; and information about assessment of the risk of bias. This information will be collected independently by the two reviewers with discrepancies identified and resolved through discussion and, if required, with the third author. Where data are missing, attempts will be made to retrieve the data by contacting study authors. The key data to be extracted are presented in Textbox 3.

Textbox 3. Key data to be extracted.

- Study ID:
- Reviewer ID and name:
- Date of completion of this form:
- Title of report:
- Source [journal year; volume: pages]:
- Authors:
- Type of report [eg, full paper or abstract or unpublished]:
- Country where the trial was conducted:
- Funders of the study:
- Dates study was conducted:
- Type of study design [eg, observational or clinical trial (randomized, parallel, or cluster, etc)]
- Was the study multicenter? If so, how many centers were there?
- Risk of bias criteria—[dependent on study type]
- Inclusion criteria
- Exclusion criteria
- Participant information
  i. Age
  ii. Gender
  iii. Ethnicity
- Risk assessment method used
- Screening process
- Recruitment rates
- Prevalence of undiagnosed type 2 diabetes mellitus (T2DM) and nondiabetic hyperglycemia (NDH)
- Method for diagnosis of T2DM or NDH
- Stakeholder opinions [patients or dental team or health care professionals, etc]
- Barriers to risk assessment in dental settings
- Key findings
- Additional comments

Electronic data extraction form will be developed in Microsoft Excel with care to ensure that updated versions do not overwrite previous iterations of extracted data.

Strategy for Synthesis

If the included studies are sufficiently homogenous, a quantitative synthesis will be undertaken. However, it is anticipated that the included studies will demonstrate high levels of heterogeneity, resulting in a descriptive synthesis approach. The descriptive synthesis will be structured around the primary and secondary outcomes of the review. It is anticipated that there will be limited scope for meta-analysis because of the range of different outcomes measured, although we expect the percentage of cases of undiagnosed T2DM and NDH to be well reported across the assumed small number of existing studies. However, where studies have used the same risk assessment strategy with the same outcome measure, results will be pooled and meta-analysis undertaken. Any meta-analysis conducted will use a random effects model to pool data given the expected high levels of heterogeneity expected between studies.

Results

We expect the systematic review to be completed within 18 months of the publication of this protocol and expect to observe a high degree of heterogeneity in the existing literature.

Discussion

This review is of importance as it will synthesize the existing evidence base and inform future studies in the field. Following the publication of the protocol, the review will be registered on PROSPERO. Following the completion of the review, results will be published in a suitable peer-reviewed journal.

Conflicts of Interest

None declared.

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Abbreviations

NDH: nondiabetic hyperglycemia

NHS: National Health Service
PROSPERO: prospective register of systematic reviews
T2DM: type 2 diabetes mellitus

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Appendix Manuscript II

The Role of the Dental Team in the Prevention of Systemic Disease: The Importance of Considering Oral Health as Part of Overall Health. Page 50

THE ROLE OF THE DENTAL TEAM IN THE PREVENTION OF SYSTEMIC DISEASE: THE IMPORTANCE OF CONSIDERING ORAL HEALTH AS PART OF OVERALL HEALTH

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ABSTRACT

The global burden of non-communicable disease (NCD) is significant and the World Health Organization highlighted tackling non-communicable diseases (NCDs) as a key strategic objective in their 'Global action plan for the prevention and control of noncommunicable diseases, 2013–2020'. Dental teams see a large proportion of the UK population at regular intervals, including when patients deem themselves to be in good dental health. Given that many NCDs have shared risk factors, often behavioural with implications for oral and general health, dental teams are ideally placed to provide preventative advice for diseases beyond the oral environment. This article aims to assess the key risk factors for NCDs and oral diseases as well as assess the potential for dental care professionals (DCPs) to provide patients with general health advice based on their individual risk factors.

KEY WORDS
Non-Communicable Diseases, Prevention, Dental Care Professionals, Risk Assessment

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Currently, non-communicable diseases (NCDs) account for almost 66% of deaths globally).[1] Most deaths from NCDs are related to cardiovascular disease (CVD), chronic respiratory diseases, cancer and diabetes.[2] The prevalence of NCDs is increasing globally and their impact on the global disease burden and healthcare economy is substantial. Evidence suggests that 92% of older adults (>55 years) have at least one NCD and 77% have two NCDs.[3] The reason for the increasing prevalence of NCDs is due to an increase in prevalence of common risk factors such as poor diet, sedentary lifestyle, tobacco and alcohol use.[4] According to the World Health Organization (WHO), 38 million of the 56 million deaths in 2012 were due to NCDs.[2] Furthermore, the behavioural risk factors of poor diet, physical inactivity, smoking, drinking alcohol, and being overweight/obese – the main contributors to the NCD burden – also contribute a significant economic burden accounting for over 45% of total NHS costs (approximately £43bn) in the UK in 2006-2007.[5]

Dental caries is the most common non-communicable disease (NCD),[6] and periodontitis – in its severe form – is the sixth most prevalent human disease, affecting 11.2% of the world's population.[7,8] Although the mortality rate associated with dental NCDs is low, they may result in tooth loss which is associated with compromised diet and speech, and affect patients' psychosocial wellbeing and quality of life. These conditions, along with oral cancer, are NCDs which dentists routinely screen for, and preventative advice for dental disease is often provided at the individual patient level. Given that dental diseases and NCDs, which affect systems beyond the oral environment, share several common risk factors there is potential for dental care professionals (DCPs) to expand their role in the prevention of diseases beyond the oral environment. If DCPs routinely obtain information on patients social and dietary habits, they have the potential to be a key point of contact to inform patients of the wider risks to their general health and, where appropriate, instigate preventative regimes.

In this article, we aim to explore how the different forms of routine behavioural advice provided by DCPs impacts or may impact on other non-oral NCDs. Thereby we hope to highlight the role that DCPs can play in improving the overall health of their patients.

Diet

Diet plays a crucial role in the development and progression of many diseases. The global increase in prevalence of obesity is a major contributing factor in the rise of NCDs. The Global Burden of Disease Study in 2010 determined that dietary factors most detrimental to health were diets low in fruit and high in salt.[9] Various dietary factors were implicated in the development of ischaemic heart disease (IHD) and stroke, including reduced consumption of fruits, vegetables,

nuts and seeds, wholegrains, and the overconsumption of processed meat, red meat and both trans and saturated fats. In addition to cardiovascular disease, dietary factors have also been associated with diabetes and certain cancers.[9] Poor diet also contributes an economic burden – it's the behavioural risk factor that has the most significant impact on the NHS budget with poor diet-related ill-health costing the NHS approximately £5.8bn.[5]

DCPs routinely deliver dietary advice and utilise aids such as food diaries to assess patients' diets for elements which may be impacting negatively upon their dental status. These aids allow for personalised advice and suggestions targeted to the patient's individual needs, allowing for improved behaviour change. The main dietary elements which impact upon dental and oral health is consumption of sugars, acidic foods and beverages. Although globally dental caries is the most common NCD, according to the most recent Adult Dental Health Survey the prevalence of caries in the UK has dropped 18% between 1998 and 2009.[10] However, tooth surface loss has shown an increase in prevalence from 11% in 1998 to 15% in 2009.[11,12]

Patients are routinely informed about the risks of both the frequency and quantity of foods containing sugar in the diet that can lead to the development and progression of caries. Dental erosion due to consumption of highly acidic foods and drinks, especially carbonated drinks and fruit juices, are also an increasing concern. In addition to highly acidic contents, several of these beverages also contain a high amount of refined sugar. Evidence suggests that sugar-sweetened beverages have been implicated in many conditions including diabetes mellitus, increased body mass index, heart disease and ischaemic stroke.[9] DCPs routinely record patients' diet-related risk factors and provide advice relating to risk reduction for oral disease, since many of the risk factors such as sugar consumption are shared with the major NCDs including cardiovascular disease and diabetes, it may be within the scope of DCPs practice to provide preventative advice for patients' general and dental wellbeing.

Smoking

Smoking is a major risk factor for periodontitis, and recent analysis of National Health and Nutrition Examination Survey (NHANES) data in the USA found that current smokers were about four times as likely to have periodontitis than those who had never smoked.[13] The 2009 Adult Dental Health Survey found that 45% of adults had periodontal pocketing, exceeding 4mm.[11] Provision of smoking cessation advice by DCPs is a well-established practice and DCPs are experienced in delivering brief interventions to improve oral health.

The links between smoking and periodontal disease and oropharyngeal cancers are well established. Smoking has also been identified as a major risk factor for many respiratory diseases, cardiovascular disease and certain cancers. According to global cancer statistics, the global burden of cancer is increasing and this is largely attributed to the ageing and growth of the world's population and the increase in adoption of behavioural risk factors for cancer.[14] Although the global prevalence of smoking is actually in decline; prevalence of smoking in low – and middle-income countries remains high, and tobacco is estimated to account for about six million deaths globally per year.[15] In addition to the significant morbidity and mortality related to smoking, it also contributes an economic burden with smoking-related illness costing the NHS £3.3bn in 2006-2007.[5]

As DCPs are already delivering smoking cessation advice in relation to oral diseases, they have the potential opportunity to identify those at risk of systemic disease and tailor advice to encompass the wider risks of smoking to their patients. Given the proportion of the population that have contact with DCPs annually, this may not only have an impact on the health of individuals but may confer wider benefits to the population, including economic benefits.

Exercise

Physical inactivity and low physical activity have been associated with several cancers including breast cancer which is the most prevalent cancer amongst females. Physical inactivity also has strong associations with diabetes mellitus, IHD and stroke.[9] In 2006-2007, the NHS spent £0.9bn on physical inactivity-related ill health.[16] Although physical inactivity does not directly impact on oral health, physical inactivity is associated with increased BMI and obesity. There is growing evidence of an association between obesity and periodontal disease.[17] Furthermore, physical inactivity is also associated with NCDs such as diabetes and CVD, which are also associated with periodontitis. Given that DCPs are providing lifestyle advice relating to diet and smoking cessation which may impact on oral diseases, widening the scope of the advice to include the benefits of exercise may confer benefits to patients' oral and wider health.

Alcohol

According to Ezzati et al (2002), alcohol, tobacco, hypertension, and hypercholesterolaemia were major causes of disease burden regardless of whether the country was developed or developing. They determined alcohol to have a similar effect on disability adjusted life years (DALYs) as smoking.[18] The net effect of alcohol consumption on health is unfavourable, with approximately 3.8% of all global deaths and 4.6% of global DALYs attributable to alcohol.[19] It has been suggested that in the UK alcohol-related ill health cost the NHS £3.3bn in 2006-2007.[5] Alcohol is also a known risk factor for liver disease, CVD and certain forms of cancer, including oral cancers where it has a synergistic effect with smoking. DCPs currently offer tailored patient advice, where appropriate, regarding recommended safe levels of alcohol consumption in relation to elevated risk of oropharyngeal cancers. As advice is already being given in relation to oral

risks it may be suggested that DCPs are ideally placed to provide advice on the implications of alcohol consumption beyond the oral environment, including the impact on cardiovascular health and liver disease.

In addition to DCPs being well versed in the delivery of risk assessment and preventative advice for many of the risk factors for oral diseases and NCDs. There is evidence to suggest that DCPs may have access to different cohorts of the population who may not attend their general medical practitioner (GP) or other healthcare professionals. Evidence suggests that members of the public usually only attend their GP when they are unwell. By contrast, many people visit their dentists on a regular (6-12 monthly) basis even if they are dentally healthy. Evidence from the United States suggests that 24% of people did not have contact with a general healthcare provider in 2008, yet 23% of those did see a dentist during that timeframe.[21] With approximately 60% of the UK population registered with a dentist,[10] dental teams may be ideally placed to target patients for preventative advice, risk assessment and early disease identification as they may have access to a population of patients who would not necessarily attend their GP regularly.

In recent years, evidence for potential associations between oral and systemic diseases has been steadily growing. The most robust evidence for associations between oral and systemic diseases exists between periodontitis and diabetes,[22] and between periodontitis and cardiovascular disease.[23] There is growing evidence linking periodontitis to other NCDs such as obesity,[24] rheumatoid arthritis[25] and chronic kidney disease.[26-28] It is likely that the underlying biological mechanisms behind these associations are similar between different NCDs and therefore understanding this in one disease may help understand the links between periodontitis and other NCDs. The mechanisms are thought to involve bacteria (either alive or non-viable) or their products which enter the systemic circulation from inflamed periodontal tissues, where they trigger an acute phase response and activate white blood cells. Such inflamed tissues lose their barrier function due to the formation of microscopic ulcers, which form in response to plaque-induced inflammation.

Conclusion

In conclusion, the growing burden of NCD is a significant problem and as such targeting NCDs has been prioritised by the WHO. Evidence is now emerging that dental teams in the UK may have access to a cohort of the population who are not accessing prevention and screening services elsewhere. Dental teams have access to approximately 60% of the population[29] and are experienced in risk assessing patients as well as delivering dietary and smoking cessation advice. DCPs are experienced and skilled in the process of early disease identification for oral and dental diseases; several of the most prevalent NCDs have shared risk factors with dental NCDs and many have independent associations with periodontitis. An argument could be made that dental teams are ideally placed to provide preventative advice for shared risk factors of the most common NCDs and potentially offer early risk identification and possibly disease identification for NCDs. Where the NCD has a recognised and accepted association with periodontitis; such as diabetes, CVD and chronic kidney disease, the support for dental teams offering this additional service may be even greater.

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Appendix 2: Supplementary Material associated with Manuscript 6.

Development and external validation of a multivariable prediction model to identify non-diabetic hyperglycaemia and undiagnosed type 2 diabetes: Diabetes risk assessment in Dentistry Score (DDS).

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Appendix 2 Table 1: Potential covariates in SHIP-TREND-0 considered for inclusion in the model

Variable description	Parameterisation
Undiagnosed non-diabetic hyperglycaemia / type 2 diabetes (Dependent Variable)	Dichotomous 0 = Normo-glycaemic, no self-reported physician's diagnosis of type 2 diabetes or anti-diabetic medications 1 = HbA1c ≥ 6.0% (42 mmol/mol) using venous blood collection and a standard laboratory analytical technique AND no self-reported physician's diagnosis of type 2 diabetes or anti-diabetic medications
Sex	Dichotomous 0 = Female 1 = Male
Age	Continuous variable – following assessment entered as linear term
BMI in kg/m^2 Derived from self-reported height and weight data	Continuous variable – following assessment entered as linear term
History of hypertension / anti-hypertensive medication Self-reported	Dichotomous 0 = No 1= Yes
First degree relative (parent or sibling) with type 2 diabetes Self-reported	Dichotomous 0 = No 1= Yes
Smoking status	Categorical 0 = Never smoker 1 = Former smoker 2 = Current smoker
Years of Education	Categorical 0 = less than 10 years 1 = 10 years 2 = More than 10 years
Edentulism (complete)	Dichotomous 0 = No, dentate 1= Yes, edentulous
Self-reported Bleeding on Brushing	Dichotomous 0 = No 1= Yes, sometimes or often
Self-reported mobility of teeth	Dichotomous 0 = No 1= Yes
Dental visit in the last 12 months	Dichotomous 0 = No 1= Yes
Regular dental attender or only if a dental problem (symptomatic attender)	Dichotomous 0 = No 1= Yes
Self-rated oral health (Likert scale)	Categorical 0 = Very Good 1 = Good

	2 = Satisfactory 3 = Unsatisfactory 4 = Bad
Number of missing teeth (including wisdom teeth)	Continuous variable – following assessment entered as linear term
Presence of removable prosthesis (complete or partial)	Dichotomous 0 = No 1= Yes
Number of crowns	Continuous
Have you been treated for gum disease in the past five years (periodontitis treatment)	Dichotomous 0 = No 1= Yes
CDC/ AAP definition of Periodontitis	Categorical 0: No/mild 1: Moderate 2: Severe 3: Edentulism
Having ≥1 tooth with ≥4mm pocket	Categorical 0 = No 1 = Yes 2 = Edentulous
Having ≥2 teeth with ≥4mm pockets	Categorical 0 = No 1 = Yes 2 = Edentulous
Having ≥1 tooth with ≥6mm pockets	Categorical 0 = No 1 = Yes 2 = Edentulous
Having ≥2 teeth with ≥6mm pockets	Categorical 0 = No 1 = Yes 2 = Edentulous
Having ≥1 site with ≥4mm pocket	Categorical 0 = No 1 = Yes 2 = Edentulous
Having ≥2 sites with ≥4mm pockets	Categorical 0 = No 1 = Yes 2 = Edentulous
Number of teeth with ≥4mm pockets	Categorical – Quintiles + additional category for edentulous subjects
Number of sites with ≥4mm pockets	Categorical – Quintiles + additional category for edentulous subjects
Number of teeth with ≥5mm pockets	Categorical – Quintiles + additional category for edentulous subjects
Number of sites with ≥5mm pockets	Categorical – Quintiles + additional category for edentulous subjects
Number of teeth with ≥6mm pockets	Categorical – Quintiles + additional category for edentulous subjects
Number of sites with ≥6mm pockets	Categorical – Quintiles + additional category for edentulous subjects

Table Legend: Appendix table 1 shows potential covariates in SHIP-TREND-0 considered for inclusion in the model.

Appendix 2 Table 2: Table showing variables included in the Multiply Imputed Chained Equation (MICE)

Variable Name	Parameterisation	Conditional on edentulism
Undiagnosed non-diabetic hyperglycaemia / type 2 diabetes (Dependent Variable)	Logistic	No
History of hypertension / anti-hypertensive medication	Logistic	No
First degree relative (parent or sibling) with type 2 diabetes	Logistic	No
Edentulism (complete)	Logistic	No
Dental visit in the last 12 months	Logistic	No
Presence of removable prosthesis (complete or partial)	Logistic	No
Have you been treated for gum disease in the past five years (periodontitis treatment)	Logistic	No
Self-reported mobility of teeth	Logistic	Yes
Self-reported bleeding on brushing	Logistic	Yes
Smoking Status	Ordered logistic	No
Self-rated oral health (Likert scale)	Ordered logistic	Yes
CDC/ AAP definition of Periodontitis	Ordered logistic	Yes
Examination location	Multinomial logistic	No
Age	Linear	No
Body Mass Index (BMI) derived from self-reported height and weight.	Linear	No
HbA1c	predictive mean matching	No
Waist Circumference	predictive mean matching	No
Mean Clinical Attachment Loss	predictive mean matching	Yes
Number of teeth with Crowns	predictive mean matching	Yes
Number of missing teeth excluding Wisdom teeth	predictive mean matching	Yes
Number of missing teeth (including wisdom teeth)	predictive mean matching	Yes
Mean PPD	predictive mean matching	Yes
Number of teeth with ≥4mm pockets	predictive mean matching	Yes
Number of sites with ≥4mm pockets	predictive mean matching	Yes
Number of teeth with ≥5mm pockets	predictive mean matching	Yes
Number of sites with ≥5mm pockets	predictive mean matching	Yes
Number of teeth with ≥6mm pockets	predictive mean matching	Yes
Number of sites with ≥6mm pockets	predictive mean matching	Yes

Table Legend: Appendix Table 2, table showing variables included in the Multiply Imputed Chained Equation (MICE)

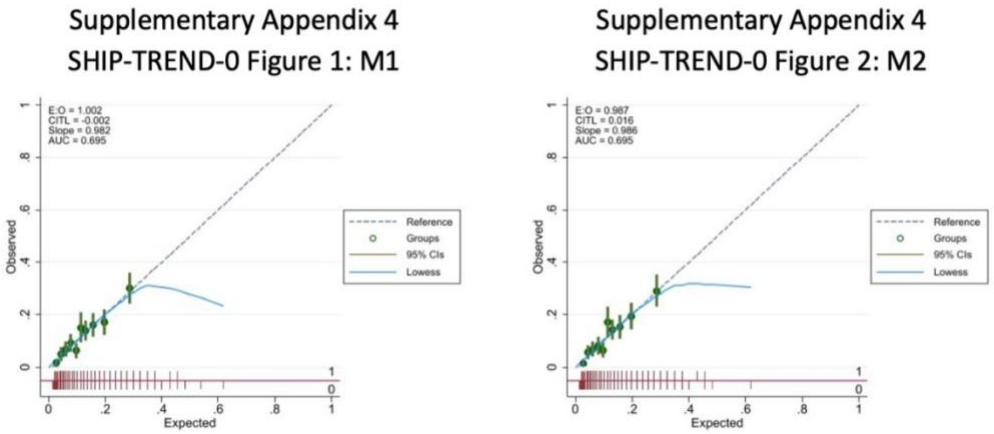
Appendix 2 Table 3: Proportion of missing data associated with each variable

Variable	% Missing Data as percentage in SHIP-TREND (Development dataset)	% Missing Data as percentage in SHIP-START-0 (Validation dataset)
Undiagnosed non-diabetic hyperglycaemia / type 2 diabetes (Dependent Variable)	0.45	0.91
Age	0.00	0.00
Male sex	0.00	0.00
Ethnicity – White European	0.00	0.00
BMI in kg/m2	0.00	0.25
Smoking status	0.50	0.48
First degree relative (parent or sibling) with type 2 diabetes	0.25	0.61
History of hypertension / anti-hypertensive medication	0.38	1.21
HbA1c	0.20	0.58
Edentulism	2.24	0.45
Number of missing teeth (including wisdom teeth)	2.24	0.45
Presence of removable prosthesis (complete or partial)	11.00	0.45
Dental visit in the last 12 months	10.93	0.61
Self-reported bleeding on brushing	15.81	1.14
Self-reported mobility of teeth	15.81	1.44
Probing pocket depth variables	18.05	1.49
Have you been treated for gum disease in the past five years (periodontitis treatment)	11.47	*66.85

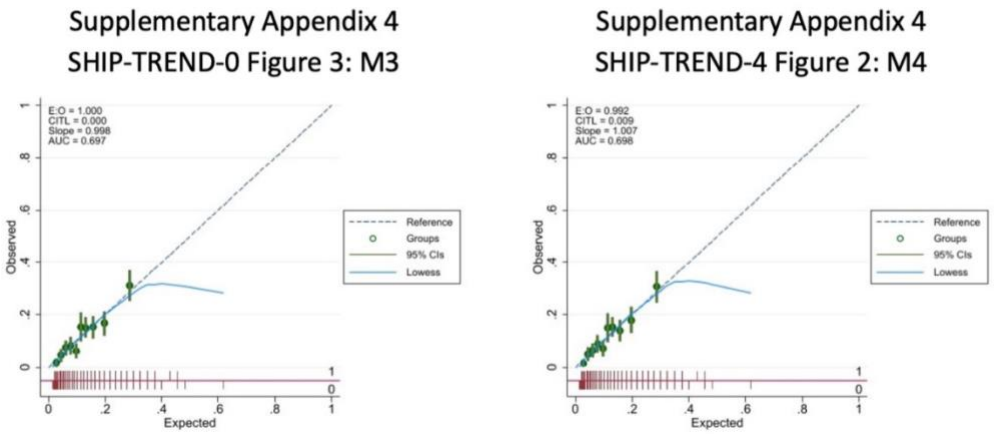
Table Legend: Appendix table 3 shows the proportion of missing data associated with each variable

Appendix 2 Figure 4:

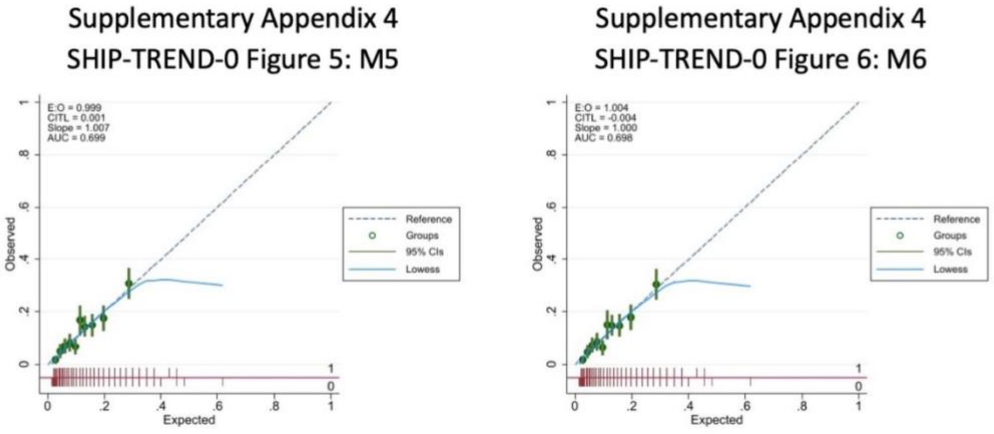
Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for each multiply imputed set M1-M20.



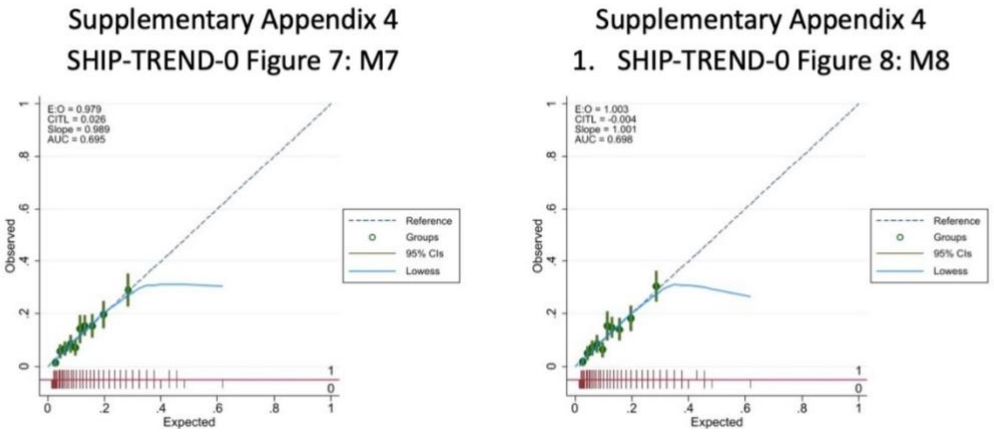
A: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M1 and M2



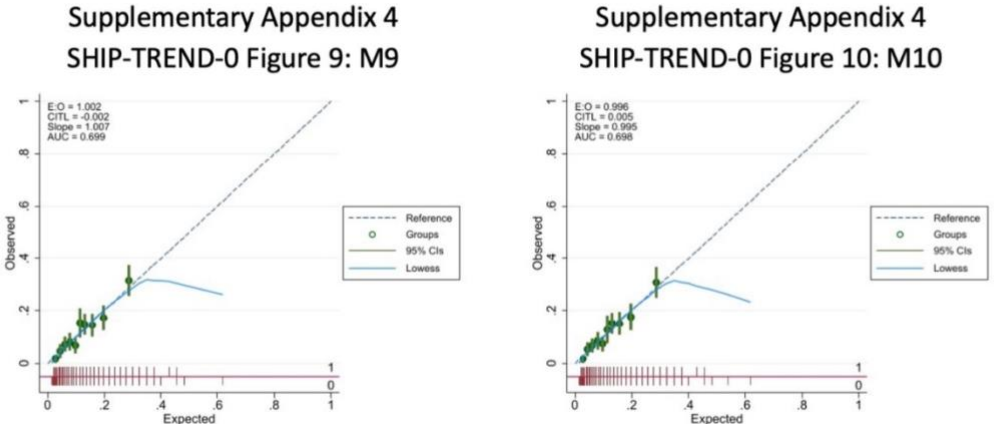
B: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M3 and M4



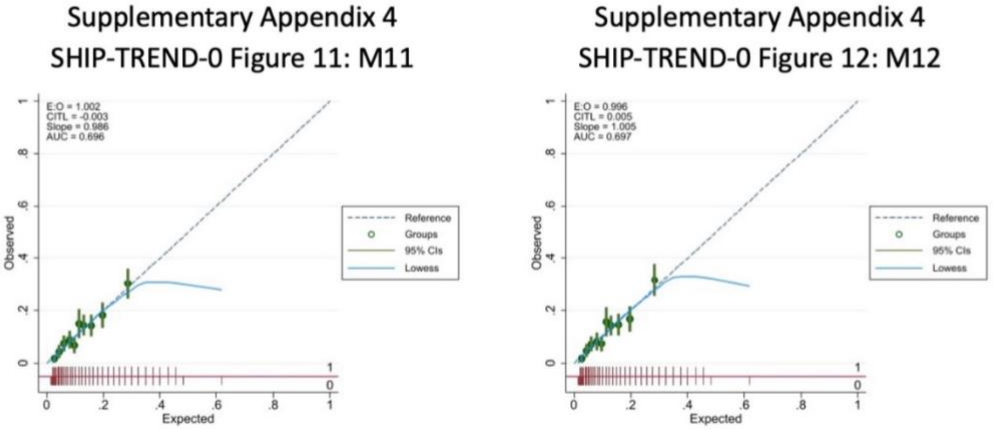
c: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M5 and M6



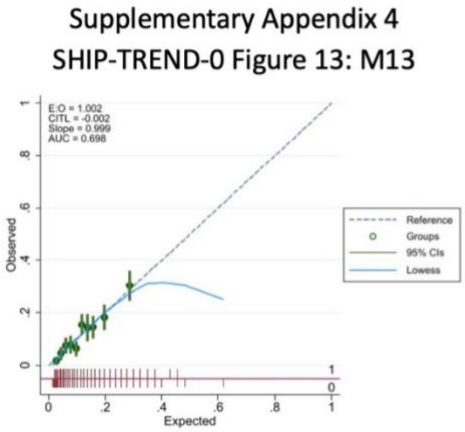
d: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M7 and M8

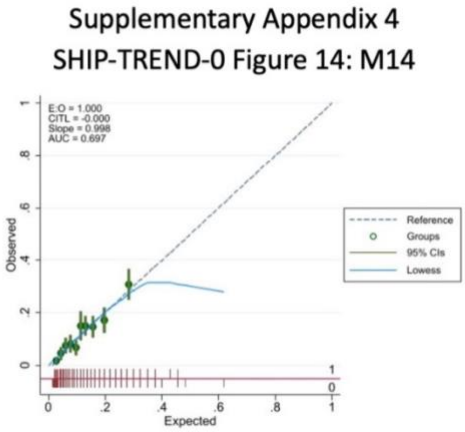


e: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M9 and M10

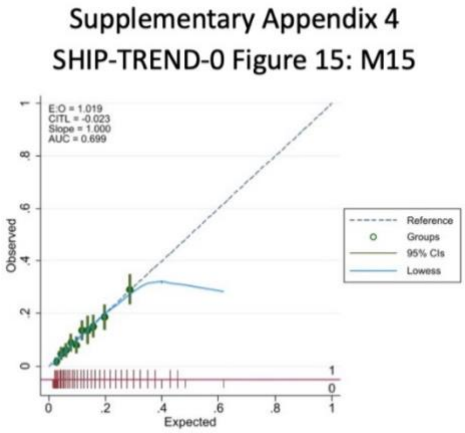


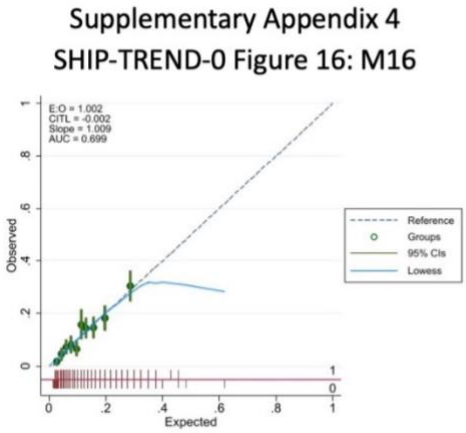
f: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M11 and M12



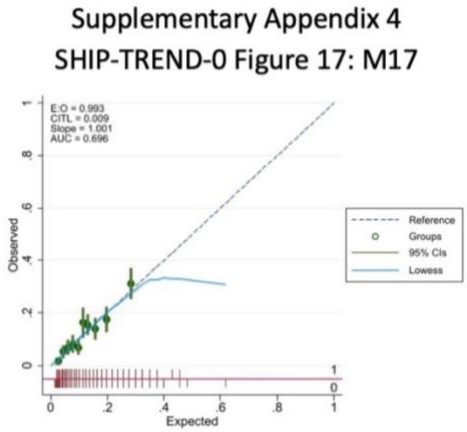


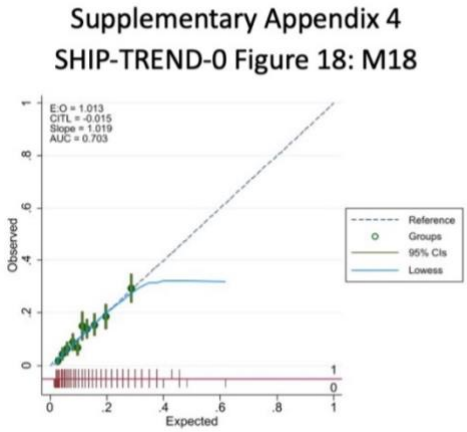
g: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M13 and M14



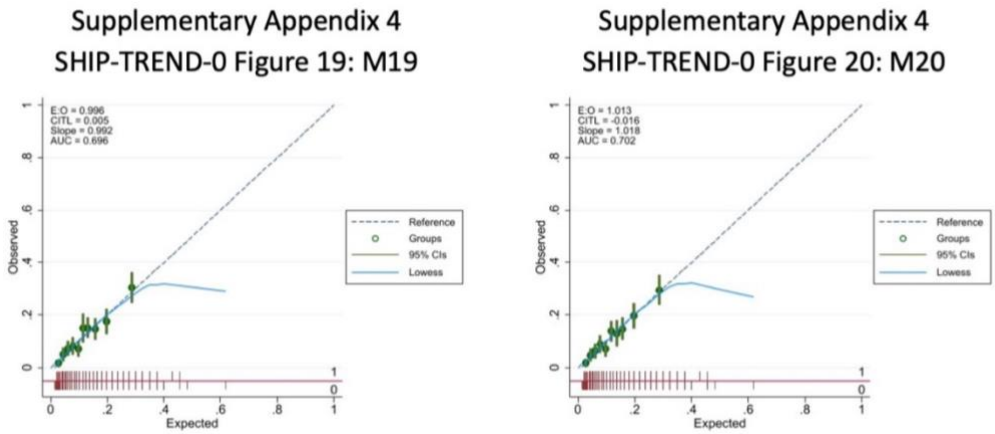


h: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M15 and M16





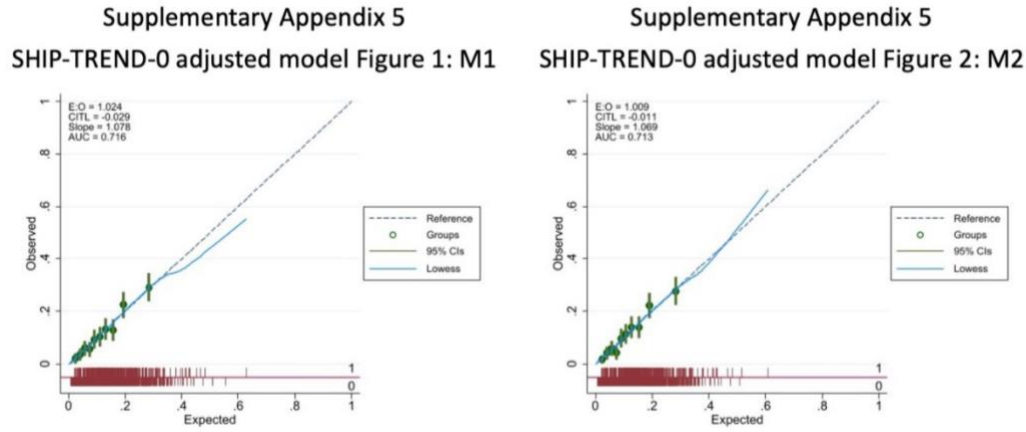
i: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M17 and M18



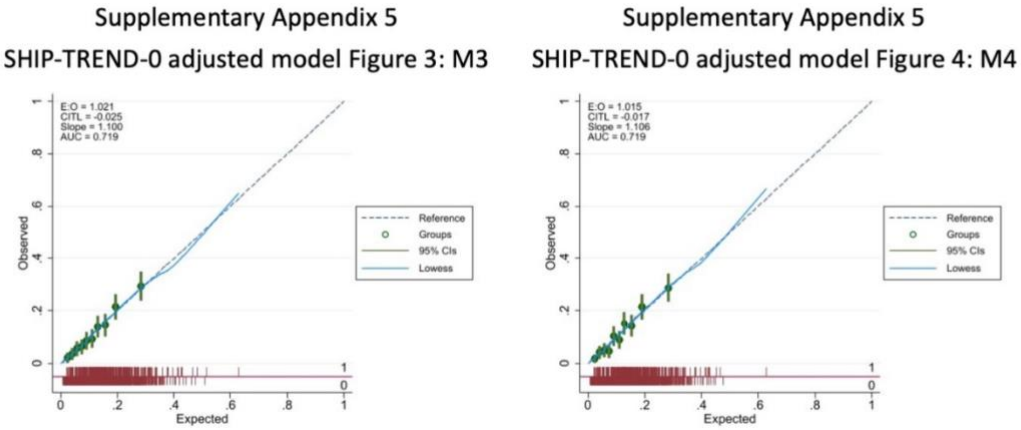
j: Calibration plots for the unadjusted model in SHIP-TREND-0 prior to internal validation for M19 and M20

Appendix 2 Figure 5:

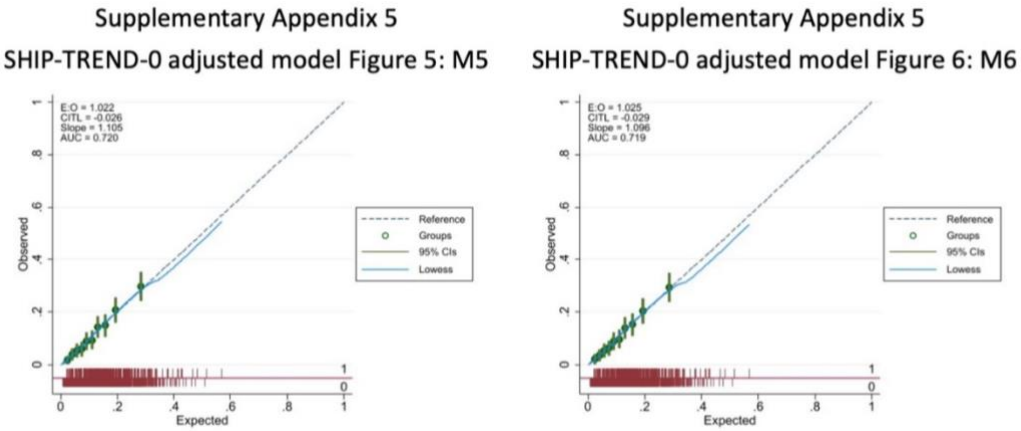
Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M1-M20



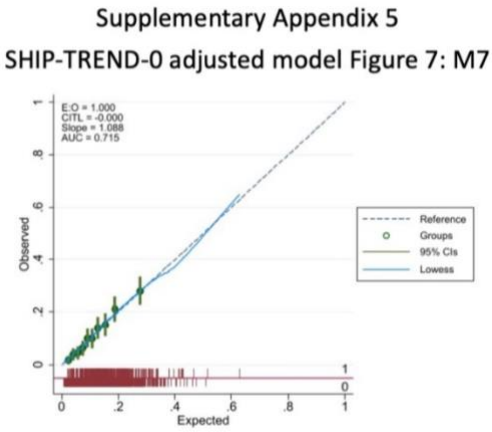
k: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M1 and M2

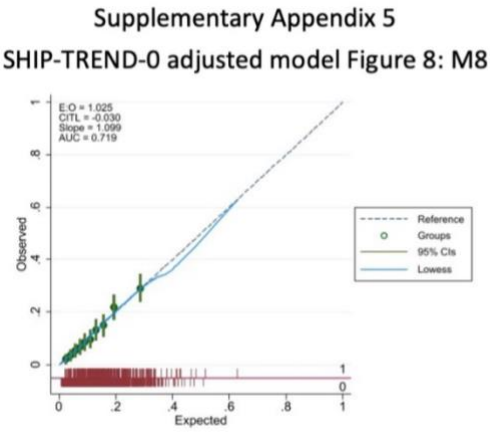


l: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M3 and M4

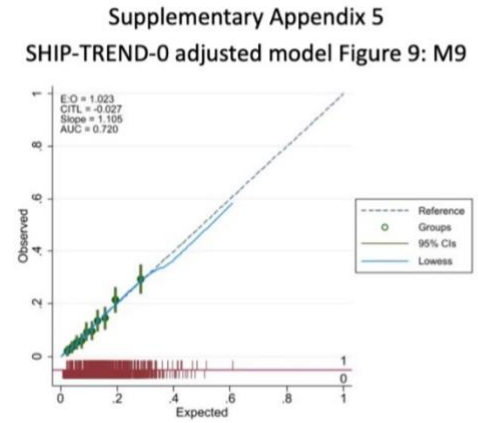


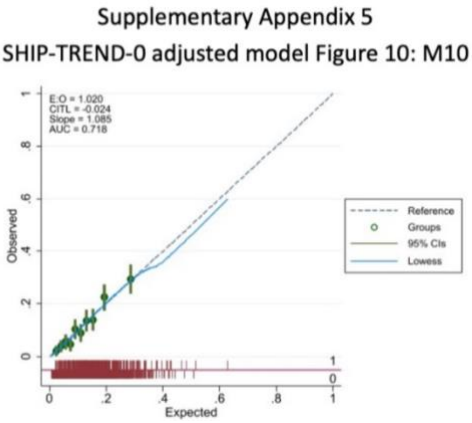
m: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M5 and M6



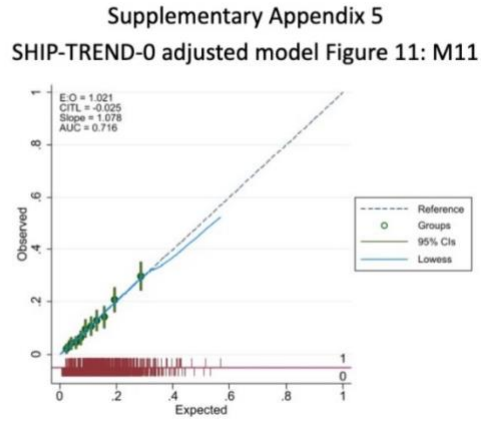


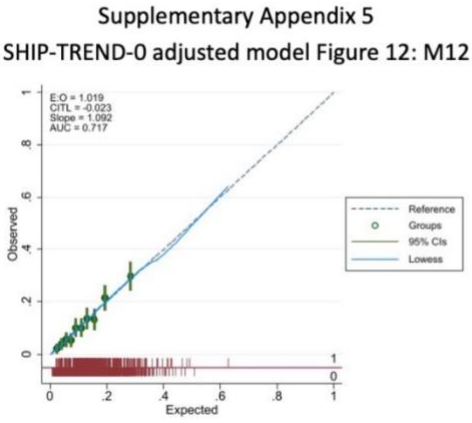
n: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M7 and M8





o: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M9 and M10

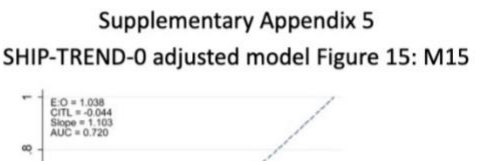


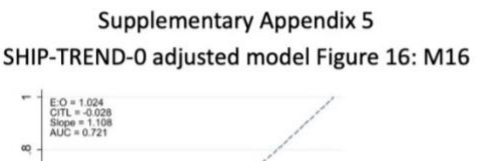


p: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M11 and M12

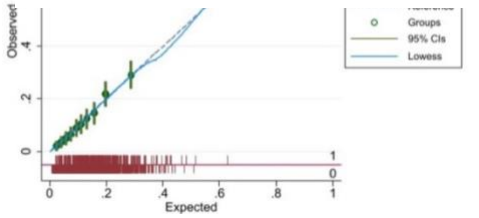
r: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M15 and M16

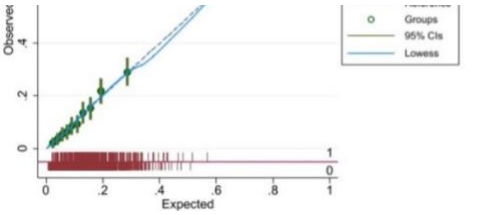
q: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M13 and M14

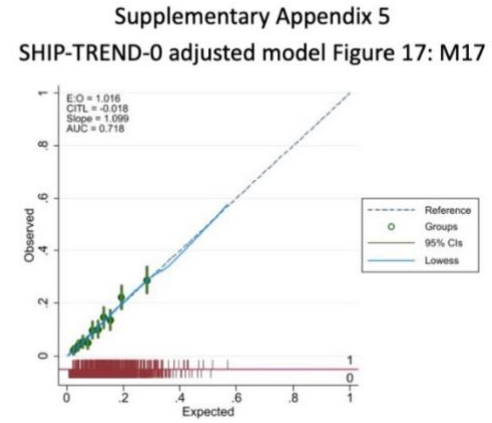


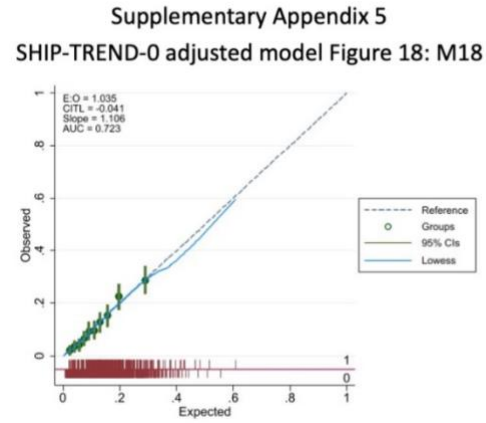


s: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M17 and M18



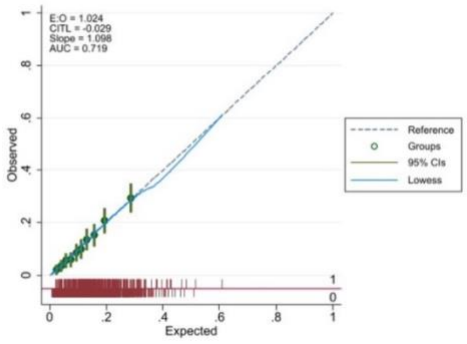






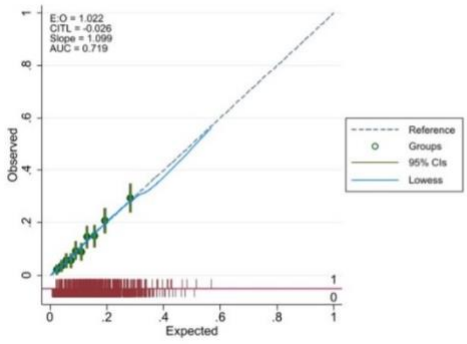
Supplementary Appendix 5

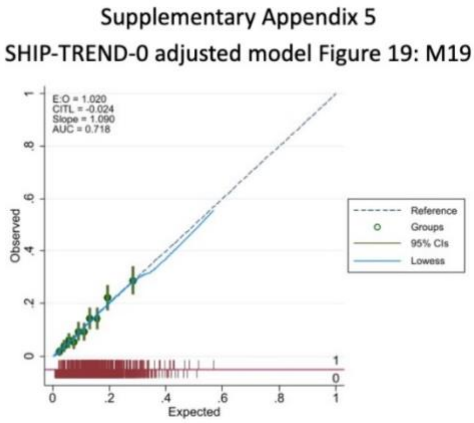
SHIP-TREND-0 adjusted model Figure 13: M13

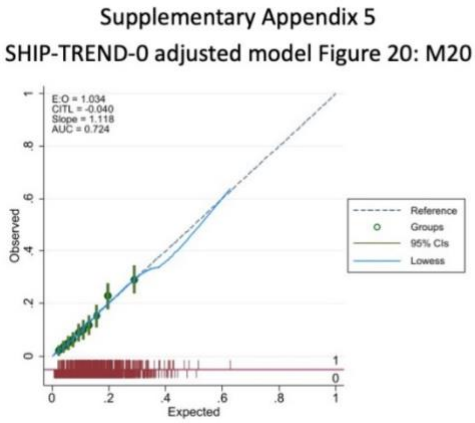


Supplementary Appendix 5

SHIP-TREND-0 adjusted model Figure 14: M14



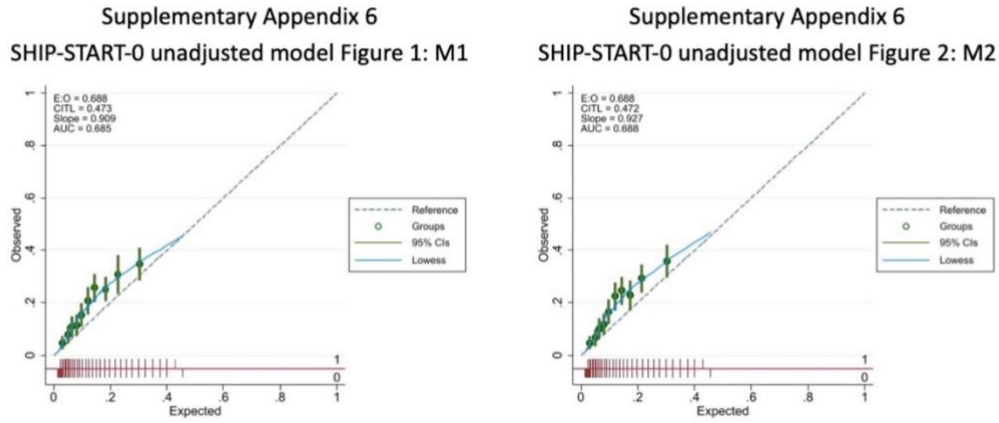




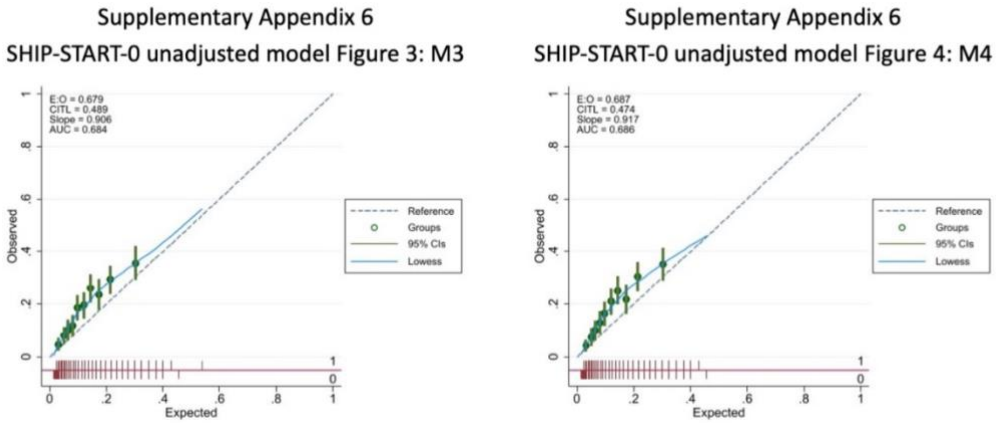
t: Calibration plots for the adjusted model in SHIP-TREND-0 for each multiply imputed set M19 and M20

Appendix 2 Figure 6:

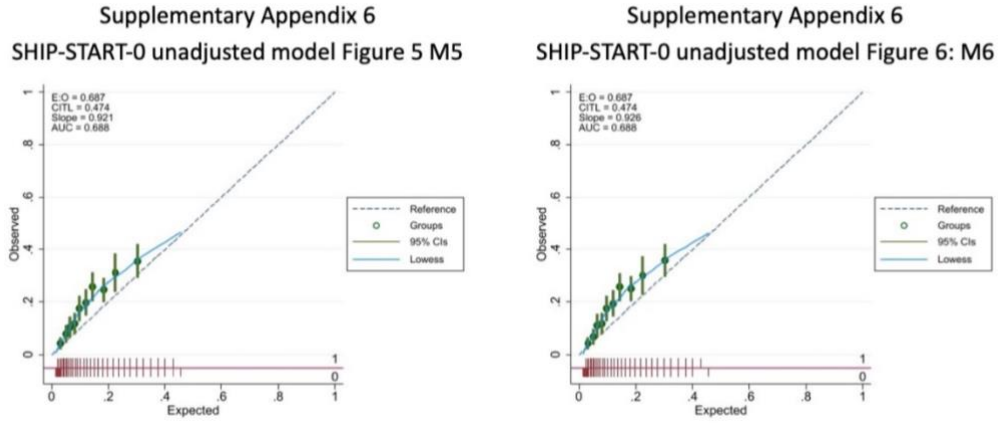
Calibration plots for the unadjusted model for each multiply imputed set M1-M20 in SHIP-START-0



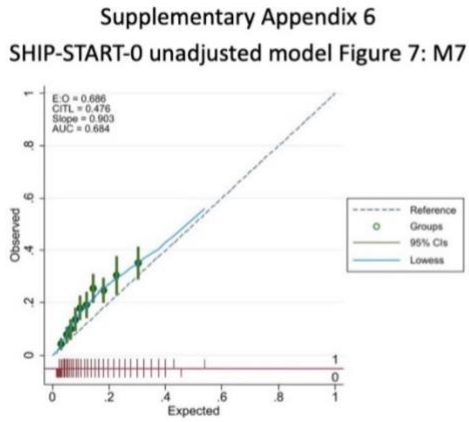
u: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M1 and M2

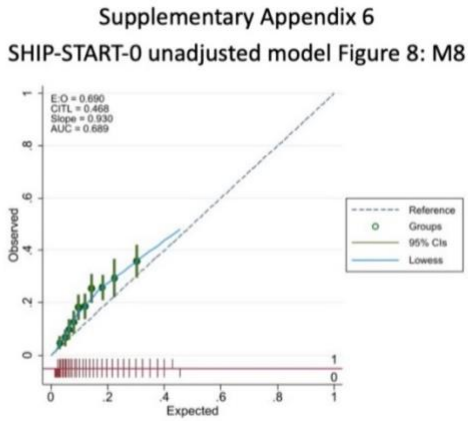


v: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M3 and M4

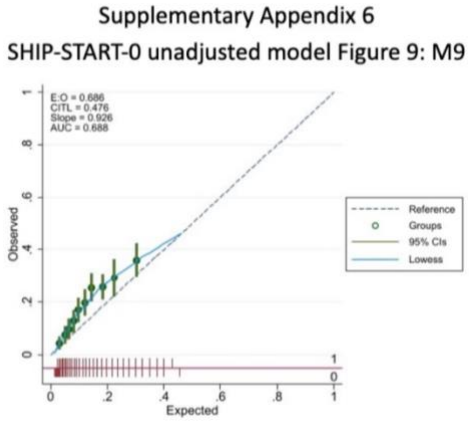


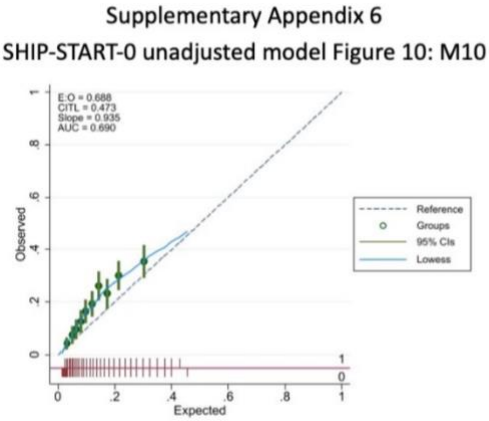
w: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M5 and M6



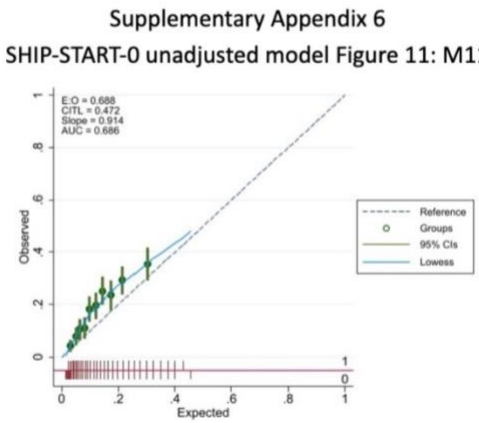


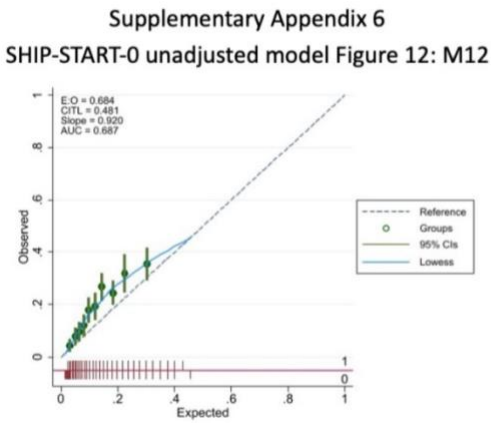
x: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M7 and M8



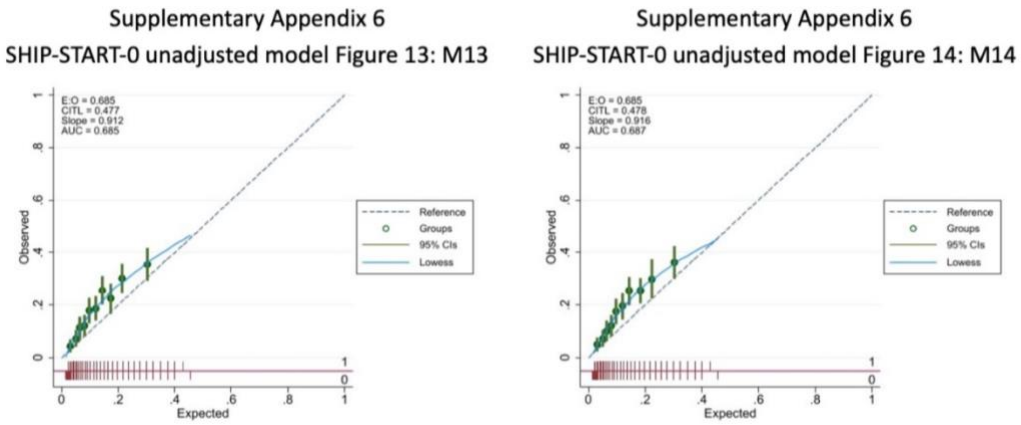


y: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M9 and M10

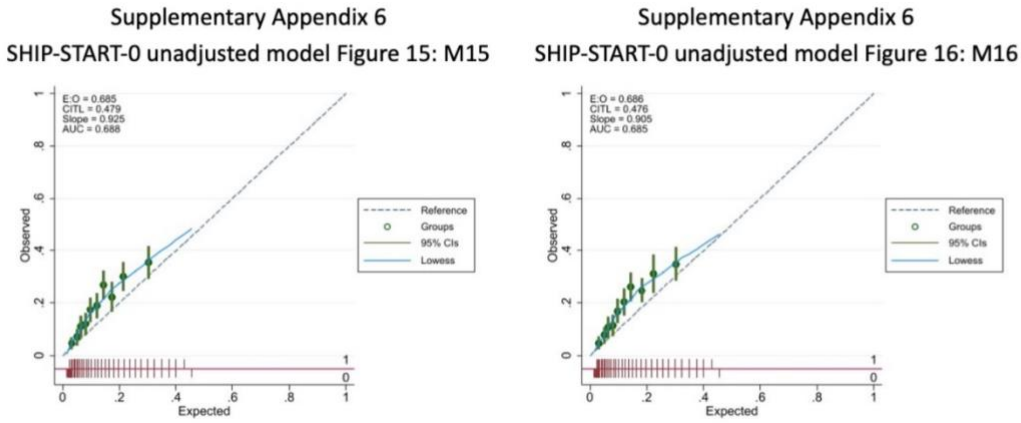




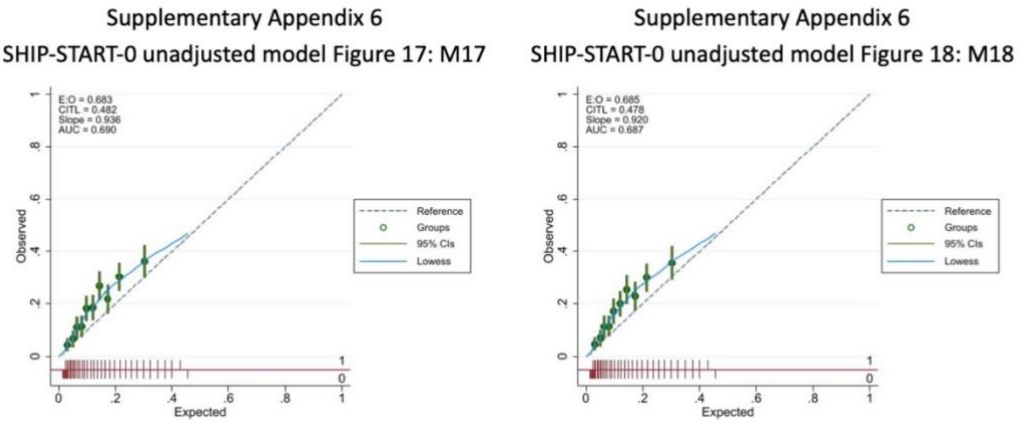
z: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M11 and M12



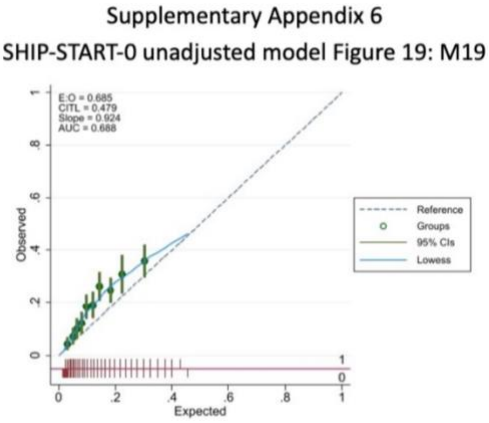
Ai: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M13 and M14

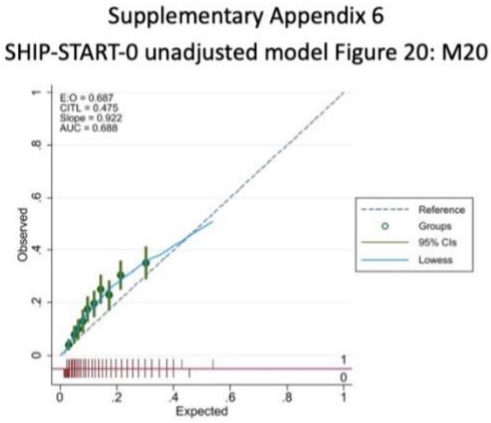


Aii: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M15 and M16



Aiii: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M17 and M18

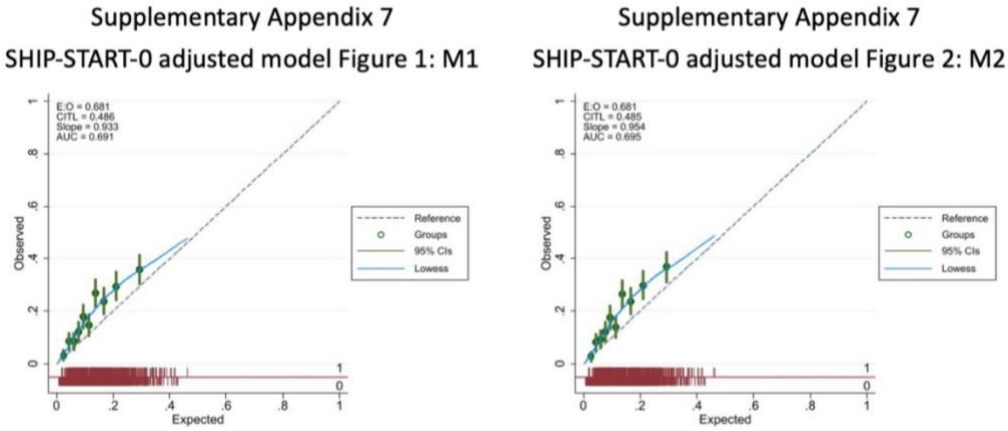




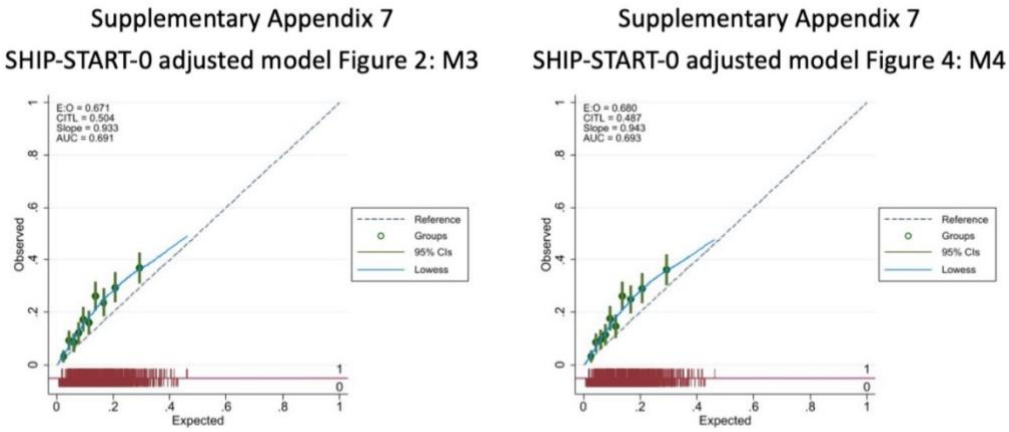
Aiv: Calibration plots for the unadjusted model in SHIP-START-0 for multiply imputed set M19 and M20

Appendix 2 Figure 7:

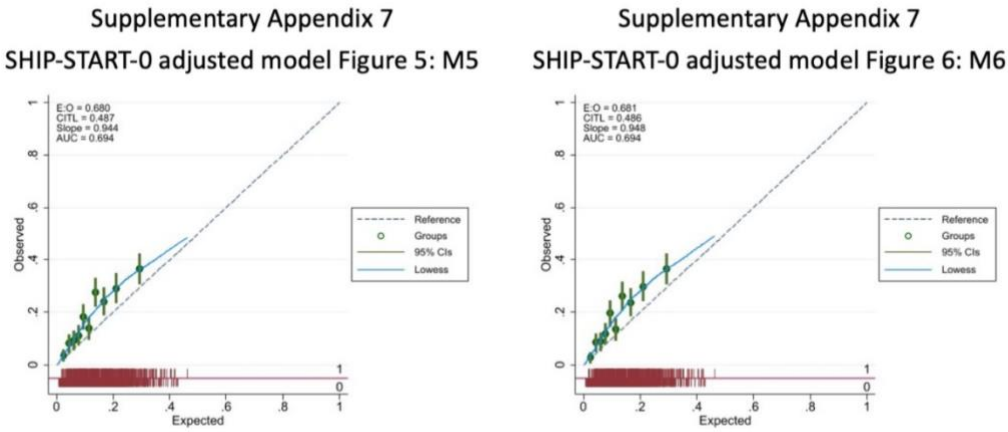
Calibration plots for the adjusted model developed for each multiply imputed set M1-M20 in SHIP-START-0



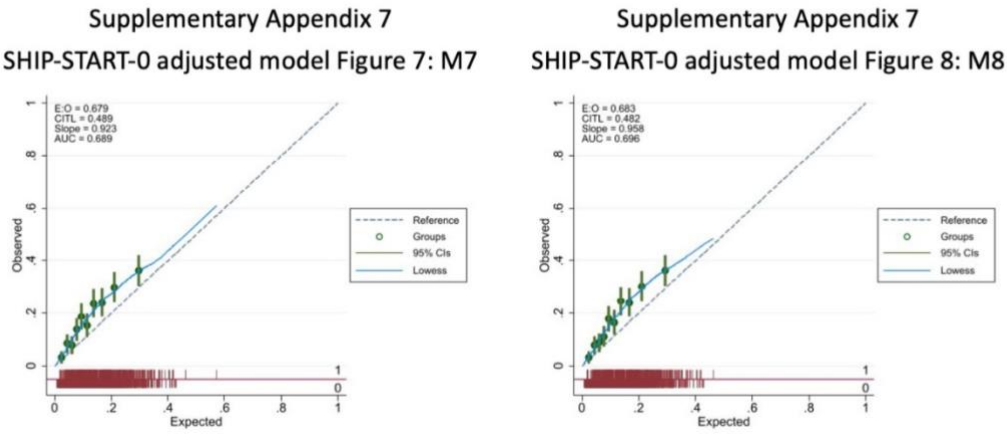
Av: Calibration plots for the adjusted model developed in SHIP-START-0 for each multiply imputed set M1 and M2



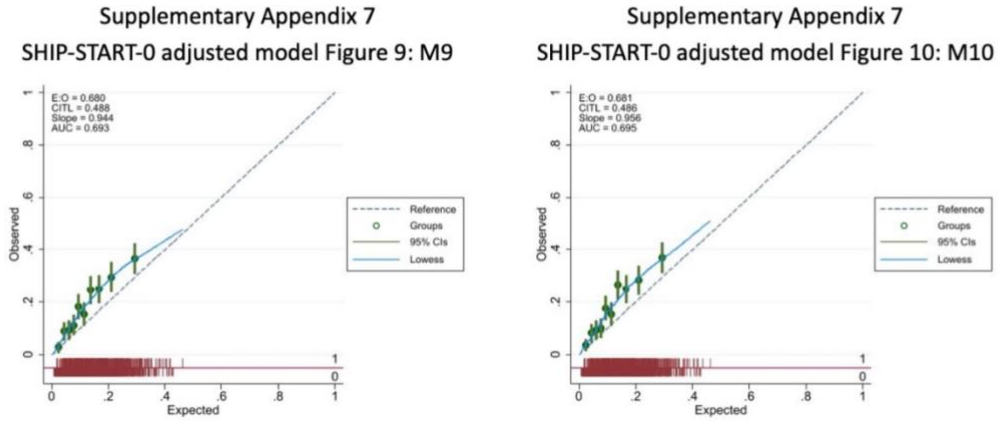
Avi:Calibration plots for the adjusted model developed in SHIP-START-0 for each multiply imputed set M3 and M4



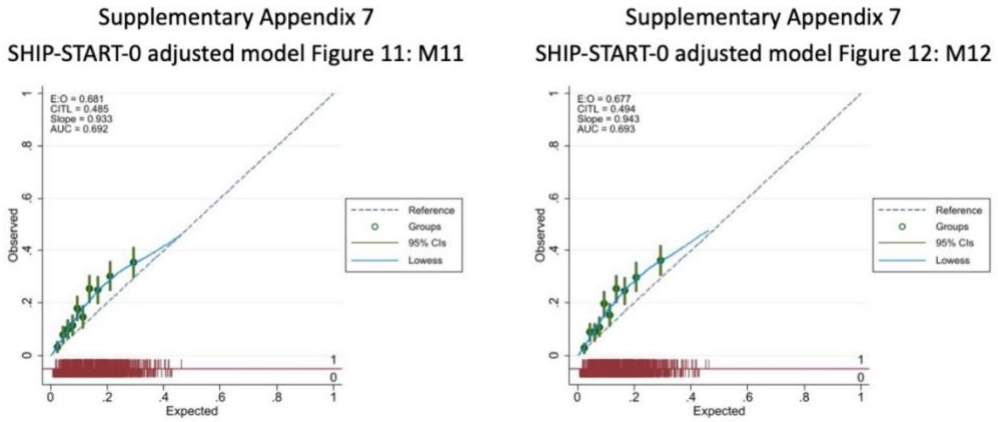
Avii: Calibration plots for the adjusted model developed in SHIP-START-0 for each multiply imputed set M5 and M6



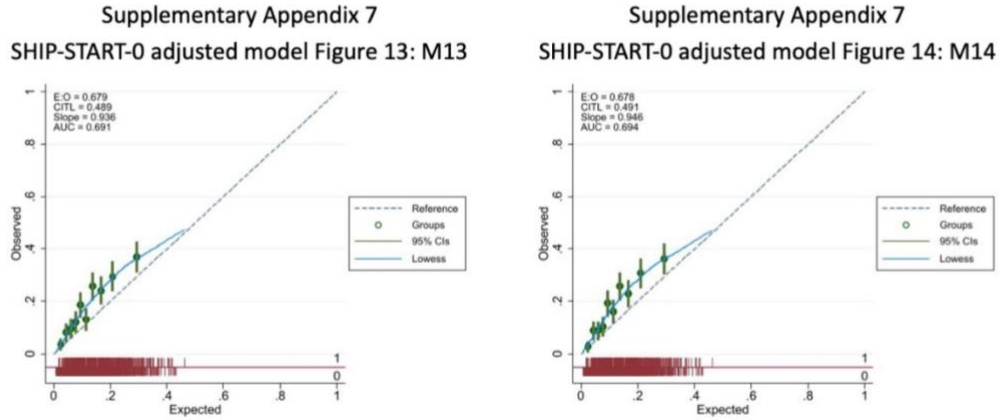
Aviii: Calibration plots for the adjusted model developed in SHIP-START-0 for each multiply imputed set M7 and M8



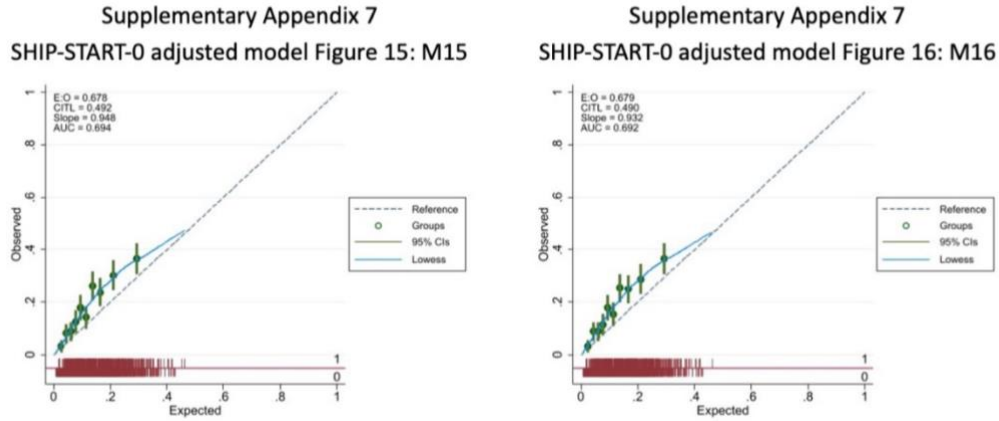
Aix: Calibration plots for the adjusted model developed in SHIP-START-0 for each multiply imputed set M9 and M10



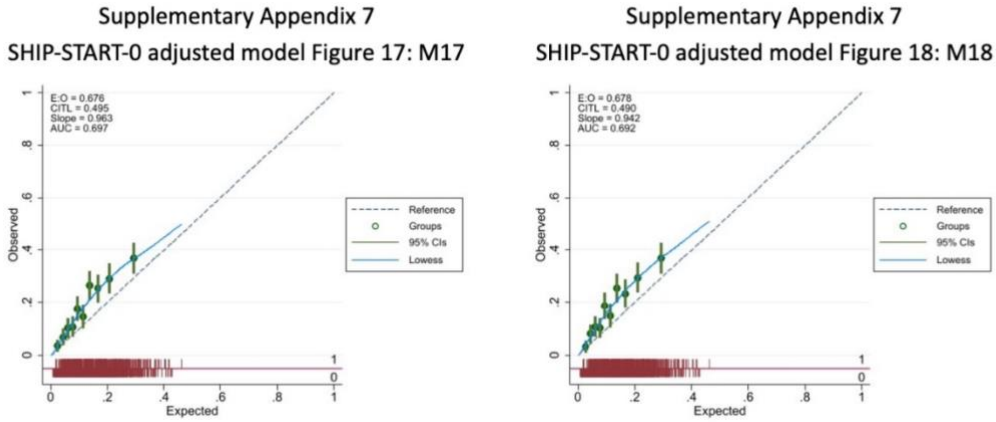
Ax: Calibration plots for the adjusted model developed in SHIP-START-0 for each multiply imputed set M11 and M12



Axi: Calibration plots for the adjusted model developed in SHIP-START-0 for each multiply imputed set M13 and M14

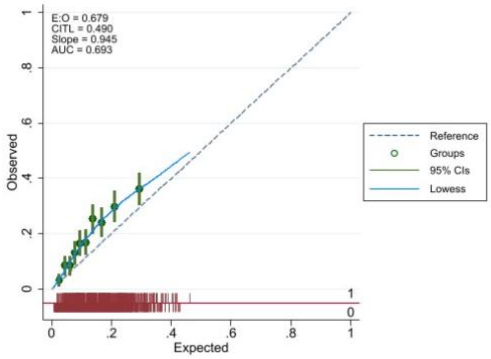


Axii: Calibration plots for the adjusted model developed in SHIP-for each multiply imputed set M15 and M16

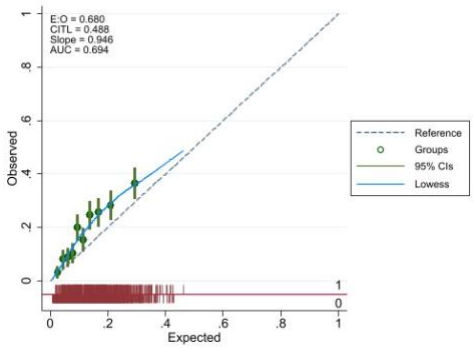


Axii: Calibration plots for the adjusted model developed in SHIP-for each multiply imputed set M17 and M18

Supplementary Appendix 7
SHIP-START-0 adjusted model Figure 19: M19



Supplementary Appendix 7
SHIP-START-0 adjusted model Figure 20: M20



A xiii: Calibration plots for the adjusted model developed in SHIP-for each multiply imputed set M19 and M20

Appendix 2 Table 8

Development of the point score system

Variable	Category	Mid-point for each category	W_{ij}-W_{iREF}	Beta	Beta*(W_{ij} - W_{iREF})	Points= Beta*(W_{ij} - W_{iREF}) / B	Round to nearest integer	Determine the minimum possible points total	Determine maximum possible points total
Sex	Female	**0=W_{0REF}**	0	0	0	0	0	0	
	Male	1	0	0.2378013	0.2378013	0.955215193	1		1
Age	40-49 (<50)	**44.5=W_{1REF}**	0	0.0497901	0	0	0	0	
	50-59 (<60)	54.5	10		0.497901	2	2		
	60-69 (<70)	64.5	20		0.995802	4	4		
	>70 (max 84)	77	32.5		1.61817825	6.5	7		7
Former smoking	no	**0=W_{2REF}**	0		0	0	0	0	
	yes	1	0	0.1938261	0.1938261	0.778572849	1		1
Current smoking	no	**0=W_{3REF}**	0			0	0	0	
	yes	1	0	0.6190377	0.6190377	2.486589503	2		2
BMI	<25	**20.965=W_{4REF}**	0	0.0648614	0	0	0	0	
	25-<30	27.5	6.535		0.423869249	1.702624614	2		
	>=30-<35	32.5	11.535		0.748176249	3.005321335	3		
	>35	44.71	23.745		1.540133943	6.186506727	6		6
Loose teeth	no	**0=W_{5REF}**	0	0	0	0	0	0	
	yes	1	0	0.3158367	0.3158367	1.268672688	1		1
Edentulism	no	**0=W_{6REF}**	0	0	0	0	0	0	
	yes	1	0	0.4928332	0.4928332	1.979643343	2		2

Family history Periodontitis	no	**0=W_{7REF}**	0	0	0	0	0	0	
	yes	1	0	0.3652556	0.3652556	1.467181628	1		1
Periodontitis hx <=5years	yes	**0=W_{8REF}**	0	0	0	0	0	0	
	no	1	0	0.240147	0.240147	0.964637548	1		1
Sites >= 5mm	0	**0=W_{9REF}**	0	0	0	0	0	0	
	≥3 sites	1	0	0.1056278	0.1056278	0.424292379	1		1
								0	23

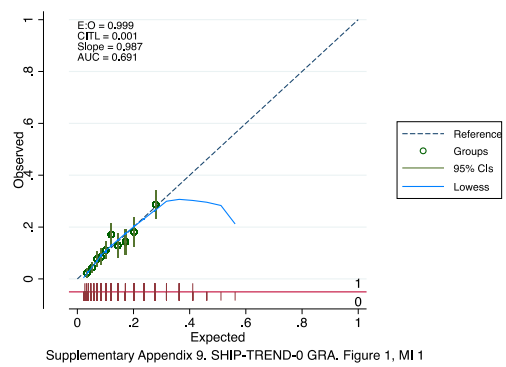
Intercept: $Beta_{(0)}$ = -7.691597

We defined the number of regression units that corresponded to one point in the point scoring system. Note that the scaling factor (constant - or the number of regression units that will correspond to one point) is based on age. Here, we let B reflect the increase in risk associated with a 5-year increase in age, the same scaling factor (B) is then used for all variables therefore: $\boldsymbol{B}$ **= 0.0497901 x 5 = 0.24895**

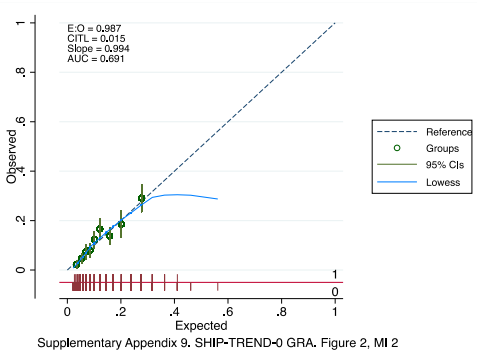
Table legend: Appendix Table 8 shows the method used to develop the point score system

Appendix 2 Figure 9:

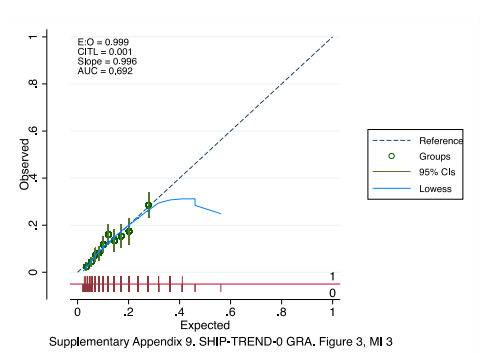
Calibration plots for the DDS for each multiply imputed data sets M1-M20 in SHIP-TREND



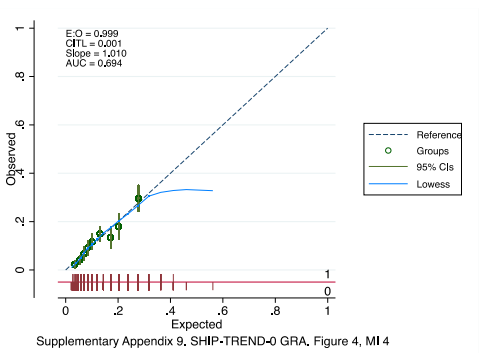
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 1, MI 1



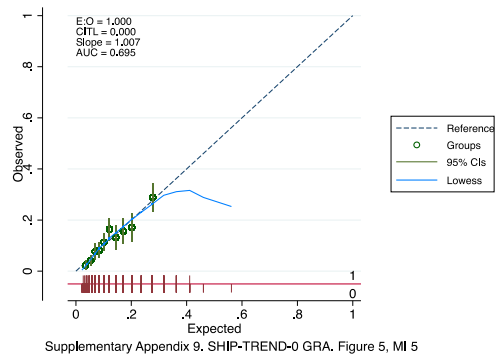
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 2, MI 2



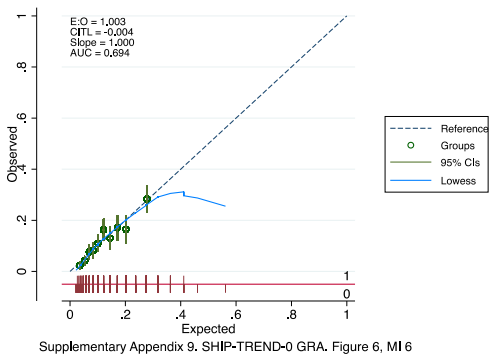
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 3, MI 3



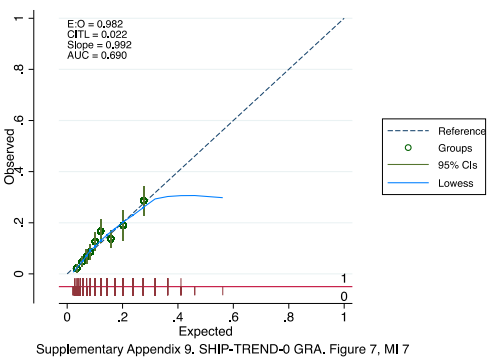
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 4, MI 4



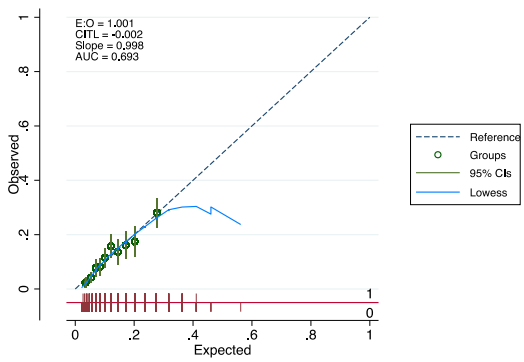
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 5, MI 5



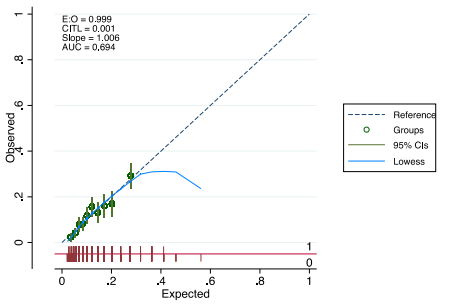
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 6, MI 6



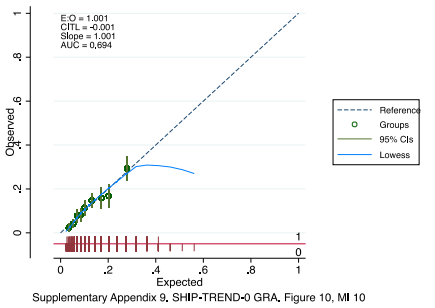
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 7, MI 7



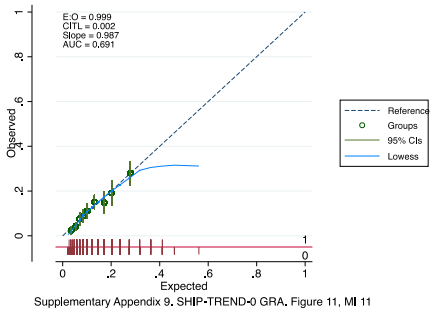
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 8, MI 8



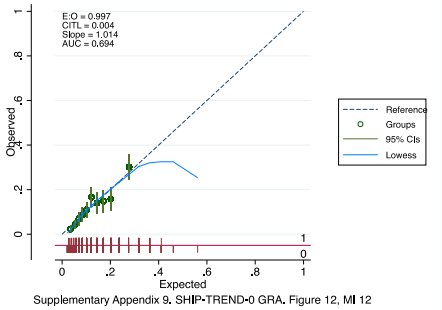
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 9, MI 9



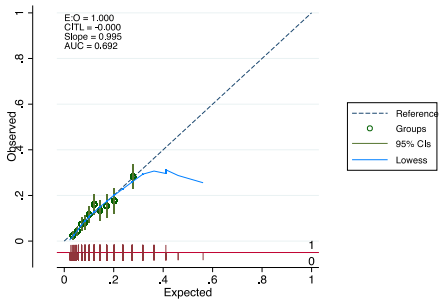
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 10, MI 10



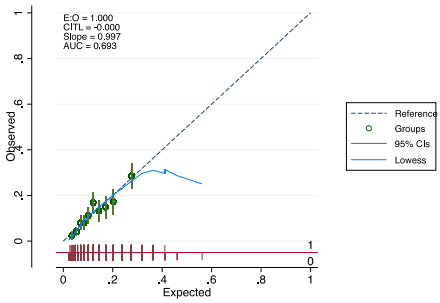
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 11, MI 11



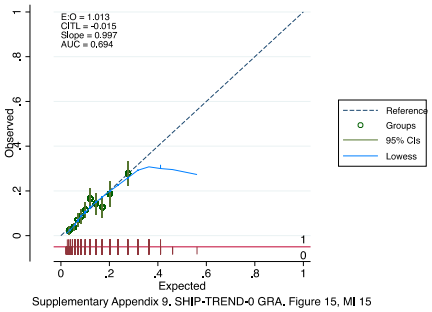
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 12, MI 12



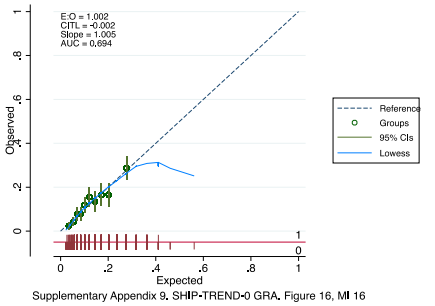
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 13, MI 13



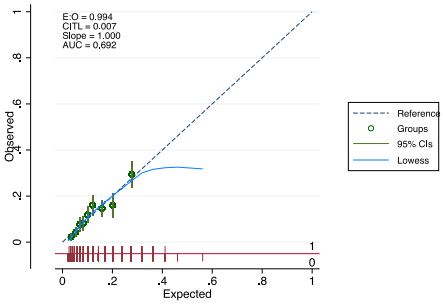
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 14, MI 14



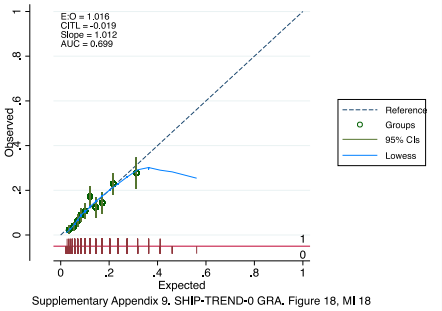
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 15, MI 15



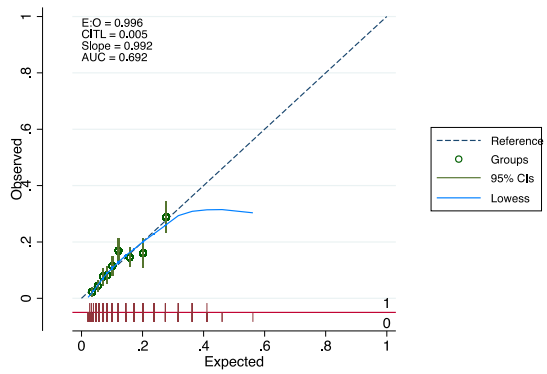
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 16, MI 16



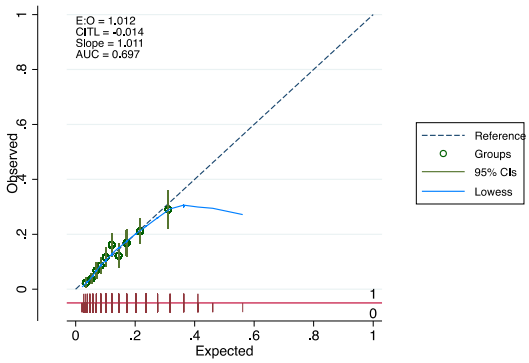
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 17, MI 17



Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 18, MI 18



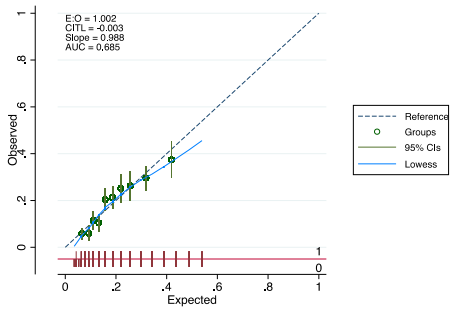
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 19, MI 19



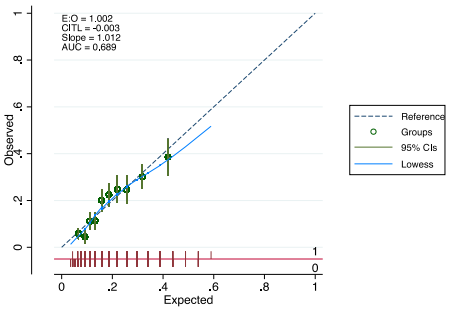
Supplementary Appendix 9. SHIP-TREND-0 GRA. Figure 20, MI 20

Appendix 2 Figure 10:

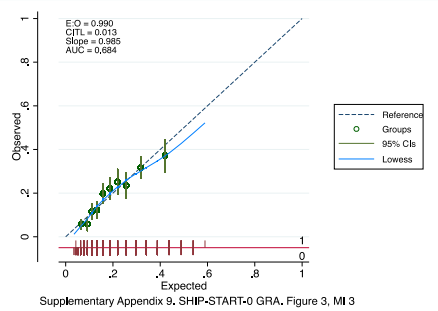
Calibration plots for the DDS for each multiply imputed data sets M1-M20 in SHIP-START-0



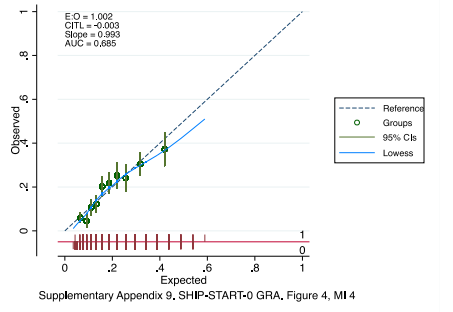
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 1, MI 1



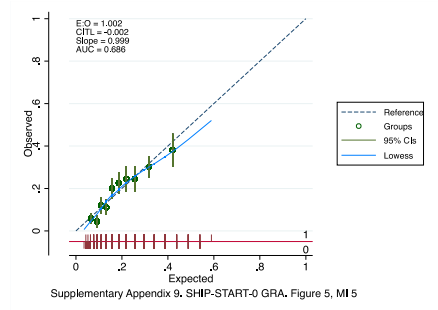
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 2, MI 2



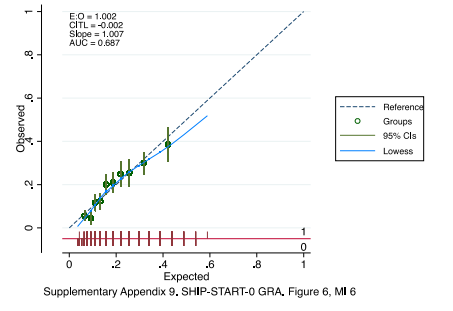
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 3, MI 3



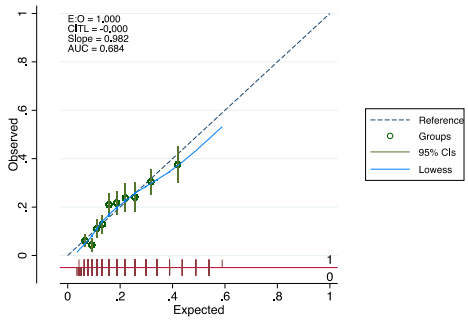
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 4, MI 4



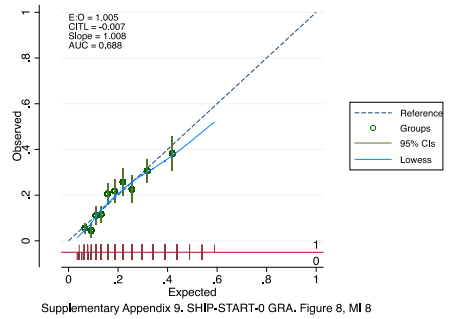
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 5, MI 5



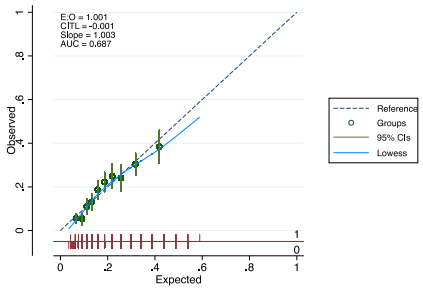
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 6, MI 6



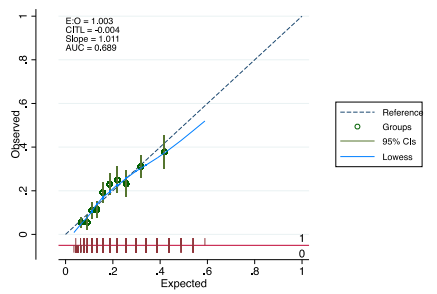
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 7, MI 7



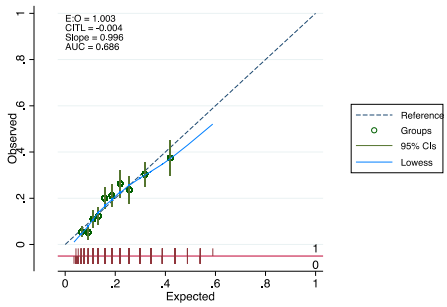
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 8, MI 8



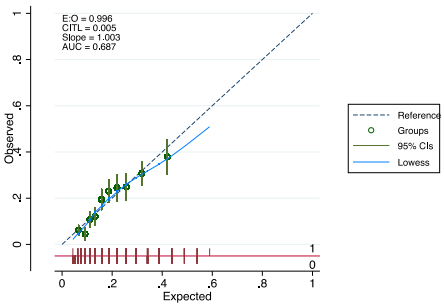
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 9, MI 9



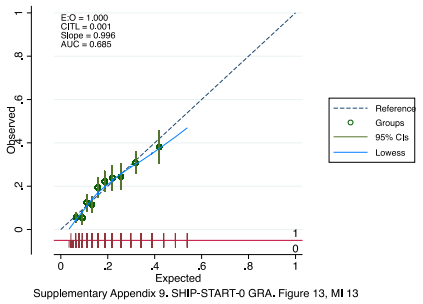
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 10, MI 10



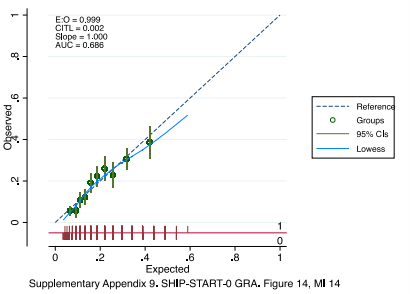
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 11, MI 11



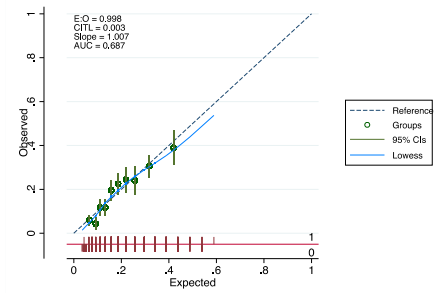
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 12, MI 12



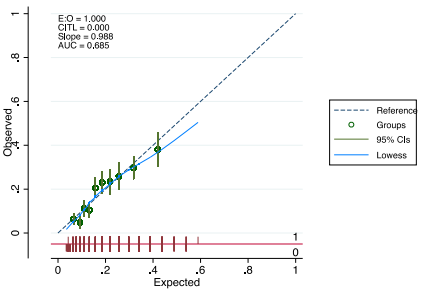
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 13, MI 13



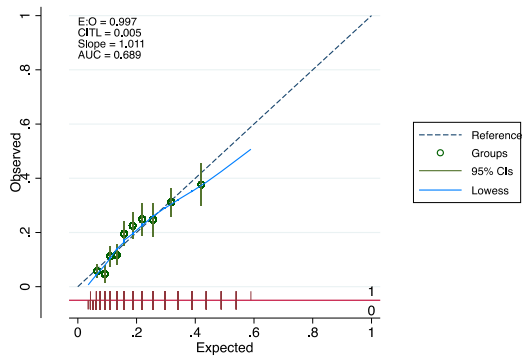
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 14, MI 14



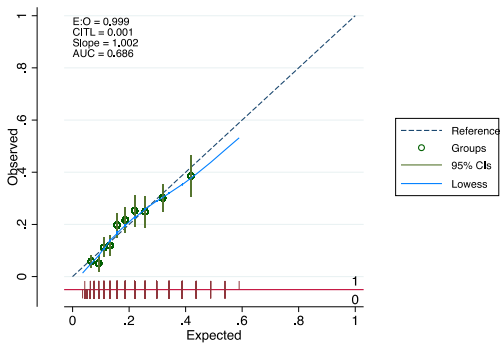
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 15, MI 15



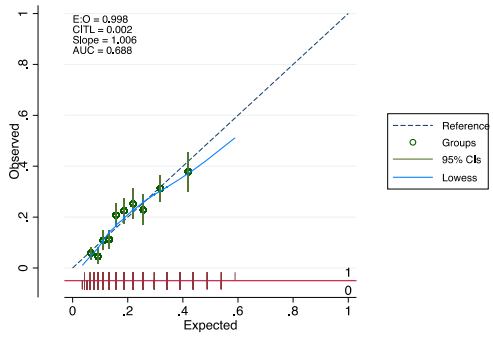
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 16, MI 16



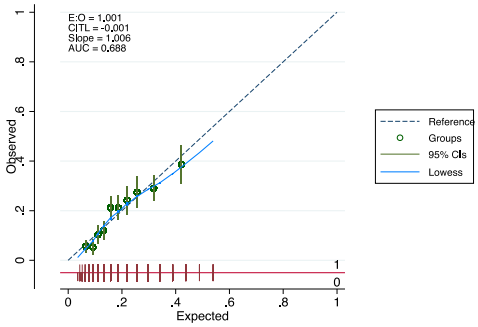
Supplementary Appendix 9. SHIP-START-0 GRA. Figure 17, MI 17



Supplementary Appendix 9. SHIP-START-0 GRA. Figure 18, MI 18



Supplementary Appendix 9. SHIP-START-0 GRA. Figure 19, MI 19

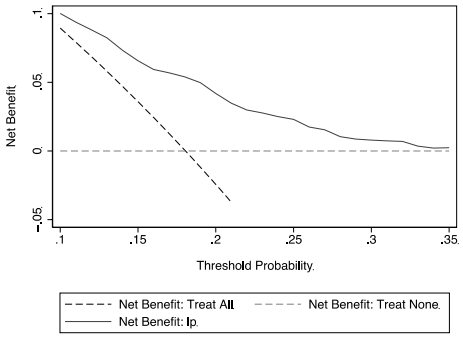


Supplementary Appendix 9. SHIP-START-0 GRA. Figure 20, MI 20

Appendix 2 Figure 11:

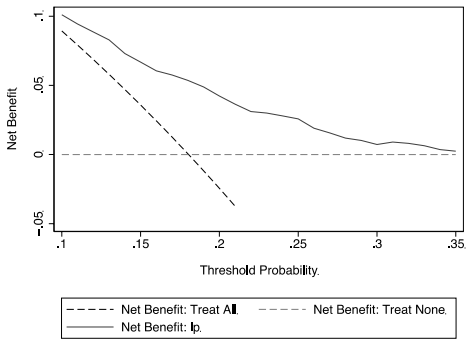
Decision Curve Analysis (DCA). DCA graphs for the adjusted model developed for each multiply imputed data set M1-M20 in SHIP-START-0

MI 3



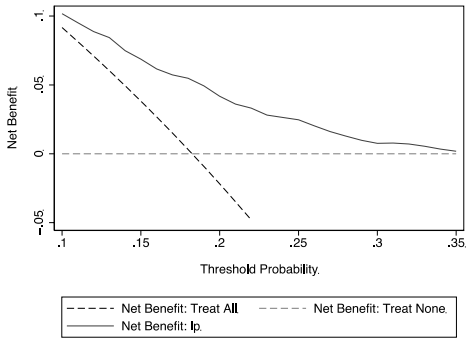
DCA Curve, SHIP-START-0, M1

MI 1



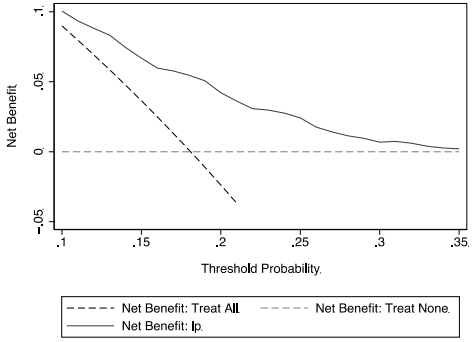
DCA Curve, SHIP-START-0, M2

MI 2



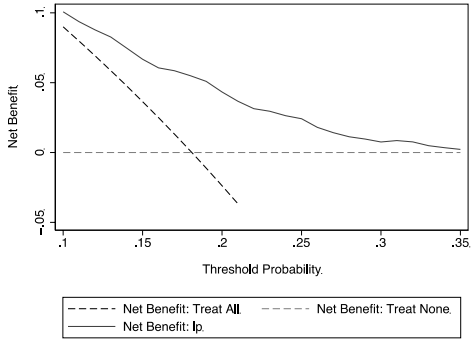
DCA Curve, SHIP-START-0, M3

MI 6



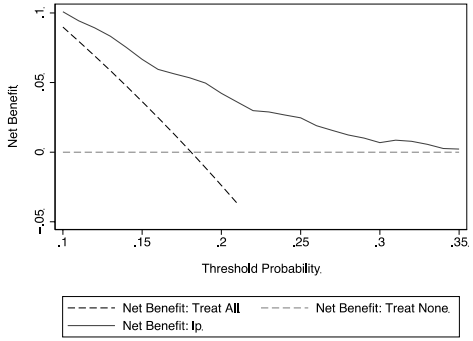
DCA Curve, SHIP-START-0, M4

MI 5



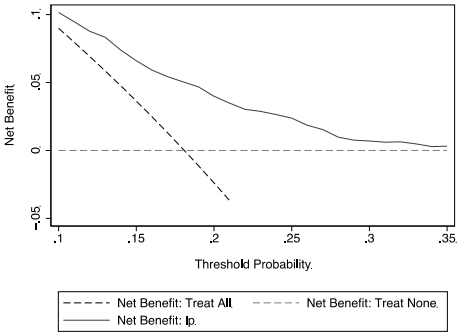
DCA Curve, SHIP-START-0, M5

MI 4



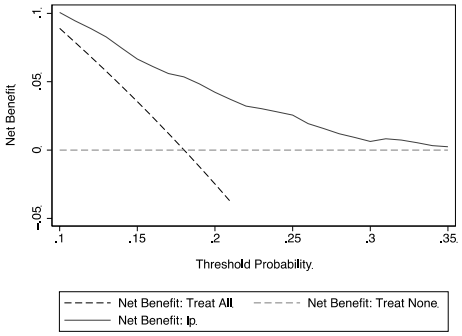
DCA Curve, SHIP-START-0, M6

MI 7



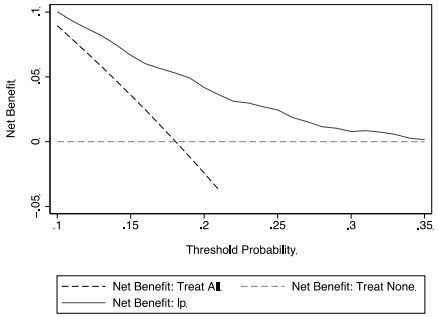
DCA Curve, SHIP-START-0, M7

MI 8



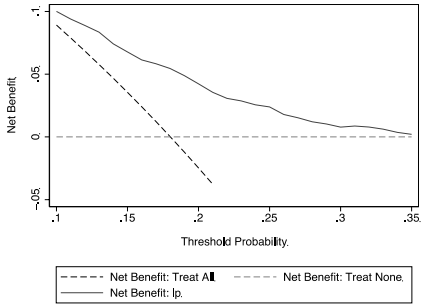
DCA Curve, SHIP-START-0, M8

MI 9



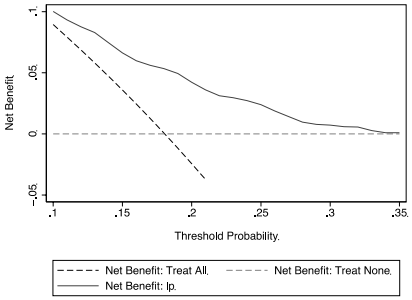
DCA Curve, SHIP-START-0, M9

*MI **10***



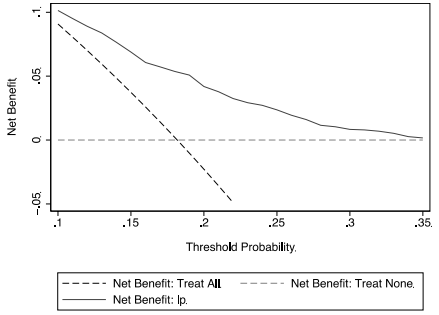
DCA Curve, SHIP-START-0, M10

MI 11



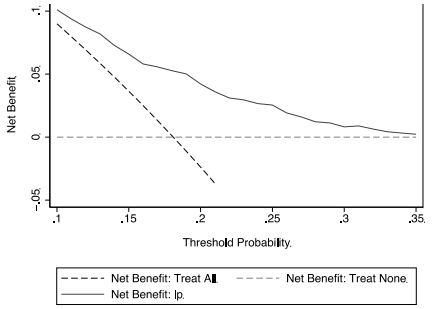
DCA Curve, SHIP-START-0, M11

MI 12



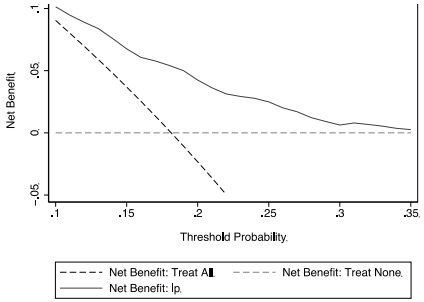
DCA Curve, SHIP-START-0, M12

MI 13



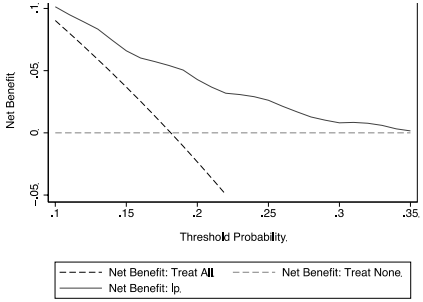
DCA Curve, SHIP-START-0, M13

MI 14



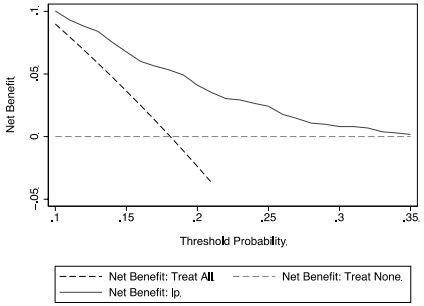
DCA Curve, SHIP-START-0, M14

MI 15



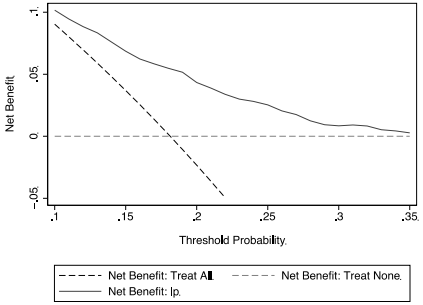
DCA Curve, SHIP-START-0, M15

MI 16



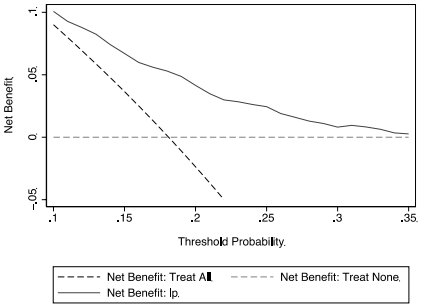
DCA Curve, SHIP-START-0, M16

MI 18



DCA Curve, SHIP-START-0, M17

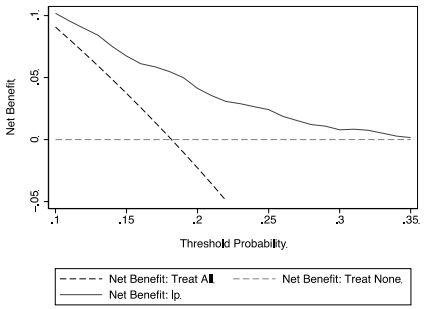
MI 17



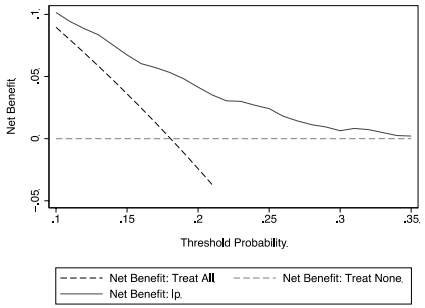
DCA Curve, SHIP-START-0, M18

MI 19

MI 20



DCA Curve, SHIP-START-0, M19



DCA Curve, SHIP-START-0, M20

Appendix 2 Figure 12:

Supplementary table of existing literature where models using dental parameters have been developed, demonstrating whether the model has also been externally validated and whether the model was reported in full allowing independent external validation.

Reference	Year	Sample size	Outcome variable	Variables	External Validation of model reported in manuscript	Reported full model to allow external validation
(76)	2007	4,830	Undiagnosed diabetes. .	Age, sex, race/ethnicity, family history of diabetes, self-reported hypertension, hypercholesterolemia and periodontitis	No	No - Full model (intercept and Beta coefficients) not reported
Li S, Williams PL, Douglass CW. Development of a clinical guideline to predict undiagnosed diabetes in dental patients. J Am Dent Assoc. 2011 Jan;142(1):28-37. doi: 10.14219/jada.archive.2011.0025. PMID: 21193764.	2011	7,545	Undiagnosed diabetes.	Waist circumference, age, self-reported oral health status, self-reported weight and self-reported race or ethnicity	Yes, External validation using NHANES 2003-2004. Demonstrated After validation, the AUCs ranged from 0.68 to 0.72	No - Full model (intercept and Beta coefficients) not reported
Lalla, E., Kunzel, C., Burkett, S., Cheng, B., & Lamster, I. B. (2011). Identification of unrecognized	2011	535	Undiagnosed pre-diabetes or diabetes	Two models. Model 1: age,	No, did not externally validate	No - Full model (intercept and Beta

diabetes and pre-diabetes in a dental setting. Journal of Dental Research, 90(7), 855-860. https://doi.org/10.1177/0022034511407069				3 dental variables and 4 self-reported risk factors (Self-reported: history of diabetes in first-degree blood relatives, presence of hypertension, high cholesterol, and being overweight or obese) Model II, "only 2 of the dental variables identified via stepwise selection (% of deep pockets, defined as ≥ 5 mm, and number of missing teeth)"	within this manuscript. But model validated in later work "Lalla, 2013" demonstrated AUC validated model of 0.58 (95% CI: 0.53, 0.62).	coefficients) not reported
Lalla, E., Cheng, B., Kunzel, C., Burkett, S., & Lamster, I. B. (2013). Dental findings and identification of undiagnosed hyperglycemia. Journal of Dental Research, 92(10), 888-892. https://doi.org/10.1177/0022034513502791	2013	591	Undiagnosed pre-diabetes or diabetes	Model II from Lalla 2011 paper + POCT HbA1c	No, did not externally validate the Model + POCT reported in this manuscript. But the "base model" was "recalibrated" in later work by "Acharya, 2018" and demonstrated (AUC) of	No - Full model (intercept and Beta coefficients) not reported

					0.59 (95% CI, 0.57–0.60) in this dataset.	
- Genco RJ, Schifferle RE, Dunford RG, Falkner KL, Hsu WC, Balukjian J. 2014a. Screening for diabetes mellitus in dental practices a field trial. Journal of the American Dental Association. 145(1):57-64.	2014	1,022	Undiagnosed pre-diabetes or diabetes	Age, sex, racial Background, self-reported height and weight, history of cigarette smoking, high blood pressure, high cholesterol levels, physical activity levels and medication use. Periodontal disease status was determined by the dentist.	No	No - Full model (intercept and Beta coefficients) not reported
Liljestrand, J.M., Havulinna, A.S., Paju, S., Männistö, S., Salomaa, V., Pussinen, P.J., 2015. Missing Teeth Predict Incident Cardiovascular Events, Diabetes, and Death. Journal of Dental Research 94, 1055–1062.. doi:10.1177/0022034515586352	2015	7,629	Undiagnosed diabetes	Age, sex, body mass index, smoking (yes/no), physical inactivity, parent with DM, *C-reactive protein* (log), and a *geographic variable* (east/west).	No	No - Full model (intercept and Beta coefficients) not reported
Herman, W. H., Taylor, G. W., Jacobson, J. J., Burke, R., & Brown, M. B. (2015). Screening for prediabetes and type 2 diabetes in dental offices. Journal of Public Health Dentistry, 75(3), 175-182. https://doi.org/10.1111/jphd.12082	2015	1,033	Undiagnosed pre-diabetes or diabetes	Sex, history of hypertension, history of dyslipidaemia, history of loss of one or more teeth, and random capillary glucose category (<110 versus ≥110 mg/dl).	No	Yes - Full model including intercept and Beta coefficients reported.

Holm, N. C., Belstrøm, D., Østergaard, J. A., Schou, S., Holmstrup, P., & Grauballe, M. B. (2016). Identification of individuals with undiagnosed diabetes and pre-diabetes in a Danish Cohort attending dental treatment. Journal of Periodontologuy, 87(4), 395-402. https://doi.org/10.1902/jop.2016.150266	2016	291	Undiagnosed diabetes	periodontitis, number of teeth, age, BMI, waist circumference, and fat percentage as predictors.	No	No - Full model (intercept and Beta coefficients) not reported
Acharya, A., Cheng, B., Koralkar, R., Olson, B., Lamster, I. B., Kunzel, C., & Lalla, E. (2018). Screening for diabetes risk using integrated dental and medical electronic health record data. Journal of Dental Research Clinical & Translational Ressearch, 3(2), 188-194. https://doi.org/10.1177/2380084418759496	2018	4,560	Undiagnosed pre-diabetes or diabetes	"Base model" included 2 dental variables, missing teeth and percentage of teeth with at least 1 deep pocket (≥5 mm), "Integrated" model included age, sex, race, ethnicity, overweight/ obesity, hypertension, hyperlipidaemia, and smoking status, in addition to "base model".	No, did not externally validate the model reported in this manuscript. Did "recalibrate" the model developed in the manuscript by Lalla 2013, "base model".	Algorithm for a propensity score that estimates the probability an individual may have prediabetes or diabetes is published.
Hegde, H., Shimpi, N., Panny, A., Glurich, I., Christie, P., & Acharya, A. (2019). Development of non-invasive diabetes risk prediction models as decision support tools designed for application in	2019	39,461 subjects with 4757 cases and	Undiagnosed diabetes	From the initial 116 medical and dental features, 107 were used after performing feature selection.	No	No - Full model (intercept and Beta coefficients) not reported

the dental clinical environment. Informatics in Medicine Unlocked, 17. https://doi.org/10.1016/j.imu.2019.100254		34,704 controls		*Including – variables not available routinely in the dental clinic: e.g. Serum Creatinine Levels. High Density Lipids (HDL) cholesterol. Hypertension readings. LDL cholesterol. WBC count. Total Triglycerides*		
Heji, E. S., Bukhari, A. A., Bahammam, M. A., Homida, L. A., Aboalshamat, K. T., & Aldahlawi, S. A. (2020). Periodontal disease as a predictor of undiagnosed diabetes or prediabetes in dental patients. European Journal of Dentistry, 15(2), 216-221. https://doi.org/10.1055/s-0040-1719208	2020	61	Undiagnosed diabetes	Smoking, hypertension, family history of diabetes, and percentage of clinical attachment loss >3 mm	No	No - Full model (intercept and Beta coefficients) not reported
Su, N., Teeuw, W. J., Loos, B. G., Kosho, M. X. F., & van der Heijden, G. (2020). Development and validation of a screening model for diabetes mellitus in patients with periodontitis in dental settings. Clinical Oral Investigations, 24(11), 4089-4100. https://doi.org/10.1007/s00784-020-03281-w	2020	204	Undiagnosed pre-diabetes or diabetes	Age, BMI, European background, cholesterol levels, previous periodontal treatment, percentage of the number of teeth with mobility, and with gingival recession	No	Yes – Full model reported
Grigoriadis, A., Räisänen, I. T., Pärnänen, P., Tervahartiala, T., Sorsa, T., & Sakellari, D. (2021).	2021	69	Pre-diabetes	“Association between the aMMP-8 PoC test and prediabetes was	No	No - Full model (intercept

Prediabetes/diabetes screening strategy at the periodontal clinic. Clinical and Experimental Dental Research, 7(1), 85-92. https://doi.org/10.1002/cre2.338				assessed by logistic regression analysis (both unadjusted and adjusted for BMI and age 45 years old), in combination with some prediabetes risk factors" … **(not defined)** … "to classify patients with and without prediabetes"		and Beta coefficients) not reported
Montero, E., Matesanz, P., Nobili, A., Luis Herrera-Pombo, J., Sanz, M., Guerrero, A., Bujaldón, A., & Herrera, D. (2021). Screening of undiagnosed hyperglycaemia in the dental setting: The DiabetRisk study. A field trials. Journal of Clinical Periodontology, 48(3), 378-388. https://doi.org/10.1111/jcpe.13408	2021	1,143	Undiagnosed pre-diabetes or diabetes)	The diagnostic models evaluated were: (a) FINDRISC alone. (b) EPB alone. (c) FINDRISC and EPB; (d) FINDRISC and point-of-care HbA1c. (e) EPB and point-of care HbA1c; and (f) FINDRISC and point-of-care HbA1c and EPB.	No	No - Full model (intercept and Beta coefficients) not reported

Table Legend: Appendix table 12, table summarising development studies published in the literature 2007-2021